IJBPAS, November, 2015, 4(11): 6281-6291

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

MATURITY ONSET DIABETES OF THE YOUNG: PRELIMINARY DATA OF THE TUNISIAN POPULATION

SOUHAÏRA BEN KHELIFA[*1], AZZA DENDANA[1], ILHEM BARBOURA[1], INES KHOCHTALI[2], HINDA CHAHED[1], SELIMA FERCHICHI[1], ABDELHEDI MILED[1]

1: Biochemistry laboratory CHU Farhat Hached Sousse 4000, Tunisia

2: Endocrinology Unit, University hospital of Monastir 5000, Tunisia

***Corresponding Author: Souhaira Ben Khelifa:** Biochemistry laboratory CHU Farhat Hached Sousse 4000, Tunisia. souhaira24@yahoo.fr

ABSTRACT

Maturity- onset diabetes of the young (MODY) is a monogenic form of T2D which is associated with pancreatic β-cell dysfunction. Characteristics of MODY diabetes remain unknown in Tunisia. We aimed in this study to evaluate the likelihood of MODY and the risk of developing complications related to diabetes in Tunisian patients. Clinical and biological features were used to select patients with strong suspicion of MODY from 450 T2 diabetics and to segregate likely GCK-MODY 2 from likely TF-MODY patients. HbA1c, C-peptide, hs-CRP and lipid profile were determined. Likely GCK-MODY 2 patients were predominant (36.92%). The prevalence of HNF1A-MODY 3 was 18.46%. No significant differences was found for the HDL, Lp (a) and the ratio Apo A/Apo B (p=0.104, p=0.223, p=0.14 respectively) comparing likely GCK-MODY 2 subjects with controls. Values of HDL-cholesterol showed also no significant differences between likely TF-MODY patients and controls (p=0.215). As for Caucasian population, mild phenotype was observed for likely GCK-MODY patients. Likely TF-MODY patients seemed to be at high risk of developing complications related to diabetes. This study was the first to give preliminary prevalence of MODY in Tunisia. Results must be confirmed by future molecular studies.

INTRODUCTION

Maturity onset diabetes of the young MODY (MIM # 606391) is the most common form of monogenic diabetes which is clinically and genetically

heterogenic [1]. MODY is non insulin dependent diabetes classically defined as autosomal dominant inheritance, young age at onset (usually before 25 years of age), Ƃ-cell dysfunction, continued secretion of endogenous insulin and absence of pancreatic autoimmunity markers [2]. To date, the MODY phenotype has been reported to be linked with mutations within 13 different genes: HNF4A (MODY1), GCK (MODY2), HNF1A (MODY3), PDX1 (MODY4), HNF1B (MODY5), NEUROD1 (MODY6), KLF11 (MODY7), CEL (MODY8), PAX4 (MODY9), INS (MODY10), BLK (MODY11) and very recently ABCC8 (MODY12) and KCNJ11 (MODY13) [3-5]. However, only four genes (GCK, HNF1A, HNF4A and HNF1β) are frequently involved in clinical practice [6]. MODY subtypes often differ in age at onset, hyperglycemia model and the association of extarpancreatic manifestations [7]. MODY is responsible for around 5% of all cases of diabetes [8]. It ´s often misdiagnosed as type 1 or type 2 diabetes. In fact, it is estimated that close to 5% of the individuals classified as having type 2 diabetes (T2D), and about 10% of those considered type 1 diabetes (T1D), are actual carriers of a MODY mutation [9]. GCK and HNF-1A MODY are the most frequent cause of MODY, accounting for approximately 70% of cases in all population studied. The reported prevalence of these two causes varies across countries due to different recruitment strategies for genetic testing. Indeed, blood glucose screening in young and asymptomatic individuals will identify a higher proportion of GCK mutations [10]. Correct diagnosis of monogenic diabetes can predict the clinical course of the patient, explain other associated clinical features and most importantly guide the most appropriate treatment. Patients with GCK mutations usually require no treatment, whiles those with HNF1A and HNF4A mutations are initially well controlled on sulphonylurea tablets [11]. Classic clinical criteria for diagnosing MODY are age at onset before 25 years, parental history of diabetes (autosomal dominant inheritance and presence of the disease in at least three consecutive generations) and evidence of endogenous insulin secretion [12]. Besides clinical criteria, several biochemical biomarkers has been developed to discriminate MODY patients from others subtypes of diabetes. Recently, it has been established that highly sensitive C-reactive protein (hs-CRP) is a clinically valid biomarker for HNF1A-MODY in European populations [13]. HbA1c showed also excellent discrimination between patients with a

GCK mutation and patients with other young-onset diabetes [14].

In Tunisia, clinical, biochemical and molecular characteristics of MODY remains unknown. We use in this work clinical as well biological features to assess the likelihood of MODY, distinguish between those with likely GCK-MODY 2 from those with likely transcription factors MODY (TF-MODY) and to evaluate the risk of developing complications related to diabetes in these patients.

MATERIAL AND METHODS

Study population

We selected in this study, from a total of 450 unrelated patients clinically classified T2D, 65 subjects with a strong clinical suspicion of MODY. They were recruited from the Endocrinology unit of the university hospital of Monastir and some clinical centers located in the Sahel region of Tunisia. Approval from the hospital authority and the ethic committee was obtained. All participants gave written informed consent. Criteria used by physicians for referring likely clinical MODY patients included family history of diabetes in at least three consecutive generations, an age at onset of diabetes before 25 years in at least one family member, absence of pancreatic autoimmunity markers (Glutamic acid decarboxylase (GAD) and insulin autoantibodies (IA2), a primary defect in β-cell function (significant C-peptide levels) and a body mass index (BMI) $\leq$ 25 kg/m^2. We discriminated then, patients with high suspicion of GCK-MODY 2 from those with high suspicion of TF-MODY, notably HNF1A and HNF4A-MODY. These are frequently described in clinical practice and have similar characteristics. Actually, HNF4A-MODY 1 should be considered for sequencing when the clinical features were strongly suggestive of HNF1A-MODY 3, but it's sequencing is negative [1]. Selection criteria for GCK-MODY 2 included Hba1c less than 7.5% as it was reported in previous studies that Hba1c showed excellent discrimination between GCK-MODY 2 patients and other young onset diabetes patients [14-15]. Diagnosis associated with pregnancy, management of the diabetes only with diet and exercises and absence of microvascular complications were also considered in our selection criteria. Hs-CRP levels less than 0.5 mg/L as well as sensitivity of patients to sulfonurea treatment were criteria used to detect patients with high suspicion of HNF1A-MODY 3. Additionally, a group of 50 unrelated non-diabetic controls was added to our study.

Laboratory methods

Blood tests were performed in the biochemical laboratory of Farhat Hached

hospital in Sousse. Fasting glucose, Triglycerides, Total Cholesterol and HDL-Cholesterol (HDL-C) were evaluated on Beckman auto-analyser by using commercial kits from Randox (Randox Diagnostics, Antrim, UK). LDL-C cholesterol was calculated using Friedewald's formula [16]. HbA1c, apolipoprotein AI (Apo AI), apolipoprotein B (Apo B), Lipoprotein a (Lp (a)), cystatin C and hsCRP were determined by immunoturbidimetric method (Roche Diagnostics, Mannheim, Germany). C-peptide was determined by chemiluminiscent microparticule immunoassay (Abbott Diagnostics, Rungis, France). Anti- GADA and Anti IA2 were performed by ELISA at diagnosis for all MODY patients (Euroimmun, Luebeck, Germany)

Statistics

Data were analyzed using the IBM SPSS statistical software package for windows version 19.0 (SPSS, Chicago, IL, USA). Results were expressed as means ± standard deviation (M±SD). Analysis between groups was by the student t-test for independent variables. Significant differences were assumed for p value less than 0.05.

RESULTS

A total of 65 patients from 450 subjects classified initially as T2D (14.44%) satisfied the inclusion criteria of MODY. They were grouped according to the clinical and biological criteria reported in the literature for the subtypes of MODY, in likely GCK-MODY 2 (36.92%) and likely TF-MODY (63.08%) groups. A total of 23 subjects of the latter group presented hs-CRP level low than 0.5 mg/L, twelve of them (18.46%) were treated with sulphonyurea tablets. Clinical and biological characteristics of the study population are given in Tables 1 and 2.

GCK-MODY 2 vs TF-MODY patients:

Female were predominant in GCK-MODY 2 (75%) and TF-MODY (58.83%) groups. Age at onset of diabetes was older in suspected GCK-MODY 2 patients than suspected TF-MODY patients (p = 0.008). BMI was lean in both groups with no significant differences (p = 0.582). Among likely GCK-MODY 2 patients, 13 women (54.16%) were diagnosed during their pregnancy, 2 (8.33%) were diagnosed on the time of our study, the others (37.5%) when glucose was screened for others pathologies. All patients with likely TF-MODY presented with signs and symptoms of hyperglycemia, including polyuria, polydipsia and nocturia. Dyslipidemia was absent in likely GCK-MODY 2 patients, but not uncommon in likely TF-MODY ones. We noted absence of hypertention in both groups. Likely GCK-MODY 2

patients were treated with OHAs (66.67%) and with diet and exercise (33.33%). Patients with high suspicion of TF-MODY were treated by insulin (26.83%), OHAs (39.02%) and combination of insulin and OHAs (34.15%).

Hba1c in likely GCK-MODY 2 patients was in the therapeutic target (≤ 7.5%), with significant differences between likely TF-MODY subjects (7.03 ± 0.91 % vs 9.98 ± 1.67 %; $p < 10^{-4}$). Significant differences between the two groups have been noted for C-peptide levels ($p < 10^{4}$).

Triglyceride, total cholesterol and LDL-cholesterol levels were lower in patients with high suspicion of GCK-MODY 2 patients compared with those with high suspicion of TF-MODY (p=0.009; p=0.029 and p=0.028 respectively). No significant differences were noted for HDL-cholesterol (p=0.187) and the ratio Apo A/Apo B (p=0.248) between both groups. Lipoprotein (a) levels were lower in likely GCK-MODY 2 patients than likely TF-MODY subjects (0.16 ±0.18 vs 0.3± 0.17, $p=10^{-4}$). For cystatin C values, no statistical differences were observed (p=0.124). Hs-CRP levels were higher in patients with likely GCK-MODY 2 than those with likely TF-MODY. Values less than 0.5 mg/L were found in 23 patients with high suspicion of TF-MODY, 12 of them (18.46 %) received yet sulfonurea treatment.

Assessing the risk of micro and macrovascular complications:

Comparison between patients highly suspected GCK-MODY 2 and controls showed no significant differences for the following parameters: triglycerides, total cholesterol, HDL and LDL-cholesterol, Lp (a) and the ratio Apo A/Apo B (p=0.531, p=0.726, p=0.104, p=0.92, p=0.223, p=0.14 respectively). However, comparison between the group of likely TF-MODY patients and that of controls showed significant increase in triglycerides, total cholesterol, LDL-cholesterol, Lp (a) and the ratio Apo A/Apo B levels (p<0.001, p=0.012, p=0.006, p<0.001 and p=0.001 respectively). Values of HDL-cholesterol showed no significant differences between highly suspected TF-MODY patients and controls (1.17 ± 0.29 vs 1.02 ± 0.21 mmol/L; p=0.215).

No significant differences were revealed for cystatin C values in likely GCK-MODY 2 and TF-MODY patients compared with controls (p=0.265 and p=0.173 respectively).

DISCUSSION

It is important to correctly diagnose MODY as it can predict the clinical course of the patient, explain other associated clinical features and most importantly guide the most appropriate treatment. Actually, clinical characteristics and basic laboratory

tests are established to help identify MODY patients. In fact, MODY is classically characterized by young age at onset, autosomal dominant family history, continued production of endogenous insulin, absence of β-cell autoimmunity and absence of signs of insulin resistance [6]. Recently, specific biomarkers were identified for some MODY subtypes. As an example the hs-CRP for HNF1A-MODY 3 and the Hba1c for GCK-MODY 2 [14-15, 17]. These finding were useful to identify in our study, from a total of 450 diabetics T2, 65 patients (14.44%) with the clinical phenotype of MODY and to classify them into likely GCK-MODY 2 (36.92%) and likely TF-MODY (63.08%) groups. In this group we succeeded to identify twelve subjects (18.46%), with a high suspicion of HNF1A-MODY 3. Likely GCK-MODY 2 and likely TF-MODY groups presented a predominance of female and lean BMI, which are variables used in an online probability model for assessing the likelihood of MODY [18]. Likely GCK-MODY 2 patients were asymptomatic at diagnosis. They presented an age at onset lower than likely TF-MODY patients. It has been reported in previous studies that the age of diagnosis in GCK-MODY 2 patients may vary substantially, and it depend very much on the time when glucose is screened for an unrelated illness or during pregnancy [19]. It has been reported also that HNF1A and HNF4A-MODY subjects develop diabetes at diverse ages (between 10 and 40 years of age) [20]. In contrast to likely TF-MODY patients who were treated mainly by insulin or by combination if insulin and OHAs, no require of insulin therapy was observed for likely GCK-MODY 2 patients. These findings were correlated with previous studies showing that in consistence with mild phenotype, patients with glucokinase mutations rarely need any specific treatment outside pregnancy, and the majority (> 85%) is managed on diet alone [21]. As for HNF1A and HNF4A patients, they are initially well controlled using sulphonylurea tablets, although insulin treatment may be required later, due to the progressive deterioration in glycaemic control throughout life [22].

Knowing the duration of diabetes is closer in the two groups (≈ 8 years), dyslipidemia and hypertension were absent in likely GCK-MODY 2 patients, but not uncommon in those with highly suspicion of TF-MODY. Few cases of the latter group developed also retinopathy. In this study, likely GCK-MODY 2 patients seemed to be at low risk of developing complications related to diabetes. In contrast, the normal HDL-cholesterol level observed in our TF-MODY patients does

not seem to be cardioprotective. In fact, the slight increase of Lp (a) levels and the ratio Apo A/Apo B gave evidence that these patients are at risk of developing macrovascular complications. Our results were supported by previous findings demonstrating that positive correlation was found between increased levels of Lp (a) and the ratio ApoA/ApoB and cardiovascular complications [23-24]. It was shown also that GCK-MODY 2 is not associated with dyslipidemia, micro or macrovascular complications [21, 25]. However, the frequency of micro and macrovascular complications in patients with HNF1A-MODY 3 and HNF4A-MODY 1 is similar to that in patients with type 1 and T2D, and is related to poor glycemic control [26-27].

CONCLUSION

Our study was based on clinical and biological rather than molecular criteria. All results were considered preliminary and can be only confirmed by a genetic study. Clinical phenotype of MODY was observed in 14.44% of T2D. We noted a predominance of GCK-MODY 2 in the Tunisian population, with preliminary prevalence of 36.92%. HNF1A-MODY 3 was estimated to be about 18.46%. This group seemed to be at risk of developing macrovascular complications.

REFERENCES

[1] Stride A, Hattersley AT. Differents genes, differents diabetes: lessons from maturity-onset diabetes of the young. Ann Med 2002; 34(3):207-216.

[2] Vaxillaire M, Froguel P. Genetic basis of maturity-onset diabetes of the young**.** Endocrinol Metab Clin North Am 2006; 35(2):371-384.

[3] Njølstad PR, Molven A. To test, or not to test: time for a MODY calculator? Diabetologia 2012; 55(5):1231-1234.

[4] Murphy R, Ellard S, Hattersley AT. Clinical implications of a molecular genetic classification of monogenic beta-cell diabetes. Nat Clin Pract Endocrinol Metab 2008; 4(4):200-213.

[5] Bonnefond A, Philippe J, Durand E, Dechaume A, Huyvaert M, Montagne L, Marre M, Balkau B, Fajardy I, Vambergue A, Vatin V, Delplanque J, Le Guilcher D,De Graeve F, Lecoeur C, Sand O, Vaxillaire M, Froguel P.. Whole-exome sequencing and high throughput genotyping identified KCNJ11 as the thirteenth MODY gene. PLoS One 2012; 7(6):e37423.

[6] Owen KR. Monogenic diabetes: old and new approaches to diagnosis. Clin Med 2013; 13(3):278-281.

[7] Murphy R, Ellard S, Hattersley AT. Clinical implications of a molecular genetic classification of monogenic

beta-cell diabetes. *Nat* Clin Pract Endocrinol Metab 2008, 4(4): 200-213.

[8] Giuffrida FM, Reis AF. Genetic and clinical characteristics of maturity-onset diabetes of the young. Diabetes Obes Metab 2005; 7(4):318-326.

[9] Caetano LA, Jorge AA, Malaquias AC, Trabach EB, Quieroz MS, Nery M, Teles MG. Incidental mild hyperglycemia in children: two MODY 2 families identified in Brazilian subjects. Arq Bras Endocrinol Metabol 2012; 56(8):519-524.

[10] Estalella I, Rica I, Perez de Nanclares G, Bilbao JR, Vazquez JA, San Pedro JI, Busturia MA, Castaño L; Spanish MODY Group. Mutations in GCK and HNF-1alpha explain the majority of cases with clinical diagnosis of MODY in Spain. Clin Endocrinol (Oxf) 2007; 67(4):538-546.

[11] Rubio-Cabezas O, Hattersley AT, Njølstad PR, Mlynarski W, Ellard S, White N, Chi DV, Craig ME; International Society for Pediatric and Adolescent Diabetes. .ISPAD Clinical Practice Consensus Guidelines 2014.The diagnosis and management o f monogenic diabetes in children and adolescents. Pediatr Diabetes 2014; 15 Suppl 20:47-64.

[12] Shields BM, McDonald TJ, Ellard S, Campbell MJ, Hyde C, Hattersley AT. The development and validation of a clinical prediction model to determine the probability of MODY in patients with young-onset diabetes. Diabetologia 2012; 55(5): 1265–1272.

[13] Thanabalasingham G, Shah N, Vaxillaire M, Hensen T, Tuomi T, Gasperikova D, Szopa M, Tjora E, James TJ, Kokko P, Loiseleur F, Andersson E, Gaget S,Isomaa B, Nowak N, Raeder H, Stanik J, Njolstad PR, Malecki MT, Klimes I, Groop L, Pedersen O, Froguel P, McCarthy MI, Gloyn AL, Owen KR. A large multi-centre European study validates high-sensitivity C-reactive protein (hsCRP) as a clinical biomarker for the diagnosis of diabetes subtypes. Diabetologia 2011; 54(11):2801-2810.

[14] Steele AM, Wensley KJ, Ellard S, Murphy R, Shepherd M, Colclough K, Hattersley AT, Shields BM.. Use of HbA1c in the Identification of Patients with Hyperglycaemia Caused by a Glucokinase Mutation: Observational Case Control Studies. PLoS One 2013; 8(6):e65326.

[15] Shober E, Grabert RM, Kapellen ATT, Reinehr T, Holl RW**.** Phenotypical of maturity-onset diabetes of the young

(MODY diabetes) in comparision with type 2 diabetes mellutis (T2DM) in children and adolescents: experience from a large multicentre database. Diabet Med 2009; 26(5):466-473.

[16] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972; 18(6):499–502.

[17] Ellard S, Bellanné-Chantelot C, Hattersley AT; European Molecular Genetics Quality Network (EMQN) MODY group. Best practice guidelines for the molecular genetic diagnosis of maturity-onset diabetes of the young. Diabetologia 2008; 51(4):546-553.

[18] Shields BM, McDonald TJ, Ellard S, Campbell MJ, Hyde C, Hattersley AT. The development and validation of a clinical prediction model to determine the probability of MODY in patients with young-onset diabetes. Diabetologia 2012; 55(5): 1265–1272.

[19] McDonald TJ, Ellard S. Maturity onset diabetes of the young: identification and diagnosis. Ann Clin Biochem 2013; 50(Pt 5):403-415.

[20] Vaxillaire M, Froguel P**.** Monogenic diabetes in the young, pharmacogenetics and relevance to multifactorial forms of type 2 diabetes. Endocr Rev 2008; 29(3):254-264.

[21] Froguel P, Zouali H, Vionnet N, Velho G, Vaxillaire M, Sun F, Lesage S, Stoffel M, Takeda J, Passa P, Permutt MA, Beckmann JS, Bell GI, Cohen D. Familial hyperglycemia due to mutations in glucokinase. Definition of a subtype of diabetes mellitus. N Engl J Med 1993; 328(10):697-702.

[22] Pearson ER, Pruhova S, Tack CJ, Johansen A, Castleden HA, Lumb PJ, Wierzbicki AS, Clark PM, Lebl J, Pedersen O, Ellard S, Hansen T, Hattersley AT. Molecular genetics and phenotypic characteristics of MODY caused by hepatocyte nuclear factor 4alpha mutations in a large European collection. Diabetologia.2005; 48(5):878-885.

[23] Carnevale Schianca GP, Fra GP, Colli E, Bigliocca M, Mella R, Scaglia E, Bartoli E. Sex differences in lipid profiles in relation to the progression of glucose abnormalities. J Diabetes 2012; 4(1):95-101.

[24] Walldius G, Jungner I. The apoB ⁄ apoA-I ratio: A strong, new risk factor for cardiovascular disease and a target for lipid-lowering therapy. A review of the evidence. J Intern Med 2006; 259(5): 493–519.

[25] Hattersley A, Bruining J, Shield J, Njolstad P, Donaghue KC. The diagnosis and management of monogenic diabetes in children and adolescents. Pediatric Diabetes 2009: 10 Suppl 12: 33–42.

[26] Malecki MT, Mlynarski W. Monogenic diabetes: implications for t herapy of rare types of disease. Diabetes Obes Metab 2008; 10(8):607-616

[27] Isomaa B, Henricsson M, Letho M, Forsblom C, Karanko S, Sarelin L, Häggblom M, Groop L. Chronic diabetic complications in patients with MODY3 diabetes. Diabetologia 1998: 41(4):467–473.

Conflict of interest

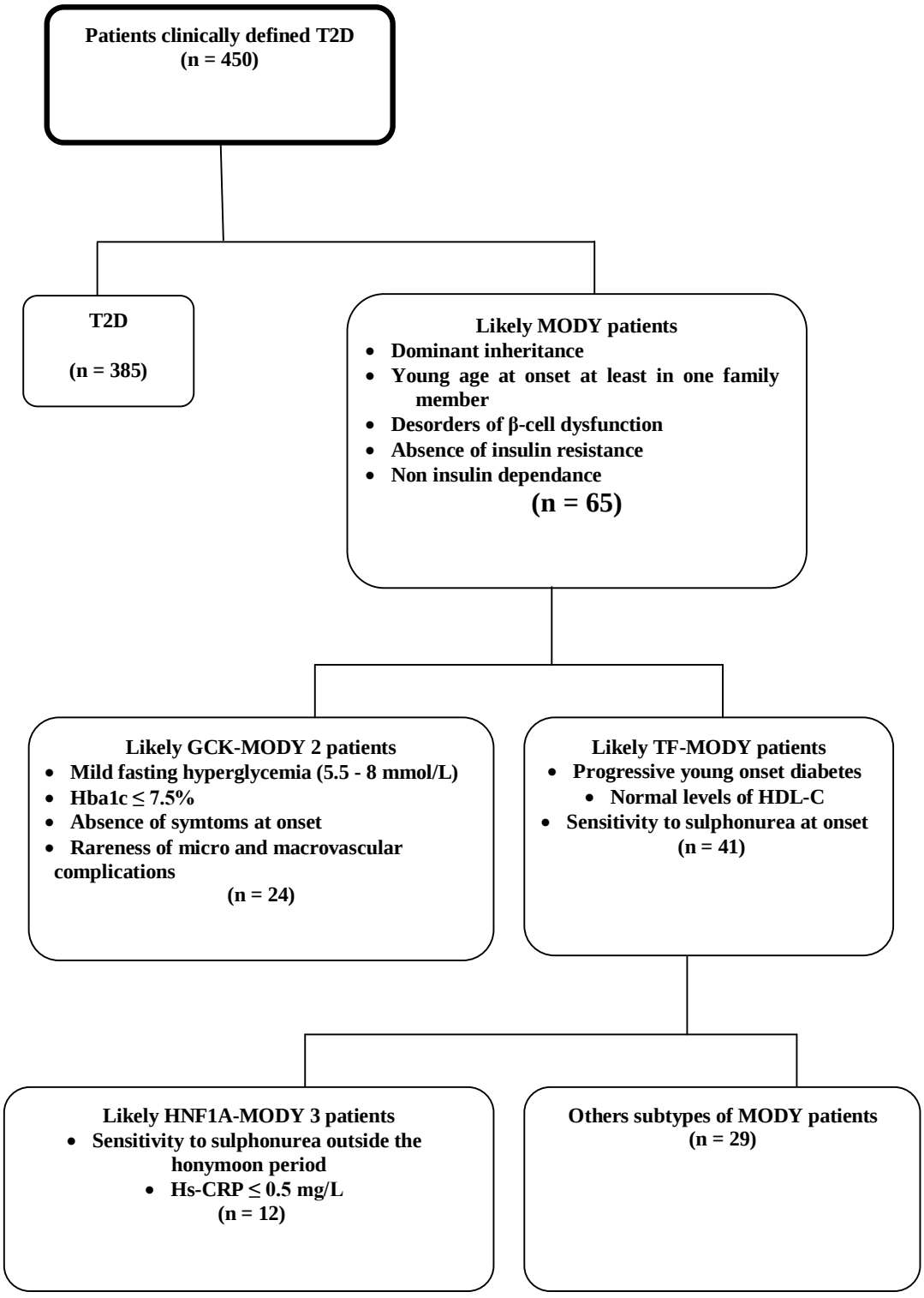
The authors declare no conflict of interest

Table 1: **Clinical characteristics of study population**

	Group 1 (n=24)	Group 2 (n=41)	Controls (n=50)
Gender (%):			
- Male	**25**	**41.47**	**44**
- Female	**75**	**58.53**	**56**
Current age (years)	**33.46 ± 10.46**	**32.02 ± 12.55**	**28.42 ± 7.55**
Age at diagnosis (years)	**21.56 ± 3.1**	**35.06 ± 9.43**	**-**
Duration (years)	**8.41 ± 8.12**	**8.19 ± 8.07**	**-**
BMI (kg/m^2)	**23.04 ± 1.7**	**22.79 ± 1.88**	**23.24±7.55**
Complications (%)			
- Dyslipidemia	**0**	**9.75**	**-**
- Hypertention	**0**	**7.31**	**-**
- Retinopathy	**0**	**4.88**	**-**
Treatment :			
- Insulin therapy (%)	**0**	**26.83**	**-**
- OHAs	**66.67**	**39.02**	**-**
- Combination therapy (Insulin + OHAs)	**0**	**34.15**	**-**
			-
- Lifestyle intervention	**33.33**	**0**	**-**

Table 2: Biological parameters in study population

Biological Parameters	(a) Group 1 (n=24)	(b) Group 2 (n=41)	(c) Controls (n=50)	P- value a and b	P- value a and c	P- value b and c
Fasting glucose (mmol/L)	**7.03 ± 0.91**	**9.98 ± 1.67**	**4.7 ± 0.56**	**< 0.001**	**< 0.001**	**< 0.001**
HbA_{1c} (%)	**6.55 ± 0.55**	**9.79 ± 1.54**	**4.84 ± 0.57**	**< 0.001**	**< 0.001**	**< 0.001**
C- peptide (ng/mL)	**0.7 ± 0.22**	**0.5 ± 0.17**	**1.02 ± 0.25**	**< 0.001**	**< 0.001**	**< 0.001**
Cystatin C (mg/L)	**0.73 ± 0.32**	**0.86 ± 0.29**	**0.79 ± 0.15**	**0.124**	**0.265**	**0.173**
Triglycerides (mmol/L)	**1.05 ± 0.3**	**1.31 ± 0.4**	**1 ± 0.23**	**0.009**	**0.531**	**< 0.001**
Total cholesterol (mmol/L)	**4.83 ± 0.86**	**5.36 ± 0.99**	**4.9 ± 0.7**	**0.029**	**0.726**	**0.012**
HDL-Cholesterol (mmol/L)	**1.04 ± 0.35**	**1.17 ± 0.29**	**1.02 ± 0.21**	**0.187**	**0.104**	**0.215**
LDL-Cholesterol (mmol/L)	**3.16±0.9**	**3.72±1.1**	**3.17±0.76**	**0.028**	**0.923**	**0.006**
Lipoprotein a (mg/L)	**0.16 ± 0.18**	**0.3 ± 0.17**	**0.2 ± 0.18**	**< 0.001**	**0.223**	**< 0.001**
Apo lipoprotein A (g/L)	**1.36 ± 0.25**	**1.51 ±027**	**1.34 ± 0.18**	**0.23**	**0.774**	**0.001**
Apo lipoprotein B (g/L)	**1.01 ± 0.34**	**0.99±0.4**	**0.93 ± 0.25**	**0.893**	**0.315**	**0.403**
ApoA/ApoB	**1.52±0.75**	**1.75±0.72**	**1.34±0.32**	**0.248**	**0.138**	**0.001**
Hs-CRP (mg/L)	**1.15 ± 0.5**	**0.68 ± 0.6**	**0.98 ± 0.48**	**0.01**	**0.168**	**0.012**


Patients clinically defined T2D
(n = 450)
T2D
(n = 385)
Likely MODY patients
Dominant inheritance
Young age at onset at least in one family member
Desorders of β-cell dysfunction
Absence of insulin resistance
Non insulin dependance
(n = 65)
Likely GCK-MODY 2 patients
Mild fasting hyperglycemia (5.5 - 8 mmol/L)
Hba1c ≤ 7.5%
Absence of symtoms at onset
Rareness of micro and macrovascular complications
(n = 24)
Likely TF-MODY patients
Progressive young onset diabetes
Normal levels of HDL-C
Sensitivity to sulphonurea at onset
(n = 41)
Likely HNF1A-MODY 3 patients
Sensitivity to sulphonurea outside the honymoon period
Hs-CRP ≤ 0.5 mg/L
(n = 12)
Others subtypes of MODY patients
(n = 29)