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Using of Clinical Indices and Biochemical Techniques in Diagnosis of Maturity-Onset Diabetes of Young in Iraqi Population

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Abstract: To choose the best course of treatment and determine the prognosis, maturity-onset diabetes of the young (MODY) must be accurately diagnosed. This study aimed to investigate potential clinical markers that could be used to distinguish MODY in young subjects. Eighty MODY3 patients were defined and contrasted with fifty healthy controls. For both age and gender, these two groups were matched. Eighty patients' clinical profiles were gathered, and statistical analysis was done on them. Compared to patients with MODY, subjects had low fasting C-peptide levels (0.56 ± 0.06 ng/mL), total cholesterol (4.46 ± 0.95 mmol/L), Triglyceride levels (1.19±0.042 mmol/L), low-density lipoprotein cholesterol (LDL-C) levels (2.29±0.079 mmol/L), high-density lipoprotein cholesterol (HDL-C) levels (1.31±0.018 mmol/L), HbA1c (7.96% ±0.21), fast blood sugar (7.91 ±0.1 mmol/L) and Anti glutamic acid decarboxylase antibody (GAD) was negative for all patient. Our results imply that fasting C-peptide, anti-GAD Ab, and lipid levels enable effective MODY discriminating. These clinical signs may serve as MODY signals in young diabetic patients, Nevertheless, genetic testing remains important and essential for the diagnosis of patients with MODY.

Keywords: C-peptide, Anti GAD, Lipid, MODY.

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Introduction

Among other non-communicable diseases, diabetes is one of the most prevalent and expensive chronic health problems and a significant source of morbidity and mortality. Diabetes patients' knowledge of their conditions has to be improved as it affects how the disease will progress (1).

A common feature of MODY is the emergence of hyperglycemia at a young age (often before the age of 25, however, a diagnosis could come at an earlier age). MODY is characterized by decreased insulin secretion and little to no insulin action abnormalities (if there is no concurrent obesity). A family history of diabetes, an autosomal dominant pattern of inheritance (2,3), the absence of beta-cell autoimmunity, and insulin resistance are further characteristics. and ß-cell malfunction characterizes a clinically diverse range of monogenic diseases (4,5,6). Because monogenic diabetes is caused by mutations in one of the genes that regulate insulin levels, differentiating it from type 1 or type 2 diabetes can be difficult. MODY accounts for 2% to 5% of all diabetes cases (7,8). Today, MODY is regarded to as a diverse group of monogenic illnesses that cause

pancreatic beta-cell malfunction and lead to a reduction in insulin output, MODY is a dangerous disease that lasts throughout a person's lifetime, even though it is uncommon. It increases the risk of heart disease, kidney failure, and blindness. (7,9).

The Online Mendelian Inheritance in Man (OMIM) (10) reports that there are currently 14 different subtypes of MODY (MODY1-14), each of which is brought on by a pathogenic variant in one of the 14 distinct genes (*HNF4A, GCK, HNF1A, PDX1, HNF1B, NEUROD1, KLF11, CEL, PAX4, INS, BLK, ABCC8, KCNJ11, APPL1*). Some genes (*HNF4A, GCK, HNF1A, HNF1B*) are more frequently damaged than others, resulting in MODY1, MODY2, MODY3, and MODY5, respectively (11,12). Genetic testing is necessary since MODY patients' treatment implications are significant (13,14).

Clinically, people with GCK-MODY show modest, stable fasting hyperglycemia and don't typically need anti hyperglycemic medication unless they're pregnant. Low doses of sulfonylureas, which are the first-line treatment for patients with *HNF1A*- or *HNF4A*-MODY, are typically effective, in certain cases, insulin will be needed over time. Renal cysts and uterine abnormalities are linked to HNF1B mutations or deletions (renal cysts and diabetes syndrome (RCAD). There have been reports of other, incredibly rare variants of MODY involving the transcription factor genes pancreatic and duodenal homeobox 1 (*PDX1*) insulin promoter factor-1 (*IPF1*) and neuronal differentiation 1(NEUROD1)(15).

Materials and methods

Study groups and blood sampling

Eighty patients with diabetes (n = 80) all matched the requirements for the MODY diagnosis. Participants in the study were those who attended The Central Child Hospital / Endocrinology and Diabetes Center and 50 apparently healthy individuals as a control group from January 2021 to August 2021. all suspected MODY patients were diagnosed with the help of specialist medical staff according to the included and excluded criteria. the inclusion criteria for MODY are as follows, a strong family history of any kind of diabetes, Insulin independence, Absence of pancreatic antigen autoantibodies and indications of endogenous insulin production, Ketoacidosis is not present, Obesity is not present normal BMI (16), Mild stable hyperglycemia, Diagnosed before the age of 25, Negative Glutamic Acid Decarboxylase autoimmune antibodies Anti GAD. (17), Low C-peptide, Normal or elevated triglyceride levels, and Normal high-density lipoprotein cholesterol. while the Exclusion Criteria, if any of the following circumstances existed, subjects were ruled out of the study, Glutamic Acid Decarboxylase autoimmune antibodies, Obesity. Diabetes without family history and diabetes caused by emotional trauma. Fifty apparently healthy individuals with no family history of diabetes were matched in age and gender with MODY patients.

Measurements

HbA1c, fast blood sugar (F.B.S), C-peptide, anti-glutamic acid decarboxylase (GAD) antibody, triglycerides (TG), cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and fasting glucose are all indicators of diabetes. All diabetic patients provided information about their age, initial symptoms, diabetes management, and parental history of the disease (first-degree relatives, mother or

father). Height (cm) / weight (kg) was used to compute body mass index (BMI) $^{(m2)}$. Obesity was defined as a BMI more than 30 kg/m2 (18). All participants gave their consent after being fully informed. The kit used in the study (HDL cholesterol kit, Hemoglobin A1c (A1c_E) Assay, Human c-p (c- Peptide) kit, LDL Cholesterol Direct kit, Cholesterol kit, triglyceride kit, and Glucose Kit from (Siemens Healthineers/ Germany). Medizym® anti-GAD (medipan / Germany).

Statistical analysis

The results were computed using a Statistical Analysis System- SAS (2018) (19), program was used to detect the effect of different factors on study parameters. The Chi-square test was used to compare percentages (0.05 and 0.01 probability) significantly.

The distribution of patients according to the age

The study was done on 80 MODY patients (50 (62.5%) Male and 30 (37.5%) Female) and 50 apparently healthy individuals as control group who were matched with patients in age and sex to exclude the effect of them on the molecular study.

The age of patients in the present study was ranged from 1 to 28 years, with a mean+ SE of 10.40 $\pm$0.65. According to World Health Organization WHO, (20), the patients in the current study were divided into three groups, childhood (1-9 years), Adolescent (10-19 years) and Adulthood (20-28 years). Most patients were within childhood and Adolescent age (37 (46.25%) and 36 (45%), respectively), while the lower was within Adulthood age (7 (8.75%) (Table 1).

Table (1): The Distribution of patients according to the age

Patients Age (Years)	Patient No. (%)
1-9(childhood)	37 (46.25%)
10-19(Adolescent)	36 (45%)
20-28(Adult hood)	7 (8.75%)
Total	80 (100%)

Results and discussion

These results are justifying by Naylor *et al.* (2018) who suggested that Early-onset of MODY diabetes was in the adolescence or in young adulthood (21).

The distribution of patients according to the body mass Index

The mean value (mean ± SE) of BMI is significantly increased (P≤0.01) in MODY patients (18.33 ± 0.32) when compared with controls (18.33 ± 0.32), but both are within the normal values of the weight according to World Health Organization (22), show table (2).

Table (2): Comparison between patients and control in BMI

Group	BMI (kg/m^2) (Mean ± SE)
Patients (80)	18.33 ±0.32
Control (50)	20.11 ±0.23
T-test	0.895 **
P-value	0.0001
**** (P≤0.01).**	

According to control group, they were selected to be within normal BMI in order to avoid catching of other disease particularly DMT2 and any effects on biochemical analysis.

The results of BMI for MODY patients in this study are in agreement with Wu *et al.*(23) who were found that MODY patients had normal BMI, compared with other DM patients who had overweight with BMI. Thus, prior to clinical laboratory examinations and further gene testing, BMI is crucial for the quick distinction of MODY from familial type 2 diabetes. As the BMI of patients under study was within normal, this is agreeing with the strategy of MODY diagnosis which depends on considering normal BMI as of the clinical aspects of MODY diagnosis (23).

Biochemical parameter

Hemoglobin A1c and fast blood sugar

For HbA1c and F.B.S values (mean+ SE), table (3) show a highly significant difference between MODY patients and control group (HbA1c: 7.96 ±0.21, 5.06 ±0.11, F.B.S: 7.91 ±0.16, 4.79 ±0.04, respectively).

Table (3): Comparison between patients and control group in FBS and HbA1c

Group	Mean ± SE	
	F.B.S. (mmol/L)	HbA1c (%)
Patients	7.91 ±0.16	7.96 ±0.21
Control	4.79 ±0.04	5.06 ±0.11
T-test	0.426 **	0.562 **
P-value	0.0001	0.0001
** (P≤0.01)		

These findings were in line with those of Delvecchio, *et al.* (2018), who discovered and recommended combining a cut-off of F.B.S. ≤ 8.3 mmol/L and >7.3 % for HbA1c to screen for HNF1A(MODY3) first, regardless of additional clinical information (24).

Lipid profile tests

Table (4) shows the mean value of selected lipid profile MODY patients were with total TC, TG, HDL and LDL (mean+ SE) of 4.46 +0.95, 1.19 + 0.042, 1.31 + 0.018 and 2.29 +0.079, respectively.

Table (4): Values of TC, TG, HDL and LDL in MODY patients

Parameters	(mmol/L) mean± SE	Range
Cholesterol	4.46/0.95	2.50-4.76
Triglyceride	1.19/0.042	0.33-1.99
HDL	1.31/0.018	1.00-1.60
LDL	2.29/0.079	1.10-3.58

These findings supported those of Fu *et al.*, (2019), who discovered that lipid levels could serve as biomarkers to distinguish MODY2 and MODY3 from T1DM. They also discovered that since total cholesterol and LDL-C were each independent predictor of the MODY2 phenotype, combinations of these biochemical indicators could be used as markers to distinguish MODY subtypes and to more precisely identify the phenotypic traits of MODY2 and MODY3 individuals (25).

At the same time, these results agreed with Naylor *et al.* (2018) who reported that all patients were with normal triglyceride levels and normal high-density lipoprotein cholesterol (HDL-C) (21).

C-peptide tests

The value of C-peptide (mean+ SE) ng/ml for MODY patients was 0.564 +0.06 ranging 0.001-2.22. Before the clinical laboratory testing and the further gene test, concentration of C-peptide is important for the promptly differential diagnosis of MODY from familial type 2 diabetes (23). All patients had decreased levels of C-peptide, which indicated a reduction in pancreatic islet function.

Immunological test: anti- glutamic acid decarboxylase antibody tests

It is considered one of the most important serological indicators for type 1 diabetes mellitus is an anti-glutamic acid decarboxylase autoantibody (Anti-GAD) (26), here we can distinguish between type 1 diabetes and MODY.

The value of Anti GAD Ab (mean+ SE) IU/ml for MODY patients was 2.49 + 0.15 ranging 0.022-5.01 considering that all MODY patients were negative for this test agreeing with other previous studies (17,27).

In the previous study McDonald *et al*., (2011) confirmed that Anti GAD Ab were found in 5 / 508 (less than 1%) of patients with MODY and 80 / 98 (82%) of patients were with T1DM. The prevalence of Anti GAD Ab in patients with MODY is the same as in control subjects (< 1%). Thus, genetic testing should only be done if other clinical characteristics strongly imply MODY rather than T1DM. The discovery of islet autoantibodies renders the diagnosis of MODY exceedingly unlikely. This is in favor of performing routine islet autoantibody testing before moving on to costlier molecular genetic testing (28).

Depending on Fu, *et al*., (2019), triglyceride levels can distinguish MODY2 from MODY3 while fasting C-peptide and anti-GAD-Ab levels can distinguish between MODY3 and T1D, this is indicative of all the individuals examined They have been diagnosed infected with type MODY3, and multiple biochemical signs can be used to create markers that help differentiate between different MODY subtypes. Our research could be used to identify young diabetic patients in Iraq who are at a high risk of developing MODY2 or MODY3 (25).

Conclusion

All patients were screened and passed all the diagnostic criteria for MODY3, but we recommend that they undergo genetic testing to ensure that they are the type of MODY and to determine the appropriate treatment for them.

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