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DIABETIC Medicine

LETTER

Impact of overweight on glucose homeostasis in MODY2 and MODY3

Maturity-onset diabetes of the young (MODY) is the most common type of monogenic diabetes, as it accounts for approximately 1%–2% of all cases of diabetes.[1] MODY2 is caused by mutations in the gene encoding glucokinase (*GCK*), whereas MODY3 is due to mutations in the hepatocyte nuclear factor 1A (*HNF1A*) gene. Obesity has become prevalent and the aim of this study was to investigate to what extent BMI and age affected fasting serum glucose and glycosylated haemoglobin (HbA_{1c}) in female and male MODY2 and MODY3 probands.

We searched the Norwegian MODY Registry at the Department of Paediatrics and Adolescents, Haukeland University Hospital, for probands diagnosed with either MODY2 or MODY3.[2,3] The study was approved by the regional ethics committee and carried out according with the Declaration of Helsinki. Informed consent was obtained from the patients or their parents. Since we included both children, adolescents and adults, a BMI z-score (BMIz) was calculated using the Norwegian BMI references.[4] Bivariate correlation between BMIz or age and fasting serum glucose or HbA_{1c} was determined by Spearman's rank analysis, whereas the rate of deterioration of fasting glucose or HbA_{1c} was determined using least linear square method. A significance level of 5% was used. Statistics were performed using IBM SPSS Statistics 24.

We recruited 98 MODY2 and 103 MODY3 probands. Three pregnant MODY2 subjects were excluded from further analysis. In MODY2 patients, fasting glucose ranged from 5.6 to 8.6 mmol/L compared to 3.8 to 20 mmol/L in MODY3. Moreover, HbA_{1c} levels also showed less variation among MODY2 probands (range: 39–63 mmol/mol; 5.7%–7.9%) as compared to MODY3 participants (range: 31–103 mmol/mol; 5%–11.6%).

Then we investigated correlation between BMIz and fasting serum glucose or HbA_{1c} in female or male probands diagnosed with MODY2 or MODY3, respectively. In MODY2, we did not find any correlation between BMIz and fasting glucose in neither females ($r = 0.066$, $p = 0.714$) nor males ($r = 0.133$, $p = 0.509$). Lack of correlation between BMIz and HbA_{1c} was also found in females ($r = 0.236$, $p = 0.128$) and males ($r = -0.091$, $p = 0.632$). Among MODY3 patients, we found no significant correlation between BMIz and fasting glucose in females ($r = -0.027$, $p = 0.877$) or males ($r = -0.074$, $p = 0.786$), and this also applied to HbA_{1c} (females $r = 0.173$, $p = 0.255$; males $r = -0.057$, $p = 0.793$).

Next we investigated how age affected fasting serum glucose and HbA_{1c} levels in our patients. Fasting glucose correlated with age in all MODY2 patients ($r = 0.410$, $p < 0.001$) (Fig. 1a) (deterioration rate: 0.02 mmol/L per year), and this persisted when we divided the group according to gender (women $r = 0.330$, $p = 0.046$; men $r = 0.476$, $p = 0.007$). In terms of HbA_{1c}, we found significant correlation with age in all MODY2 patients ($r = 0.314$, $p = 0.004$) (Fig. 1b), but we could find this in women only (women $r = 0.369$, $p = 0.009$; men $r = 0.263$, $p = 0.146$). In MODY3 individuals, we found no statistical significant correlation between age and fasting glucose (Fig. 1c) or age and HbA_{1c} (Fig. 1d).

Here we report the effect of BMIz and age on fasting glucose and HbA_{1c} in female and male MODY2 and MODY3 patients recruited to our national MODY registry. However, we were not able to find any correlation between BMIz and fasting glucose or HbA_{1c} in any of the two MODY types. This is in accordance with Stride et al. that found no correlation between FPG and 2-hour plasma glucose with BMI centile.[5] Moreover, both Stride et al.[5] and Pearson et al.[6] found a correlation between age and fasting serum glucose in both MODY2 and MODY3. Moreover, levels of fasting serum glucose have also been reported to increase with age in a large group of *GCK* and *HNF1A* mutation carriers.[5] Our MODY2 patients also showed similar deterioration of fasting glucose with increasing age, but we did not find such correlation in MODY3. The main explanation for the latter is probably due to a lower number of patients with available data on fasting glucose, which was very apparent in participants above age 50 years ($n = 4$). Moreover, Steele et al.[7] found a correlation between age and HbA_{1c} in MODY2. This was also found in

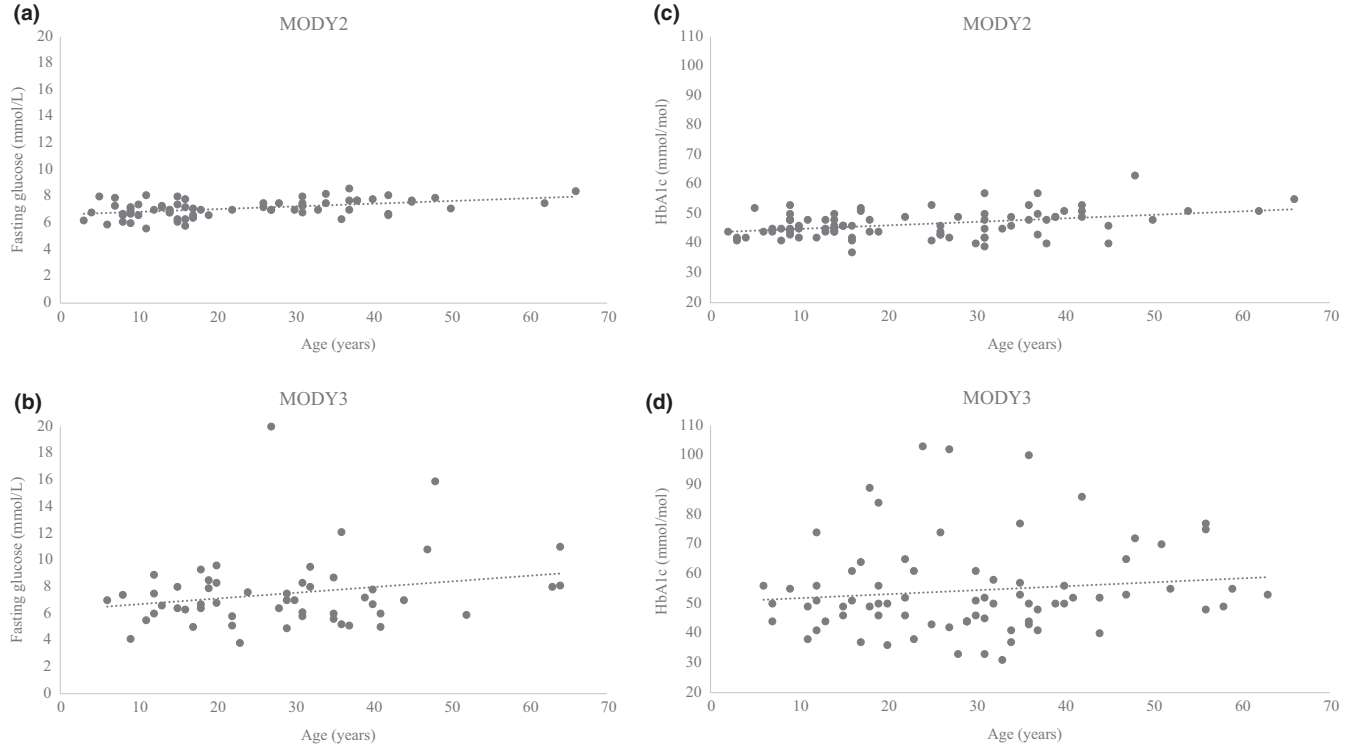

FIGURE 1 Correlation between fasting glucose and HbA_{1c} in MODY2 and MODY3 patients. Fasting serum glucose against age of MODY2 (a) or MODY3 patients (b) in addition to HbA_{1c} against age of MODY2 (c) or MODY3 (d) patients. Lines represent correlation

our group, but when subdivided according to gender, a correlation was found in women only. However, the number of men with MODY2 in our study is low, especially those above 18 years of age. A possible explanation for the deterioration of glucose homeostasis with age reported in both MODY2 and MODY3 participants, may be a progressive loss in beta-cell function adding to the physiological impairment in insulin release and glucose tolerance, as seen in the general population with age.[8,9] However, Steele et al. showed that in MODY2 participants, the deterioration with age was not significantly larger compared to the healthy control group.[7]

In conclusion, we found a deteriorating fasting glucose with age in MODY2 but not in MODY3, whereas BMIz had no such impact on either fasting glucose or HbA_{1c}. For HbA_{1c}, we found a correlation with age in female but not male MODY2 patients.

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CONFLICT OF INTEREST

We have no conflict of interest to disclose.

AUTHORS' CONTRIBUTION

IBR, TLK and JVS designed the study. IBR, TLK, JM, PBJ, PRN and JVS contributed to the data interpretation and writing the revised manuscript. JM collected data from the registry, and they were systematized by IBR, TLK and JVS. JVS is the guarantor of this work and takes responsibility for the integrity of the data and the accuracy of the data analyses.

Ingunn B. Romuld[1]
Tine-Lise Kalleklev[1]
Janne Molnes[1,2]
Petur Benedikt Juliusson[1,3,4]
Pål R. Njølstad[1,3]
Jørn V. Sagen[1,5]

[1]*Department of Clinical Science, University of Bergen, Bergen, Norway*
[2]*Department of Medical Genetics, Haukeland University Hospital, Bergen, Norway*
[3]*Department of Paediatrics and Adolescents, Haukeland University Hospital, Bergen, Norway*
[4]*Department of Health Registry Research and Development, Norwegian Institute of Public Health, Bergen, Norway*
[5]*Department of Medical Biochemistry and Pharmacology, Haukeland University Hospital, Bergen, Norway*

Correspondence
Jørn V. Sagen, Department of Clinical Science, University of Bergen, Bergen, Norway.
Email: jorn.sagen@uib.no

Ingunn B. Romuld and Tine-Lise Kalleklev are Contributed equally.

ORCID

Jorn V. Sagen https://orcid.org/0000-0002-8795-0732

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