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Efficacy of metformin versus sulfonylurea derivative in HNF4A-MODY

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Summary

This study compares the effects of metformin, sulfonylurea derivative (SU) and no treatment in HNF4A-MODY on glycemic control. In two patients with HNF4A-MODY, we changed the existing metformin treatment to SU derivative. The effect on the glycemic control was registered with a Freestyle Libre Flash glucose monitoring device. Each treatment period had a duration of 2 consecutive weeks, and in between, an intermediate period without medication. Data from the first 2 days after changing medications were excluded. We calculated time in range (TIR), and differences in the mean glucose level were tested with a one-way ANOVA test. The 24-h average glucose levels were significantly lower with either metformin (7.7 mmol/L; $P < 0.001$ and 6.3 mmol/L; $P < 0.001$) or gliclazide (7.6 mmol/L; $P < 0.001$ and 5.8 mmol/L; $P < 0.001$) compared to no treatment (9.4 and 8.9 mmol/L). The TIR with metformin or gliclazide was higher than without treatment (patient 1: 87 and 83 vs 61% and patient 2: 83 and 93 vs 67%). Treatment with either metformin or gliclazide effectively decreases blood glucose, rendering both drugs appropriate for treating HNF4A-MODY.

Learning points

- HNF4A-MODY has a mild phenotype.
- Blood glucose was responsive to long-term metformin treatment in HNF4A-MODY.
- Metformin and gliclazide seem appropriate treatments for HNF4A-MODY.

Background

Maturity-onset diabetes of the young (MODY) type HNF4A is a rare monogenic type of diabetes mellitus characterized by reduced insulin secretion. HNF4A-MODY is caused by a mutation in the gene for the protein *HNF4A* and is autosomal dominant. This mutation causes a defect in glucose-stimulated insulin secretion. There is no insulin resistance, but there is a dysfunction of the beta cells in the pancreas (1). Sulphonylurea (SU) derivatives are usually recommended as the treatment of choice for MODY because of their stimulating effect on insulin release, but supporting evidence is scarce (2, 3). The results of this study show that a SU derivative and metformin both have a good glucose-lowering effect in this type of diabetes.

Case presentation

Two patients, a 60-year-old male (patient 1) and his 61-year-old sister (patient 2), were simultaneously diagnosed with HNF4A-MODY (mutation: c.787G>A p.(Glu263Lys) in exon 7 of the *HNF4A* gene), triggered by the recent diagnosis in the 31-year-old son of patient 2. She had one other child who did not have the mutation, and her brother had no children. Both patients had previously been treated for type 2 diabetes, both with metformin monotherapy for several years. Average HbA1c in the last year was 56 mmol/mol (daily metformin dose of 1000 mg) and 49 mmol/mol (daily metformin dose of 3000 mg) for patients 1 and 2, respectively. C-peptide was 0.43 nmol/L for patient 2 and had never been determined for patient 1. In both patients, the glucose-lowering medication had

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been stable in the last 3 months before the study, and both had a stable body weight in the last 2 years, i.e. the BMI was 25 km/m² (patient 1: 85 kg) and 22 km/m² (patient 2: 61 kg). Neither of the patients had any long-term diabetes complications or significant comorbidities.

Investigation

We intended to change the metformin treatment to a SU derivative. To monitor the effects on glycemic control of this change, we instructed the patients to maintain their habits on nutrition and physical activity and applied blinded measurements with a Freestyle Libre Flash glucose monitor device (4). Three measurement periods were performed; first, while they still used metformin, secondly, without medication and thirdly, after initiation of gliclazide (ODD: 80 mg). All measurement periods had a duration of 2 consecutive weeks. Data were analyzed after excluding the first 2 days after changing medication. Differences in the mean glucose level between the treatment periods were tested with one-way ANOVA test. Time in range was calculated using the following definitions: normoglycemia (glucose: 3.5–10 mmol/L), hypoglycemia (glucose: < 3.5 mmol/L), moderately increased (glucose: 10–15 mmol/L) and severe hyperglycemia (glucose: > 15mmol/L). Patients gave written consent to use the data for publication purposes.

Treatment

During the first measurement period, the patients used metformin. Patient 1 had a daily metformin dose of 1000 mg and patient 2 had a daily metformin dose of 3000 mg. In the third measurement period, both patients received gliclazide ODD 80 mg.

Outcome and follow-up

Without medication, both patients had a considerable TIR (61 and 67%), and severe hyperglycemia did not occur, consistent with a mild phenotype of this mutation (Fig. 1). In both patients, the 24-h average glucose levels were significantly lower with either metformin (7.7 mmol/L; $P < 0.001$ and 6.3 mmol/L; $P < 0.001$) or gliclazide (7.6 mmol/L; $P < 0.001$ and 5.8 mmol/L; $P < 0.001$) compared to no treatment (9.4 and 8.9 mmol/L). For patient 1, this resulted in a TIR with metformin of 87% and with gliclazide of 83% and for patient 2, this was 83and 93%, respectively. In patient 2, the 24-h average glucose level with gliclazide was significantly lower than with metformin ($P < 0.001$). Also, in this patient, the time below target range was lower during treatment with SU derivative compared to metformin (4.52 vs 8.3%; $P < 0.001$).

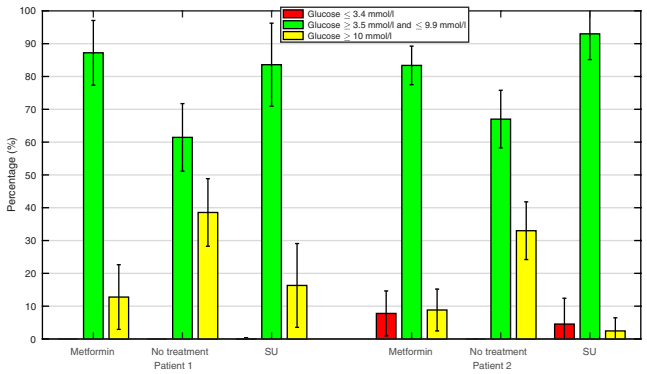

Figure 1
Overview of the time range of glucose levels during three different treatment periods for both patients. Glucose levels during the treatment with metformin and gliclazide were significantly lower ($P < 0.001$) than no treatment for both patients. In patient 2, the glucose level with gliclazide was significantly lower than with metformin ($P < 0.001$).

Discussion

HNF4A-MODY caused by the mutation c.787G>A p.(Glu263Lys) in exon of the *HNF4A* gene has a mild phenotype with time ranging from 61 to 67% without therapy, consistent with considerable residual insulin secretory capacity in the seventh decade of life in the two patients studied here. Treatment with either metformin or gliclazide effectively decreased blood glucose, resulting in clinically relevant improvement of time in range. Blood glucose was clearly responsive to long-term metformin treatment, as demonstrated by the dechallenge, whereas the study design does not allow for drawing conclusion on long-term efficacy of gliclazide. Somewhat unexpectedly, the time below target range was lower in patient 2 with SU treatment than with metformin although the 24-h average glucose concentration was higher with metformin. As metformin would not lead to hypoglycemia, this finding should be interpreted with care and one should consider the possibility that this finding is erroneous and caused by lower accuracy of the sensor in the low glucose range.

According to the current guideline (5), treatment with SU derivative is recommended for HNF4A-MODY. Our small study confirms that indeed gliclazide effectively lowers blood glucose and, moreover, it demonstrates that metformin too is effective in this respect. For more robust information, for example, on the comparison of efficacy between the drugs

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and whether efficacy might decrease over the long-term, larger prospective studies would be necessary.

Declaration of interest
The authors declare no conflicts of interest.

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Patient consent
Written informed consent for publication of their clinical details and/or clinical images was not obtained from the patient because the identity of the patients cannot be determined from the data.

Author contribution statement
NO and GDL designed the study. NO included the patients. NO and NDB analyzed the data. NO and GDL wrote the manuscript. NDB contributed to the discussion and reviewed the manuscript. GDL is the guarantor.

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