# Novel Treatment Options in Patients with Maturity-Onset Diabetes of the Young

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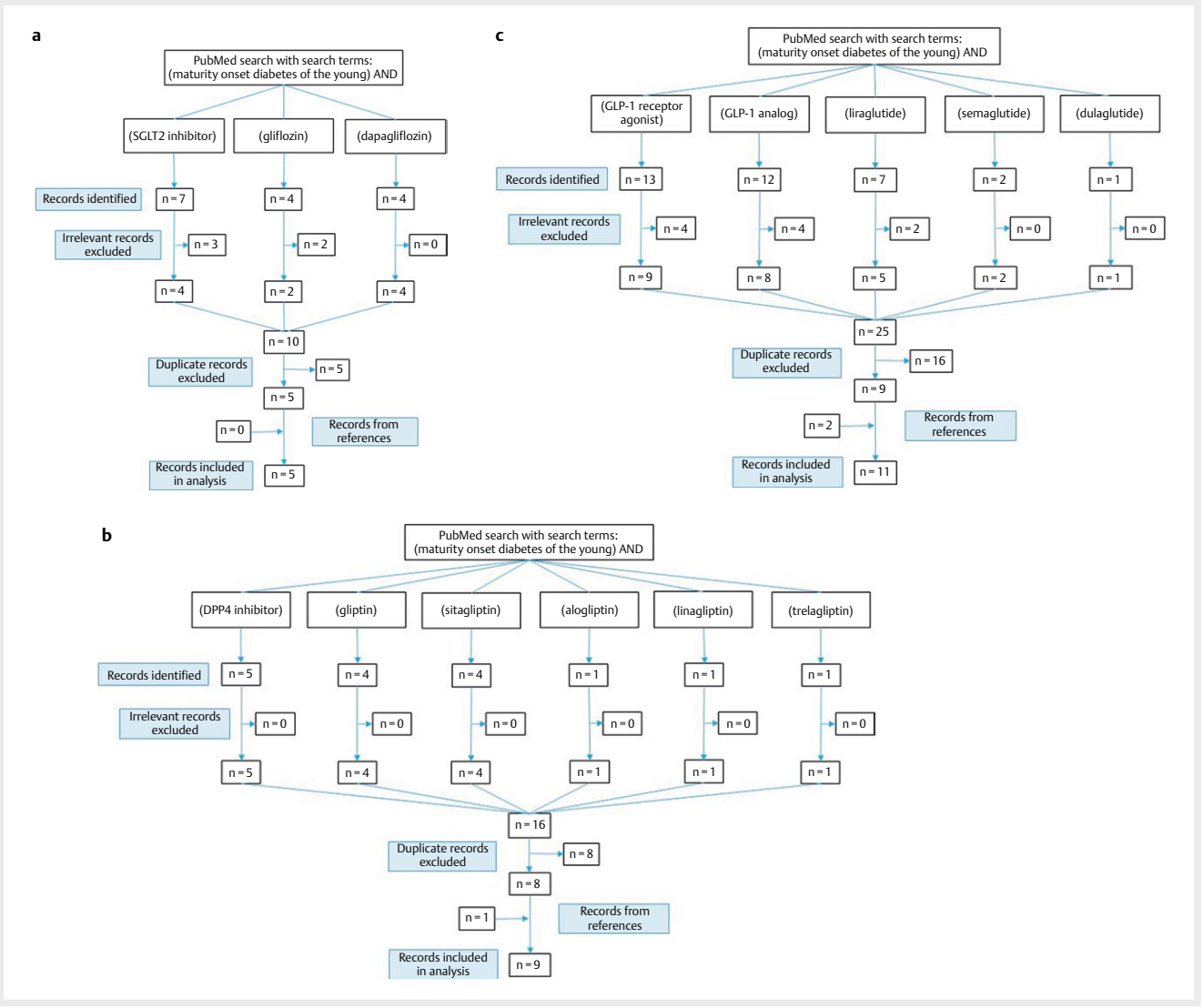
**ABSTRACT**

Maturity-onset diabetes of the young (MODY) is the most common monogenetic form of diabetes with an autosomal dominant inheritance pattern. MODY is caused by mutations in genes important for the development and function of pancreatic beta cells, resulting in impaired insulin secretion capacity. To date, 14 different types have been described. While glucokinase (GCK)-MODY (formerly MODY-2) generally requires no drug therapy, other forms of MODY, such as hepatocyte nuclear factor-1-alpha (HNF1A)-MODY (formerly MODY-3) and HNF4A (formerly MODY-1), usually respond very well to sulfonylurea therapy. However, these MODY forms are characterised by a progressive course, meaning that insulin therapy is often required as the disease progresses. Both sulfonylurea therapy and insulin therapy are associated with an increased risk of hypoglycaemia and frequent weight gain. Newer blood glucose-lowering therapies, such as SGLT2 inhibitors (SGLT2i), DPP-4 inhibitors (DPP4i) and GLP-1 receptor agonists (GLP-1RA), have a much lower risk of hypoglycaemia and usually have a favourable effect on body weight. This review aims to provide an overview of the treatment of MODY patients with SGLT2i, DPP4i and GLP-1RA on the basis of previously published clinical studies, case series and case reports.



## Introduction

More than 500 million people worldwide are affected by diabetes [1]. In more than 90 % of cases, patients suffer from type 2 diabetes and in around 5 % of cases from type 1 diabetes. Other rarer types of diabetes include monogenetic forms of diabetes, such as maturity-onset diabetes of the young (MODY). MODY shows an autosomal dominant inheritance pattern and is caused by mutations in genes important for the development or function of pancreatic β-cells. Consequently, insulin secretion capacity is impaired. There are currently 14 known MODY types, with hepatocyte nuclear factor-4 alpha (HNF4A)-MODY (formerly MODY-1), glucokinase (GCK)-MODY (formerly MODY-2), HNF1A-MODY (formerly MODY-3), and HNF1B-MODY (formerly MODY-5) being the most common variants [2]. Clinical findings that indicate the presence of MODY comprise young age at disease manifestation, positive family history affecting more than three generations, diabetes without typical signs of type 1 or type 2 diabetes (negative pancreatic autoantibodies, no obesity, lack of other metabolic characteristics). MODY diagnosis is confirmed by genetic testing. Precise diagnosis of the underlying MODY form is important because MODY variants differ considerably in their clinical course and treatment. GCK-MODY is characterized by mild hyperglycaemia that is usually well controlled by diet only. Diabetes-associated complications occur very rarely in this MODY variant [3]. In contrast, hyperglycaemia in HNF1A-MODY




▶ **Fig. 1** PubMed search strategy for maturity-onset diabetes of the young and **(a)** SGLT2 inhibitors, **(b)** DPP-4 inhibitors or **(c)** GLP-1 receptor agonists. Using the search terms "(maturity-onset diabetes of the young) AND (bexagliflozin, canagliflozin, empagliflozin, ertugliflozin, henagliflozin, ipragliflozin, luseogliflozin, remogliflozin, sotagliflozin, tofogliflozin, anagliptin, evogliptin, gemigliptin, gosogliptin, omarigliptin, retagliptin, saxagliptin, tenegliptin, vildagliptin, exenatide, lixisenatide, or tirzepatide)" revealed no results. SGLT2: sodium-dependent glucose co-transporter 2; DPP-4: dipeptidyl peptidase 4; GLP-1: glucagon-like peptide 1.

and HNF4A-MODY is severe and progressive, resulting frequently in micro- and macrovascular complications [4, 5]. Initially, patients with these MODY forms respond well to sulfonylurea treatment. However, due to the progressive disease course, insulin therapy is required in about 40 % of patients. Both insulin and sulfonylurea treatments carry an increased risk of hypoglycaemia and weight gain. By contrast, newer blood glucose-lowering agents, such as sodium-dependent glucose co-transporter 2 inhibitors (SGLT2i), dipeptidyl peptidase 4 inhibitors (DPP4i), and glucagon-like peptide 1 receptor agonists (GLP-1RA), significantly reduce hypoglycaemia risk and exhibit neutral to beneficial effects on weight [6]. However, knowledge on their use in MODY patients is still limited. Therefore, the present review aims to provide an overview of the treatment with SGLT2i, DPP4i and GLP-1RA in MODY patients.

## Materials and Methods

PubMed database was searched until June 11, 2024. The search terms "(maturity onset diabetes of the young) AND (SGLT2 inhibitor, gliflozin, bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, henagliflozin, ipragliflozin, luseogliflozin, remogliflozin, sotagliflozin, tofogliflozin, DPP-4 inhibitor, gliptin, alogliptin, anagliptin, evogliptin, gemigliptin, gosogliptin, linagliptin, omarigliptin, retagliptin, saxagliptin, sitagliptin, tenegliptin, trelagliptin, vildagliptin, GLP-1 receptor agonist, GLP-1 analogue,

▶ **Table 1** SGLT2 inhibitor treatment in patients with MODY.

| Reference | MODY type | Patient characteristics | Previous treatment | SGLT2 inhibitor | Outcome |
|---|---|---|---|---|---|
| Hohendorff et al. [7] | GCK (MODY-2) HNF1A (MODY-3) | 14 HNF1A-MODY, 19 GCK-MODY, and 12 type 2 diabetes pts: 7 f, 12 f, 4 f; age [mean ± SD] 34.1 ± 11.0, 40.3 ± 10.8, 61.8 ± 5.6 yrs, time from diabetes diagnosis 11.4 ± 6.8, 8.7 ± 7.1, 5.8 ± 4.2 yrs, BMI 24.4 ± 4.9, 23.4 ± 2.8, 31.3 ± 5.3 kg/m$^2$, HbA1c 6.0 ± 0.7 [42.0 ± 5.3], 6.4 ± 0.4 [46.0 ± 2.0], 6.9 ± 0.9 % [52.0 ± 7.5 mmol/mol] | Current therapy, including hypoglycaemic agents, was not changed. | Single morning dose of 10 mg dapagliflozin | Higher glycosuria in HNF1A- (20.51 ± 12.08) and GCK-MODY (23.19 ± 8.10) than in T2DM (9.84 ± 6.68 mmol/mmol) (both $p < 0.05$), but not between both MODY forms ($p = 0.7231$) |
| Phan et al. [8] | HNF1A (MODY-3) | 25 yrs, f, age at diagnosis 14 yrs, BMI 23.50 kg/m$^2$, HbA1c 8.8 % | Insulin degludec 2 U/d | 10 mg dapagliflozin od, ketogenic diet (carbohydrate intake < 10 g/d) | Shortly after starting dapagliflozin discontinuation of insulin and metformin due to episodes of hypoglycaemia, 50 d after starting dapagliflozin, admission to hospital due to euglycaemic diabetic ketosis, discontinuation of dapagliflozin and initiation of 850 mg metformin bid |
| Sriravindrarajah et al. [9] | HNF1A (MODY-3) | 30 yrs, f, age at diagnosis 18 yrs, HbA1c 8.3 % [67 mmol/mol] | Gliclazide 120 mg bid, metformin 2000 mg bid | Empagliflozin 10 mg od in addition to regular treatment | Glycaemic control immediately improved with blood glucose levels ranging from 4.2 to 7.5 mmol/l, reduction of dly doses of metformin to 1000 mg bid and of gliclazide to 60 mg bid |
| Brodosi et al. [10] | NEUROD1 (MODY-6) | 48 yrs, m, age at diagnosis 25 yrs, BMI 21.7 kg/m$^2$, HbA1c 8.6 % | Insulin glargine 18–22 U, insulin lispro 5 U before breakfast, 6 U before lunch and 6 U before dinner, metformin 500 mg tid | Dapagliflozin/ metformin 5/1000 g bid | Discontinuation of insulin lispro, dapagliflozin/metformin was stopped 10 d later due to severe abdominal pain, further treatment with 500 mg metformin tid and insulin glargine |
| Ovsyannikova et al. [11] | ABCC8 (MODY-12) | 28 yrs, m, age at diagnosis 27 yrs, BMI 25 kg/m$^2$, HbA1c 5,9 % | Gliclazide 60 mg/d | Dapagliflozin 10 mg/d | On combined treatment, glycaemic excursions diminished, and no hypoglycaemic episodes were detected by CGM. At 3-mth follow-up, HbA1c 6.0 %, no episode of hypoglycaemia, weight reduction by 4 kg |

ABCC8, gene coding for ATP-binding cassette transporter sub-family C member 8; bid, twice daily; BMI, body mass index; CGM, continuous glucose monitoring; d, day; dly, daily; f, female; GCK, glucokinase; HNF1A, gene coding for hepatocyte nuclear factor 1α; m, male; MODY, maturity-onset diabetes of the young; mth, month; NEUROD1, gene coding for neurogenic differentiation 1; od, once daily; pts, patients; SD, standard deviation; SGLT2, sodium-dependent glucose co-transporter 2; tid, three times a day; U, unit; yrs, years.

dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, or tirzepatide)“ were used. Only original articles, case reports or case series written in English or German were considered. Patients with positive pancreatic autoantibodies were excluded. Subsequently, references of included articles were manually screened for relevant articles (▶ **Fig. 1**). This research revealed five articles regarding SGLT2i [7–11], nine articles regarding DPP4i [12–20], and eleven articles regarding GLP-1RA [21–30].

# Results

## Sodium-dependent glucose co-transporter 2 inhibitor use in patients with maturity-onset diabetes of the young

The metabolic effects of dapagliflozin were tested in 14 patients with HNF1A-MODY and 19 patients with GCK-MODY in comparison to 12 patients with type 2 diabetes (T2D), all with excellent

▶ **Table 2** DPP-4 inhibitor treatment in patients with MODY.

| Reference | MODY type | Patient characteristics | Previous treatment | DPP-4 inhibitor | Outcome |
|---|---|---|---|---|---|
| Tonouchi et al. [12] | HNF4A (MODY-1) | 13 yrs, f, first diagnosis, BMI 17.5 kg/m², HbA1c 10.7 % | Basal-bolus insulin therapy using insulin aspart and glargine | 12.5 mg alogliptin dly which was increased to 25 mg dly | Discontinuation of insulin lispro and, subsequently, glargine, temporarily treatment with glimepiride 2 mg dly for 3 mths, adequate glycaemic control (HbA1c 6.3–7.0 %) using alogliptin monotherapy for at least 18 mths |
| Koliaki et al. [13] | GCK (MODY-2) | 52 yrs, f, age at diagnosis 46 yrs, BMI 21.1 kg/m², HbA1c 6.0 % | Sitagliptin 100 mg dly, repaglinide 2.0 mg dly | Sitagliptin 100 mg od | After MODY diagnosis, discontinuation of repaglinide, patient insisted on continuing treatment with sitagliptin. Continued stable glycaemic control |
| Lumb and Gallen [14] | HNF1A (MODY-3) | 57 yrs, f, age at diagnosis 18 yrs, HbA1c 9.6 % | Gliclazide 160 mg bid, rosiglitazone 8 mg od | Sitagliptin 100 mg dly | Home blood capillary glucose readings improved significantly, with a HbA1c of 7.9 % 6 wks after introduction of therapy |
| Katra et al. [15] | HNF1A (MODY-3) | Pt 1: 39 yrs, f, age at diagnosis 32 yrs, BMI 26.3 kg/m², HbA1c 7.2 %<br>Pt 2: 62 yrs, f, age at diagnosis 21 yrs, BMI 22.2 kg/m², HbA1c 8.8 % | Pt 1: 160 mg gliclazide dly, 2000 mg metformin dly<br>Pt 2: gliclazide 240 mg/d, insulin aspart 6 U/d at mealtime | Pt 1: sitagliptin 100 mg/d<br>Pt 2: vildagliptin 50 mg bid | At reexamination after 3 mths, HbA1c levels of both pts had fallen to 6.3 %, with significant improvement in glycaemic control on CGM. |
| Tan et al. [16] | HNF1A (MODY-3) | Pt 1: 39 yrs, f, age at diagnosis 12 yrs, BMI 25.4 kg/m², HbA1c 7.8 % [61.7 mmol/l]<br>Pt 2: sister of pt 1, 37 yrs, age at diagnosis 12 yrs, BMI 30.8 kg/m², HbA1c 9.1 % [76 mmol/l] | Pt 1: gliclazide 280 mg/d, insulin glargine 14 U om<br>Pt 2: gliclazide 400 mg/d, insulin glargine 10 U om | Pt 1: sitagliptin 50 mg dly<br>Pt 2: sitagliptin 50 mg dly, which was increased to 100 mg dly | Pt 1: short-lived (about 3 mths) improvement in glucose control (close to 1 % decrease in HbA1c)<br>Pt 2: no improvement of glycaemic control |
| Christensen et al. [17] | HNF1A (MODY-3) | 19 pts, age [mean ± SD] 43 ± 14 yrs, diabetes duration [median, interquartile range] 20 [8–34] yrs, BMI 24.8 ± 2.8 kg/m², HbA1c 7.4 ± 0.2 % [57.1 ± 7.3 mmol/mol] | Glimepiride (n = 18), diet (n = 1) | Randomized, double-blinded, crossover trial: glimepiride + linagliptin 5 mg (16 wks), washout (4 wks), glimepiride + placebo (16 wks) (or vice versa) | Linagliptin improved glycaemic variability (p = 0.0401) and control (p = 0.0048) without increasing risk of hypoglycaemia. |
| Mangrum et al. [18] | PDX1 (MODY-4) | 26 yrs, m, age at diagnosis 26 yrs, BMI 23 kg/m², estimated HbA1c 10–11 % | Pioglitazone, glyburide 5 mg dly | Sitagliptin 100 mg dly | Discontinuation of glyburide, reduction of HbA1c to 8.5 % 3 mths after initiation of sitagliptin |
| Yoshiji et al. [19] | PDX1 (MODY-4) | 18 yrs, m, age at diagnosis 16 yrs, BMI 15.0 kg/m², HbA1c 6.8 % (51 mmol/mol) | Gliclazide 20–40 mg dly | Sitagliptin 25–50 mg dly | HbA1c 6.0–6.5 % (42–48 mmol/mol) on monotherapy with sitagliptin |
| Zhou et al. [20] | ABCC8 (MODY-12) | 13 yrs, m, first diagnosis, BMI 23 kg/m², HbA1c 13.1 % | Insulin | Trelagliptin | Blood glucose level returned to normal and drug treatment was discontinued after 3 wks. Reinitiation of trelagliptin after 3 yrs due to fluctuations in blood glucose levels, resulting in stable blood glucose levels. |

ABCC8, gene coding for ATP-binding cassette transporter sub-family C member 8; bid, twice daily; BMI, body mass index; CGM, continuous glucose monitoring; d, day; dly, daily; DPP-4, dipeptidyl peptidase 4; f, female; GCK, glucokinase; GLP-1, glucagon-like peptide-1; HNF1A, gene coding for hepatocyte nuclear factor 1α; HNF4A, gene coding for hepatocyte nuclear factor 4α; m, male; MODY, maturity-onset diabetes of the young; mth, month; mthly, monthly; od, once daily; om, every morning; PDX, gene coding for pancreatic and duodenal homeobox 1; Pt, patient; pts, patients; SD, standard deviation; U, unit; wk, week; wkly, weekly; yrs, years.

▶ **Table 3** GLP-1 receptor agonist treatment in patients with MODY.

| Reference | MODY type | Patient characteristics | Previous treatment | GLP-1RA | Outcome |
|---|---|---|---|---|---|
| Broome et al. [21] | HNF4A (MODY-1) | Pt 1: 22 yrs, m, age at diagnosis 20 yrs, HbA1c 8.7 %<br>Pt 2: father of pt 1, diagnosis in his early 20 s, HbA1c 9.6 % | Pt 1: glimepiride 4 mg bid<br>Pt 2: long- and short-acting insulin therapy | Pt 1: semaglutide 0.25 mg wkly, which was titrated to 1.0 mg wkly over 8 wks<br>Pt 2: liraglutide 0.6 mg od which was titrated to 1.8 mg over 3 wks | Pt 1: improvement of HbA1c to 6.2 % after 6 mths, fewer hypoglycaemic events<br>Pt 2: improvement of HbA1c to 5.9 % and fewer hypoglycaemic events, discontinuation of short-acting insulin |
| Ahluwalia et al. [22] | HNF1A (MODY-3) | 53 yrs, m, age at diagnosis 39 yrs, BMI 38.0 kg/m$^2$, HbA1c 7.7 % | metformin 1500 mg and gliclazide 240 mg dly | Exenatide 5 µg bid which was later increased to 10 µg bid | Within 4 mths weight loss of 9 kg and reduction in HbA1c to 6.3 %, discontinuation of gliclazide |
| Østoft et al. [23] | HNF1A (MODY-3) | 16 pts, 8 f, mean age 39 [range 23–67] yrs., BMI [mean ± SEM] 24.9 ± 0.5 kg/m$^2$, HbA1c 6.4 ± 0.2 % (47 ± 3 mmol/mol) | 15 pts were treated with oral blood glucose-lowering drugs at inclusion (glimepiride [n = 11], repaglinide [n = 2], tolbutamide [n = 1], gliclazide [n = 1]) and 1 pt with diet only. | After a 1-wk washout of blood glucose-lowering drugs, 6 wks of treatment with liraglutide and placebo (tablets) as well as sufonylurea (glimepiride) and placebo (injections), in randomized order, in a double-blind, cross-over trial; liraglutide was initiated at 0.6 mg od and escalated by 0.6 mg every wk to the target dose of 1.8 mg od | Fasting and postprandial plasma glucose decreased during the treatment periods, with no difference between treatments, 18 episodes of hypoglycaemia with glimepiride vs 1 episode with liraglutide |
| Docena et al. [24] | HNF1A (MODY-3) | Pt 1: 21 yrs, f, age at diagnosis 10 yrs, BMI 29.6 kg/m$^2$, persistently poor glycaemic control<br>Pt 2: grandmother of pt 1, age at diagnosis 9 yrs, BMI 32.5 kg/m$^2$, HbA1c 7.7 %<br>Pt 3: mother of pt 1, first diagnosed with gestational diabetes at 16 yrs, BMI 30.8 kg/m$^2$, HbA1c 9.0 % | Pt 1: metformin, pioglitazone, once-daily insulin detemir<br>Pt 2: continuous subcutaneous insulin infusion (CSII)<br>Pt 3: continuous subcutaneous insulin infusion (CSII) | Combined basal insulin and liraglutide 1.8 mg od regimen | Pt 1: HbA1c of 7.4 to 7.7 % after discontinuation of metformin, pioglitazone and basal insulin, decrease of HbA1c to 6.4 % after addition of glimepiride 1 mg dly, BMI decreased to 26.7 kg/m$^2$<br>Pt 2: HbA1c of 6.1 % with od basal insulin glargine (24 U), liraglutide (1.8 mg), and glimepride (1 mg), BMI decreased to 29.3 kg/m$^2$<br>Pt 3: HbA1c of 6.8 % with od basal insulin glargine (35 U) and liraglutide (1.8 mg), BMI decreased to 26.0 kg/m$^2$ |
| Urakami et al. [25] | HNF1A (MODY-3) | 12 yrs, f, first diagnosis, BMI 15.4 kg/m$^2$, HbA1c 8.9 % | Basal-bolus therapy using insulin aspart and glargine | Liraglutide 0.3 mg od which was gradually increased to 0.9 mg od | Insulin aspart and, subsequently, glargine were discontinued, glimepiride was given temporarily. Optimal glycaemic control (HbA1c 6.8–7.5 %), no relevant weight change, no adverse events |
| Fantasia and Steenkamp [26] | HNF1A (MODY-3) | 23 yrs, f, age at diagnosis 14 yrs, BMI 25 kg/m$^2$, HbA1c 7.9 % | Glimepiride 4 mg dly | Dulaglutide 0.75 mg wkly which was later increased to 1.5 mg wkly | 4 mths after GLP-1RA initiation improvement of HbA1c to 7.1 % and 6 kg weight loss, discontinuation of glimepiride |
| Tan et al. [16] | HNF1A (MODY-3) | 37 yrs, f age at diagnosis 12 yrs, BMI 30.8 kg/m$^2$, HbA1c 9.1 % [76 mmol/l] | Gliclazide 160 mg for lunch, soluble insulin 8 U bid, insulatard 16 U om, 8 U on, empagliflozin 25 mg every other day | Dulaglutide 1.5 mg wkly, subsequently liraglutide 1.2 mg/d | Dulaglutide with very limited glycaemic and weight benefit, liraglutide with suboptimal glycaemic control (HbA1c above 8 %) |
| Terakawa et al. [27] | HNF1B (MODY-5) | 17 yrs, f, first diagnosis, BMI 17.3 kg/m$^2$, HbA1c 9.5 % | Insulin lispro (maximum 9 U/d) and glargine (13 U/d) | Liraglutide 0.9 mg od | Insulin glargine was reduced to 7 U/d and lispro discontinued, HbA1c below 7 % for at least the next 12 mths, liraglutide was reduced to 0.6 mg/d due to nausea |

▲ **Table 3** Continued.

| Reference | MODY type | Patient characteristics | Previous treatment | GLP-1RA | Outcome |
|---|---|---|---|---|---|
| Almutair and Almulhem [28] | HNF1B (MODY-5) | 18 yrs, f, age at diagnosis 12 yrs, HbA1c 7.0 % | Long-acting and ultra-short-acting insulin (0.4 U/kg/d) | Semaglutide 0.25 mg which was increased after 4 wks to 0.5 mg wkly | Reduction of HbA1c to 5.6 % and BMI to 20.1 kg/m$^2$ and improvement of CGM metrics within 4 mths, discontinuation of insulin therapy, cessation of semaglutide treatment due to nausea, vomiting and reduced appetite after 4 mths |
| Li et al. [29] | ABCC8 (MODY-12) | Pt 1: 12 yrs, m, first diagnosis, BMI 26.9 kg/m$^2$, HbA1c 12.1 %<br>Pt 2: 25 yrs, m, first diagnosis, BMI 27.8 kg/m$^2$, HbA1c 11.2 % | Pt 1: insulin aspart<br>Pt 2: no previous treatment | Pt 1: liraglutide 1.2 mg/d<br>Pt 2: liraglutide 1.2 mg/d | Pt 1: after 2 mths blood glucose levels within the normal range (HbA1c < 6.5 %), discontinuation of insulin therapy<br>Pt 2: liraglutide was very effective |
| Nakhleh et al. [30] | ABCC8 (MODY-12) | 49 yrs, f, age at diagnosis 8 yrs, BMI 31 kg/m$^2$, HbA1c 9.1 % | Insulin basal-bolus (degludec and glulisine) treatment, average dly dose of 45 U | Once wkly semaglutide, gradually uptitrated (mthly) to 1 mg per wk | 2 wks after increasing the dose of semaglutide to 1 mg complete discontinuation of insulin, HbA1c decreased to 6.8 % and 8 kg weight reduction |

ABCC8, gene coding for ATP-binding cassette transporter sub-family C member 8; bid, twice daily; BMI, body mass index; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; d, day; dly, daily; f, female; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; HNF1A, gene coding for hepatocyte nuclear factor 1α; HNF1B, gene coding for hepatocyte nuclear factor 1β; HNF4A, gene coding for hepatocyte nuclear factor 4α; m, male; MODY, maturity-onset diabetes of the young; mth, month; mthly, monthly; od, once daily; om, every morning; on, every evening; Pt, patient; pts, patients; SEM, standard error of the mean; U, unit; wk, week; wkly, weekly; wks, weeks; yrs, years.

glycaemic control. A single dose of 10 mg dapagliflozin resulted in higher glycosuria in GCK-MODY and HNF1A-MODY patients than in T2D patients, whereas there was no difference between the two MODY forms [7]. Outside of clinical trials, SGLT2i use was reported in four patients, two of whom were male and two were female (▶ **Table 1**) [8–11]. Two patients were diagnosed with HNF1A-MODY, one patient with NEUROD1-MODY (formerly MODY-6), and one patient with ATP-binding cassette transporter subfamily C member 8-MODY (ABCC8-MODY, formerly MODY-12). The mean age at presentation was 33 years, whereas the mean age at diagnosis was 21 years. The mean body mass index (BMI) was 23.4 kg/m$^2$ and the mean HbA1c 7.8 % [61.8 mmol/mol]. At presentation, two patients received gliclazide, alone (n = 1) or in combination with metformin (n = 1), whereas two patients were treated with long-acting insulin analogues, alone (n = 1) or in combination with a short-acting insulin analogue and metformin (n = 1). Dapagliflozin was given in three patients and empagliflozin in one patient. In all patients, glycaemic control improved, allowing discontinuation of insulin treatment in two patients and reduction of oral glucose-lowering agents in one patient. However, dapagliflozin intake had to be stopped in two patients because of euglycaemic diabetic ketosis and severe abdominal pain, respectively. In both cases, symptoms resolved spontaneously after discontinuation of SGLT2i treatment.

## Dipeptidyl peptidase 4 inhibitor use in patients with maturity-onset diabetes of the young

In a randomized, double-blinded, crossover trial, 19 patients with HNF1A-MODY received glimepiride and linagliptin 5 mg for 16 weeks and after a washout of 4 weeks glimepiride and placebo for 16 weeks or vice versa. Preexisting treatment comprised glimepiride in 18 patients and diet only in one patient, with moderate glycaemic control. Compared to glimepiride, linagliptin improved glycaemic variability as well as control, without increasing the risk of hypoglycaemia [17]. Outside of clinical trials, DPP4i use was reported in ten patients, three of whom were male and seven were female (▶ **Table 2**) [12–16, 18–20]. One patient was diagnosed with HNF4A-MODY, one patient with GCK-MODY, five patients with HNF1A-MODY, two patients with PDX1-MODY (formerly MODY-4), and one patient with ABCC8-MODY. The mean age at presentation was 36 years, whereas the mean age at diagnosis was 21 years. The mean BMI was 22.7 kg/m$^2$ and the mean HbA1c 9.0 % [74.9 mmol/mol]. At presentation, six patients received gliclazide, alone (n = 1) or in combination insulin glargine (n = 2), insulin aspart (n = 1), rosiglitazone (n = 1), or metformin (n = 1), whereas one patient was treated with basal-bolus insulin therapy (n = 1), one patient with non-specified insulin therapy (n = 1), and one patient with pioglitazone and glyburide (n = 1). One patient was already being treated with the DPP4i sitagliptin and repaglinide at the time of MODY diagnosis (n = 1). Sitagliptin was added to therapy in seven further patients, whereas three patients received alogliptin, vildagliptin or trelagliptin. In the majority of patients, after initiation of DPP4i treatment, glycaemic control was improved (n = 8) or remained stable (n = 1). Subsequently, insulin (n = 2) and sulfonylurea (n = 1) treatment was stopped in three patients. However, in two patients, the introduction of sitagliptin led to no or just a short-lived improvement of glycaemic control.

### Glucagon-like peptide 1 receptor agonist use in patients with maturity-onset diabetes of the young

In a randomized, double-blinded, crossover trial, 16 HNF1A-MODY patients with excellent glycaemic control received, after a one-week washout of blood glucose-lowering drugs, linaglutide and placebo (tablets) as well as sulfonylurea (glimepiride) and placebo (injections). Fasting and postprandial plasma glucose decreased during the treatment periods. However, the number of hypoglycaemic events was significantly reduced in patients treated with linaglutide compared to sulfonylurea [23]. Outside clinical trials, GLP-1 RA use was reported in fourteen patients, five of whom were male and nine were female (▶ **Table 3**) [16, 21, 22, 24–30]. Two patients were diagnosed with HNF4A-MODY, seven patients with HNF1A-MODY, two patients with HNF1B-MODY, and three patients with ABCC8-MODY. The mean age at presentation was 26 years, whereas the mean age at diagnosis was 16 years. BMI was reported in eleven patients and the mean BMI was 27.7 kg/m$^2$. HbA1c was given in 13 patients and mean HbA1c was 9.0 % [75 mmol/mol]. Treatment at presentation included basal-bolus insulin therapy, alone (n = 4) or in combination with gliclazide and empagliflozin (n = 1), continuous subcutaneous insulin infusion (CSII, n = 2), insulin aspart (n = 1), glimepiride (n = 2), and metformin with gliclazide (n = 1) or with pioglitazone and insulin detemir (n = 1). One patient had no treatment at presentation. Initiated GLP-1 RA treatment comprised liraglutide (n = 9), semaglutide (n = 3), dulaglutide (n = 2), and exenatide (n = 1). Improvement of glycaemic control was documented in all patients, except for one who received first dulaglutide and, subsequently, semaglutide. Neither dulaglutide nor semaglutide significantly decreased blood glucose levels. Further beneficial effects were weight reduction (n = 7) and fewer hypoglycaemic episodes (n = 2). GLP-1 RA treatment allowed complete discontinuation (n = 5) or reduction (n = 1) of insulin as well as sulfonylurea discontinuation (n = 2). Gastrointestinal side effects, such as nausea, vomiting and reduced appetite, necessitated dose reduction (n = 1) or discontinuation (n = 1) of GLP-1 RA treatment in two patients.

## Conclusions

Though the clinical experience with SGLT2i, DPP-4i, and GLP-1RA is still limited in MODY patients, with mainly case descriptions and case series and only a few clinical trials, they appear to be efficient and safe blood glucose-lowering agents in patients with different MODY forms. Their introduction allowed, in many cases, dose reduction or complete discontinuation of insulin or sulfonylurea treatment. Consequently, the number of hypoglycaemic episodes decreased despite improved glycaemic control. Contraindications and side effects must, of course, also be taken into account for MODY patients.

### Conflict of Interest

The author declares that he has no conflict of interest.

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