Il MODY, terapie non convenzionali: SGLT2i e GLP1RAs

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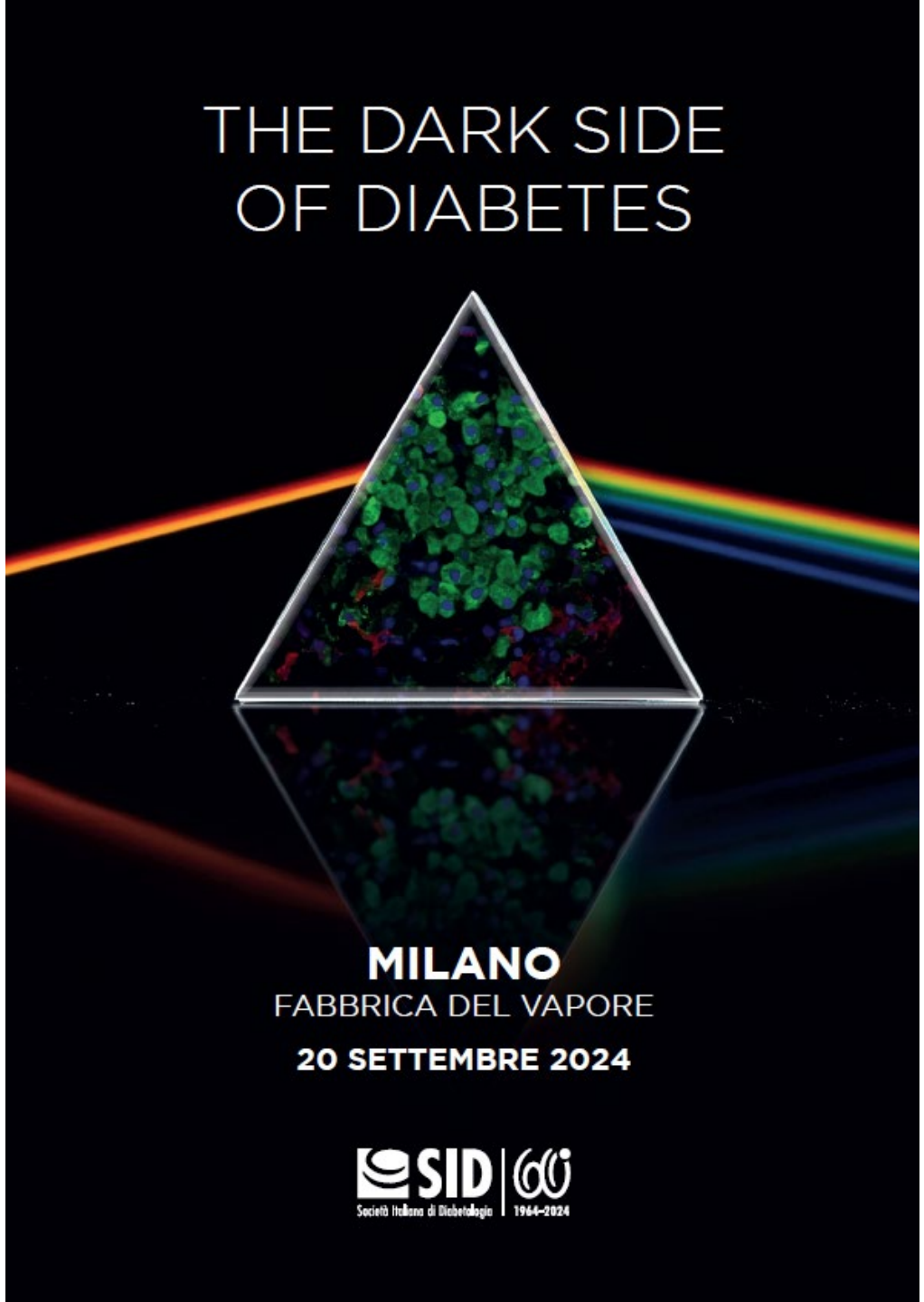


Il Dr. Andrea Laurenzi dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Abbott, Eli Lilly, Medtronic, Menarini, Novo Nordisk, Roche, Sanofi, Ypsomed

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

Introduction

- Monogenic diabetes or maturity onset diabetes of the young (MODY) is a clinically heterogeneous disorder characterized by diabetes diagnosed at a young age (<25 years) with autosomal dominant transmission and lack of autoantibodies[1]
- MODY is the most common form of monogenic diabetes, its prevalence is 2-5% of diabetes[2]
- Several different genetic abnormalities have been identified, each leading to a different type of disease. The original MODY nomenclature ("MODY1," "MODY2," "MODY3," etc) has been superseded by the term "monogenic diabetes" with the name of the gene associated with the trait

[1] Tattersall RB, Fajans SS *Diabetes*. 1975;24(1):44

[2] Gat-Yablonski G et al *Pediatr Endocrinol Rev*. 2006;3 Suppl 3:514.

Classification

Type	Genetic defect	Frequency	Beta cell defect	Clinical features	Risk of micro-vascular disease	Optimal treatment
1	Hepatocyte nuclear factor-4-alpha	<10%	Reduced insulin secretory response to glucose	Normal renal threshold for glucose.	Yes	Sulfonylureas
2	Glucokinase	15 to 31%	Defective glucokinase molecule (glucose sensor), increased plasma levels of glucose are necessary to elicit normal levels of insulin secretion	Mild, stable, fasting hyperglycemia, often diagnosed during routine screening. Not progressive.	Generally no	Diet
3	Hepatocyte nuclear factor-1-alpha	52 to 65%	Abnormal insulin secretion, low renal threshold for glucose	Low renal threshold for glucose, +glycosuria.	Yes	Sulfonylureas
4	Insulin promoter factor 1	Rare	Reduced binding to the insulin gene promoter, reduced activation of insulin gene in response to hyperglycemia	Rare, pancreatic agenesis in homozygotes, less severe mutations result in mild diabetes.	Yes	Insulin
5	Hepatocyte nuclear factor-1-beta	Rare		Pancreatic atrophy, kidney dysplasia, kidney cysts, impaired kidney function, hypomagnesemia.	Yes	Insulin or Sulfonylureas
6	Neurogenic differentiation factor-1	Rare	Pancreatic development		Yes	Insulin

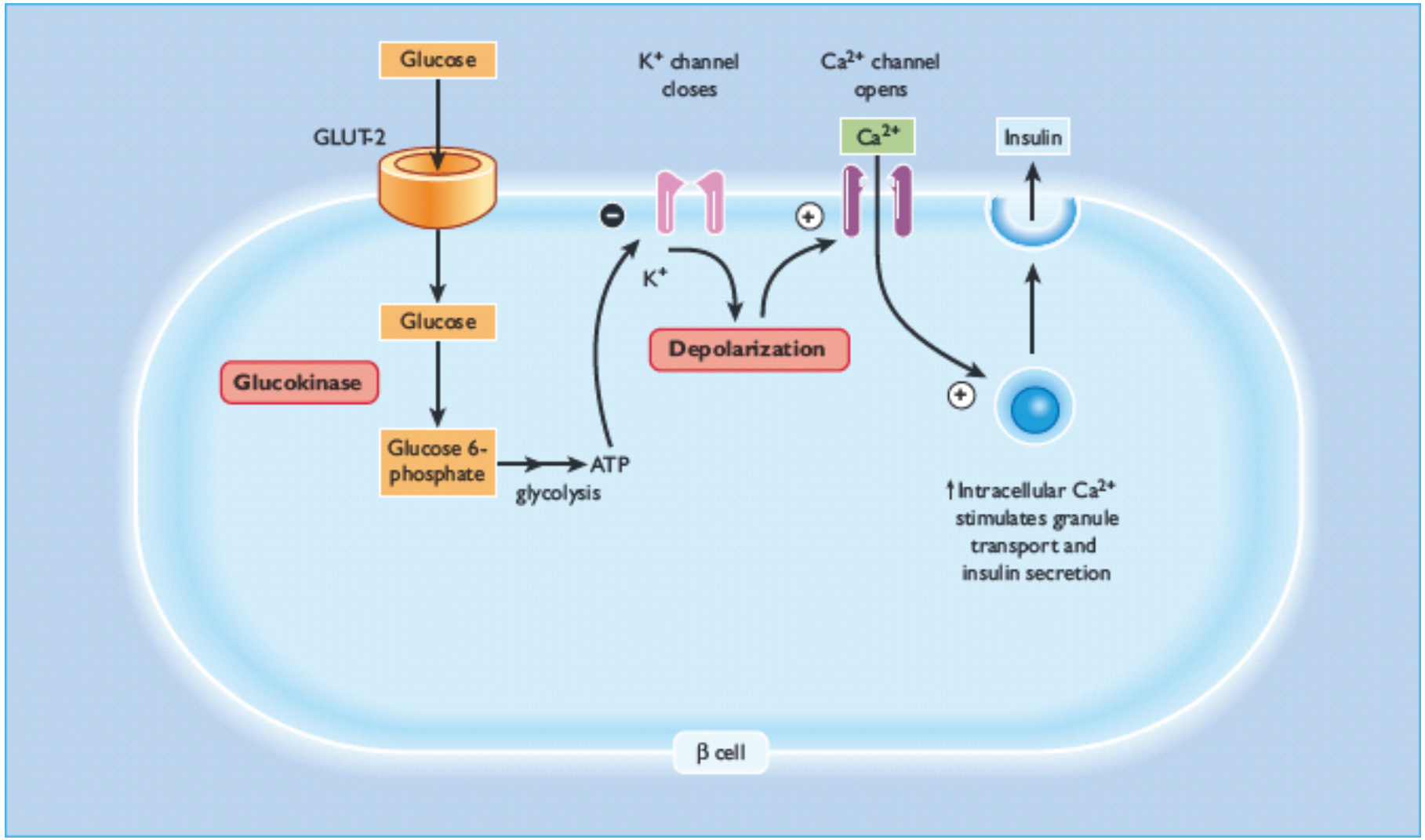
Next Generation Sequencing: Monogenic Diabetes (MD)

- **11** MODY genes (*ABCC8, APPL1, GCK*, *HNF1A*, *HNF4A*, *INS*, *KCNJ11*, *NEUROD1*, *PDX1*, *RFX6* and *ZFP57)*
- **19** genes where diabetes occurs as part of a syndrome (*CEL*, *CISD2*, *DCAF17, DNAJC3, DUT, DYRK1B, GATA4*, *GATA6*, *HNF1B*, *MANF*, *MAFA*, *PAX6*, *PCBD1*, *PIK3R1, PPP1R15B, SLC29A3, TRMT10A*, *WFS1, ZBTB20)*
- **9** genes where pathogenic variants cause diabetes through severe insulin resistance with or without partial lipodystrophy (*AKT2*, *CIDEC*, *INSR, LIPE*, *LMNA*, *PLIN1, POLD1, PPARG* and *ZMPSTE24*)
- **mtDNA** variants m.3243A>G, m.8344A>G, m.12258C>A, m.12271T>C, m.14684C>T and m.14709T>C causing mitochondrial diabetes.
- **35 genes** for neonatal diabetes under the age of 6 months (*ABCC8*, *AGPAT2*, *BSCL2*, *CISD2*, *CNOT1*, *COQ2, COQ9, EIF2B1, EIF2S3, EIF2AK3*, *FOXP3*, *GATA4*, *GATA6*, *GCK*, *GLIS3*, *HNF1B*, *IER3IP1*, *IL2RA*, *INS*, *INSR*, *KCNJ11, LPL, LRBA*, *MNX1*, *NEUROD1*, *NEUROG3*, *NKX2-2*, *PDX1*, *PTF1A* (coding and distal enhancer regions), *RFX6*, *SLC19A2*, *SLC2A2*, *STAT3*, *WFS1* and *ZFP57*)
- **15** genes is sequenced for patients with neonatal diabetes and autoimmune disease (*AIRE*, *CTLA4, DOCK8, FOXP3*, *IL2RA*, *ITCH*, *JAK1, LRBA*, *NFKB1*, *SIRT1*, *SLC29A3*, *STAT1*, *STAT3*, *STAT5B* and *TNFAIP3*)

HNF4α-MODY

- *HNF4A* **(Hepatocyte nuclear factor-4-alpha)** gene on chromosome 20 causes MODY1
- *HNF4A* is expressed 1) in pancreatic beta cells and 2) in the liver. The precise mechanism by which a defect in *HNF4A* causes hyperglycemia is not clear, but it has been associated with 1) **reduced insulin secretory response to glucose**, suggesting a primary genetic defect in insulin secretion and 2) *HNF4A* plays a central role in the hepatic synthesis of lipoprotein and coagulation proteins, these functions are largely maintained in *HNF4A* diabetes, suggesting that this disorder is primarily one of impaired pancreatic beta cell function
- The secretory defect is progressive, and patients typically present with hyperglycemia in adolescence or early childhood.
- Patients respond to sulfonylureas but may require insulin as the secretory defect progresses.
- These patients are at risk for the hyperglycemia-associated microvascular and macrovascular complications of diabetes.

GCK-MODY


Glucose
GLUT-2
Glucose
Glucokinase
Glucose 6-phosphate
ATP
glycolysis
K+ channel closes
K+
Depolarization
Ca2+ channel opens
Ca2+
Insulin
↑Intracellular Ca2+ stimulates granule transport and insulin secretion
β cell

GCK-MODY

- *GCK* **(Glucokinase)** gene on chromosome 7 causes MODY2
- Defects in the expression of *GCK*, which phosphorylates glucose to glucose-6-phosphate and acts as a glucose sensor, result in a **higher threshold for glucose-stimulated insulin secretion. The resulting hyperglycemia is often stable and mild** (eg, fasting glucose 97 to 150 mg/dL and HbA1c 5.8% to 7.6%)
- It is not associated with the vascular complications common in other types of diabetes and patients with *GCK* gene mutation can often be managed with diet alone
- In pregnant individuals with GCK-MODY, management depends on the fetal genotype (thus, when available, noninvasive prenatal genotyping should be performed):
  1) If the fetus inherits the maternal *GCK* variant (which will prevent fetal hyperinsulinemia and excessive growth despite maternal hyperglycemia), maternal hyperglycemia does not require treatment.
  2) If the fetus does not inherit the pathogenic variant, maternal insulin therapy is indicated to prevent excessive fetal growth.

HNF1α-MODY

- *HNF1A* **(Hepatocyte nuclear factor-1-alpha)** on chromosome 12 causes MODY3
- *HNF1A* mutations are more common among Europeans
- *HNF1A* is a weak transactivator of the insulin gene in beta cells and its variants can lead to **abnormal insulin secretion**. Some genetic variants also result in a **low renal threshold for glucose**. Thus, testing for glycosuria two hours after a glucose load could be used to screen children of variant carriers and guide the need for further evaluation.
- Patients with *HNF1A* diabetes have a similar clinical phenotype as patients with *HNF4A* diabetes, showing increased insulin sensitivity and marked sensitivity to the hypoglycemic effects of sulfonylureas
- Thus, *HNF1A* mutated diabetes can be successfully treated with sulfonylurea monotherapy
- These patients are at risk for micro- and macrovascular complications of diabetes. In addition, patients with diabetes caused by a mutation in *HNF1A* appear to have an increased risk of cardiovascular mortality compared with unaffected family members

HNF1β-MODY

- *HNF1B* **(Hepatocyte nuclear factor-1-beta)** pathogenic variants produce a syndrome formerly called MODY5.
- Affected patients can develop a variety of manifestations in addition to early-onset diabetes. These include **pancreatic atrophy** (on CT scan), abnormal renal development (renal dysplasia that can be detected on ultrasonography in the fetus, single or multiple renal cysts, glomerulocystic disease, oligomeganephronia [a form of renal hypoplasia]), **slowly progressive renal insufficiency**, hypomagnesemia, elevated serum aminotransferases, and genital abnormalities (epididymal cysts, atresia of vas deferens, and bicornuate uterus). In addition, some patients have a phenotype consistent with autosomal dominant tubulointerstitial kidney disease.
- In most cases MODY 5 patients need insulin therapy

Sulonylureas are the first option in many MD

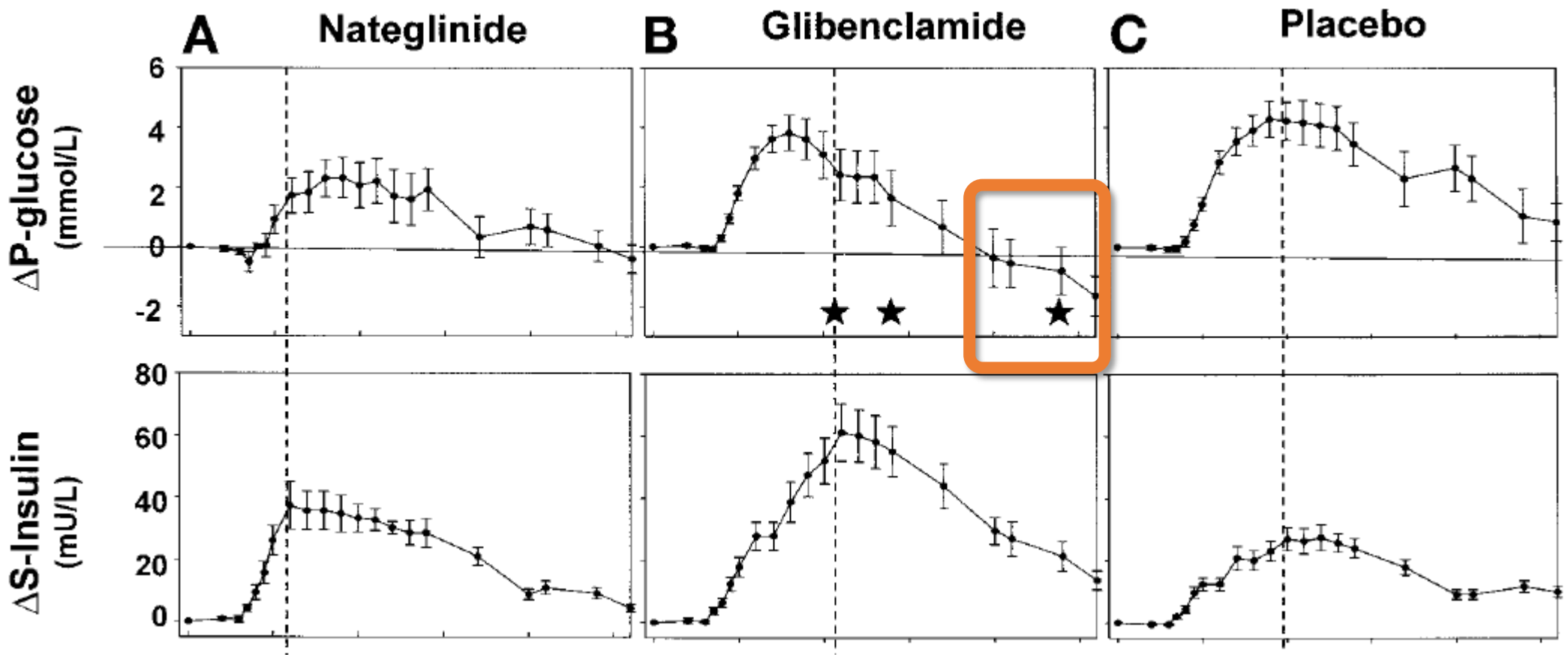
Table 1—Clinical implications of some common and important causes of monogenic diabetes

Gene	Inheritance/phenotypes	Disease mechanism/special features	Importance of genetic diagnosis
GCK	AD: *GCK*-MODY (common) AR: *GCK*-NDM (very rare)	Reduced function of glucokinase enzyme raises set point for insulin secretion that is otherwise normal; high population prevalence of causal variants (~1 in 1,000)	***No treatment needed*** for most patients (except possibly during pregnancy)
HNF1A	AD: *HNF1A*-MODY (common)	LOF of β-cell transcription factor; glucosuria is common; risk for benign hepatic adenomas (rarely can become large and/or complicated)	Excellent glycemic control usually possible with low-dose oral sulfonylureas
HNF4A	AD: *HNF4A*-MODY (uncommon)	LOF of β-cell transcription factor; carriers may have history of large birth weights and/or hyperinsulinemic hypoglycemia	Often responsive to low-dose oral sulfonylureas
HNF1B	AD: *HNF1B*-MODY (uncommon)	LOF of pancreatic/renal transcription factor; renal cysts/genitourinary malformations (may be more penetrant than diabetes); hypomagnesemia; exocrine pancreatic insufficiency, altered liver function tests, hyperuricemia, developmental delay (as part of chromosome 17q deletion syndrome)	Optimal treatment for diabetes not well established; genetic diagnosis will inform monitoring and management of other features
ABCC8	AD/AR: *ABCC8*-NDM (common) *ABCC8*-MODY (rare)	Activating missense mutations in β-cell K_{ATP} channel SUR1 subunit impair glucose-stimulated insulin secretion; NDM may have a spectrum of neurodevelopmental dysfunction	Usually responds to high-dose oral sulfonylureas; genetic diagnosis facilitates monitoring/intervention for neurodevelopmental problems
KCNJ11	AD: *KCNJ11*-NDM (common) *KCNJ11*-MODY (rare)	Activating missense mutations in β-cell K_{ATP} channel Kir6.2 subunit impair glucose-stimulated insulin secretion; NDM often have a spectrum of neurodevelopmental dysfunction	Usually responds to high-dose oral sulfonylureas; genetic diagnosis facilitates monitoring/intervention for neurodevelopmental problems
6q24 (imprinted locus)	Most common cause of transient NDM	Overexpression of maternally imprinted 6q24 genes causes impairment of β-cell development and function; after remission of NDM within first year of life, diabetes will often recur in adolescence or adulthood	Diabetes recurring later in life is often responsive to noninsulin therapies
INS	AD/AR: *INS*-NDM (common) AD: *INS*-MODY (rare)	Missense mutations cause insulin protein misfolding and progressive β-cell death (other mechanisms occur more rarely)	Early intensive insulin treatment; future treatments may feasibly target molecular mechanism(s)

AD, autosomal dominant; AR, autosomal recessive; Kir6.2, inward rectifier potassium channel 6.2; SUR, sulfonylurea receptor.

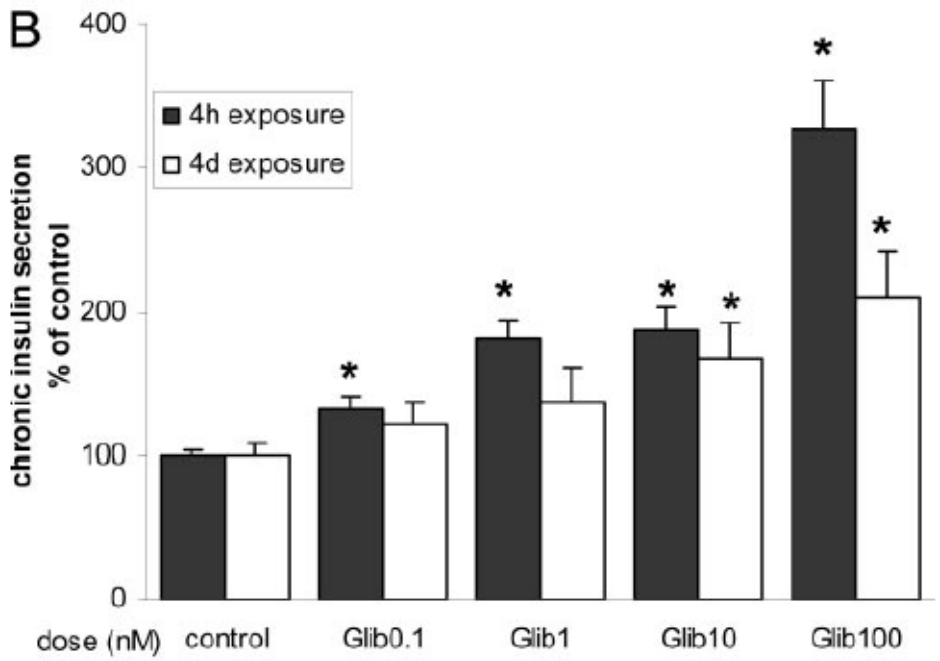
Riddle MC et al. *Diabetes Care* 2020;43:3117–3128

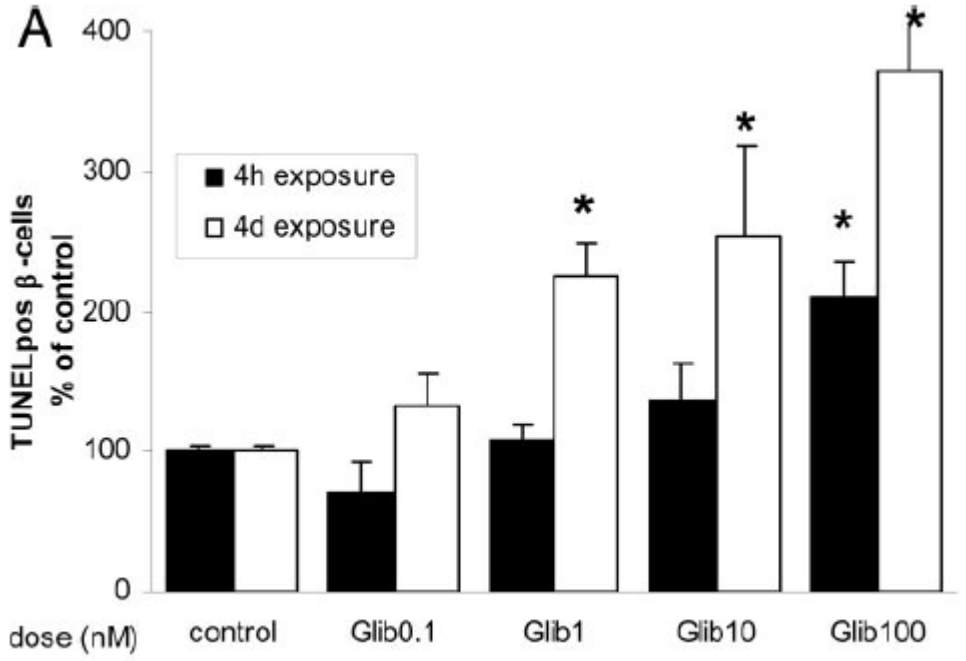
Glibenclamide rises hypoglicaemic risk in MD



Tuomi et al *Diabetes Care* Vol 29, n. 2, Feb 2006

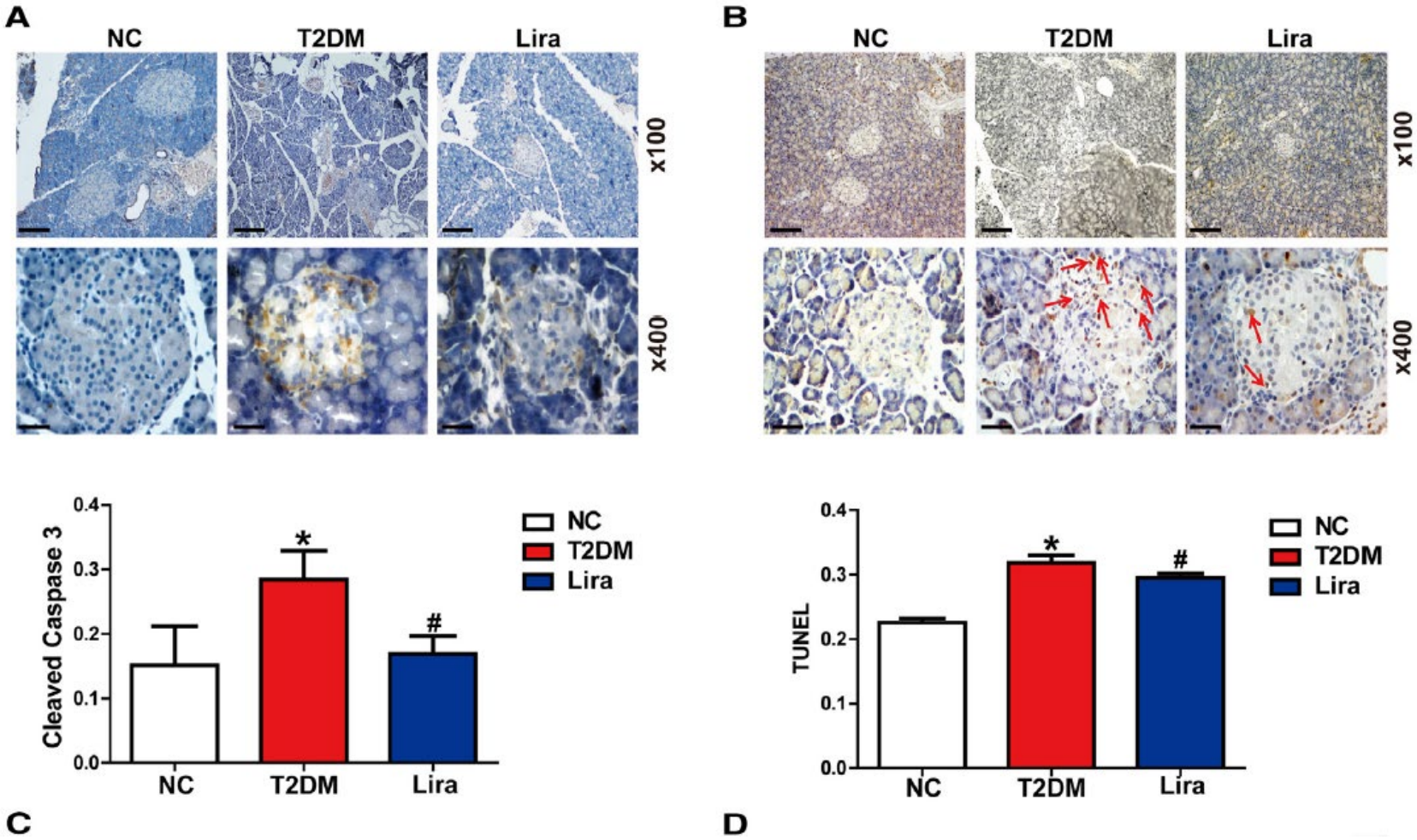
Glibenclamide rises β-cells apoptosis





Maedler et al. *J Clin Endocrinol Metab*, January 2005, 90(1):501–506

Liraglutide reduces β-cells apoptosis



M. Ding et al. *Journal of Diabetes and Its Complications* 33 (2019) 267–277

GLP1-RA and SGLT2-i as adjuncitve therapy

Table 1 Description of subtypes of maturity-onset diabetes of the young and treatment options

MODY type Gene (gene location)	Protein function	Age at onset	Phenotype	Treatment
MODY1 *HNF4A* (20q13.12)	Transcription factor	< 18 years	Progressive decrease in insulin secretion; worsening of glucose control; high risk of microvascular complications; low levels of apolipoproteins and triglycerides; neonatal macrosomia; neonatal hypoglycemic events	Diet, sulphonylureas, insulin
MODY2 *GCK* (7p13)	Enzyme	Pre-adolescence	Mild hyperglycemia Excellent prognosis	Treatment is unnecessary (usually)
MODY3 *HNF1A* (12q24.31)	Transcription factor	< 25 years	Decreased insulin secretion; high risk of microvascular complications; low glucos renal threshold	Sulphonylureas (additional meglitinides, GLP-1 RA, SGLT-2 inhibitors), insulin
MODY4 *PDX1* (13q12.2)	Transcription factor	Postpuberty	Mild form of diabetes	OHAs, insulin
MODY5 *HNF1B* (17q12)	Transcription factor	< 25 years	Decreased insulin secretion with progressive worsening of glucose control; genitourinary malformations (renal cysts, azoospermia, uterus anomaly, etc)	OHAs (sulfonylurea or repaglinide), insulin
MODY6 *NEUROD1* (2q31.3)	Transcription factor	Variable	Different degrees of hyperglycemia	OHAs, insulin
MODY7 *KLF11* (2p25.1)	Transcription factor	Variable	Decreased sensitivity to insulin; mild hyperglycemia	Insulin
MODY8 *CEL* (9q34.13)	Lipolytic enzyme	> 25 years	Impaired endocrine and exocrine pancreatic function	OHAs, insulin
MODY9 *PAX4* (7q32.1)	Transcription factor	Postpuberty	Progressive hyperglycemia; occurrences of ketoacidosis	Diet, OHAs, insulin
MODY10 *INS* (11p15.5)	Hormone	> 10 years	Hyperglycemia; diabetes	Diet, insulin

Table 1 continued

MODY typeGene (gene location)	Protein function	Age at onset	Phenotype	Treatment
MODY11 *BLK* (8p23.1)	Enzyme	Variable	Hyperglycemia; diabetes	Diet, OHAs, insulin
MODY12 *ABCC8* (11p15.1)	Subunit of ATP-sensitive channels	Variable	Diabetes	Sulphonylureas
MODY13 *KCNJ11* (11p15.1)	Subunit of ATP-sensitive channels	After second decade of life	Diabetes	Sulphonylureas
MODY14 *APPL1* (3p14.3)	Adaptor protein	10–50 years	Hyperglycemia; diabetes	Diet, OHAs, insulin

GLP-1 RA Glucagon-like peptide-1 receptor agonist, *MODY* maturity-onset diabetes of the young, *OHAs* oral hypoglycemic agents, *SGLT-2* sodium-glucose co-transporter-2

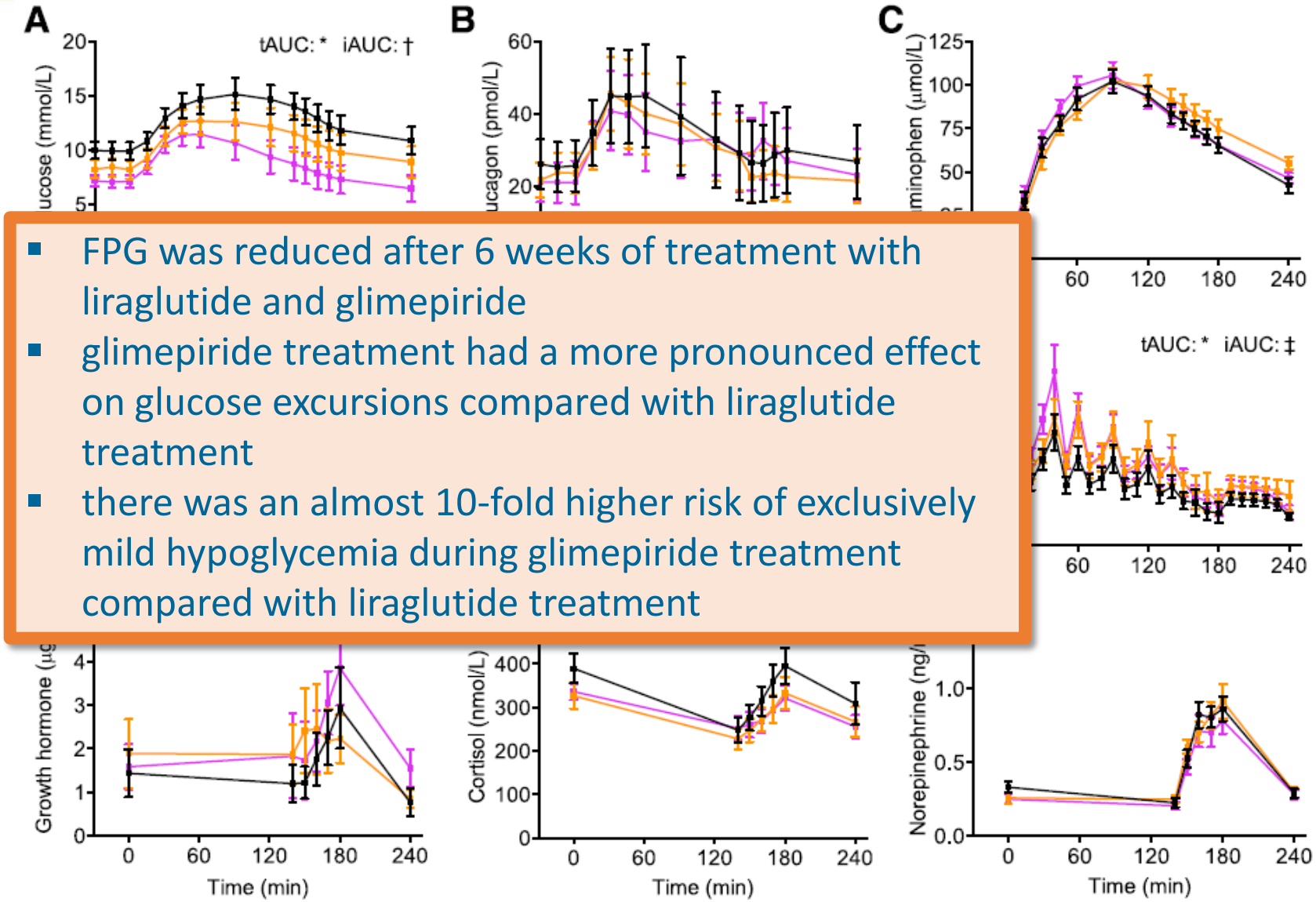
Sulphonylureas (additional meglitinides, GLP-1 RA, SGLT-2 inhibitors), insulin

Delvecchio M *Diabetes Ther* (2020) 11:1667–1685

Liraglutide vs glimepiride in HNF1α-MODY

- 16 patients, RCT, double blind, crossover

baseline (black line)
liraglutide (orange line)
glimepiride (purple line)



- FPG was reduced after 6 weeks of treatment with liraglutide and glimepiride
- glimepiride treatment had a more pronounced effect on glucose excursions compared with liraglutide treatment
- there was an almost 10-fold higher risk of exclusively mild hypoglycemia during glimepiride treatment compared with liraglutide treatment

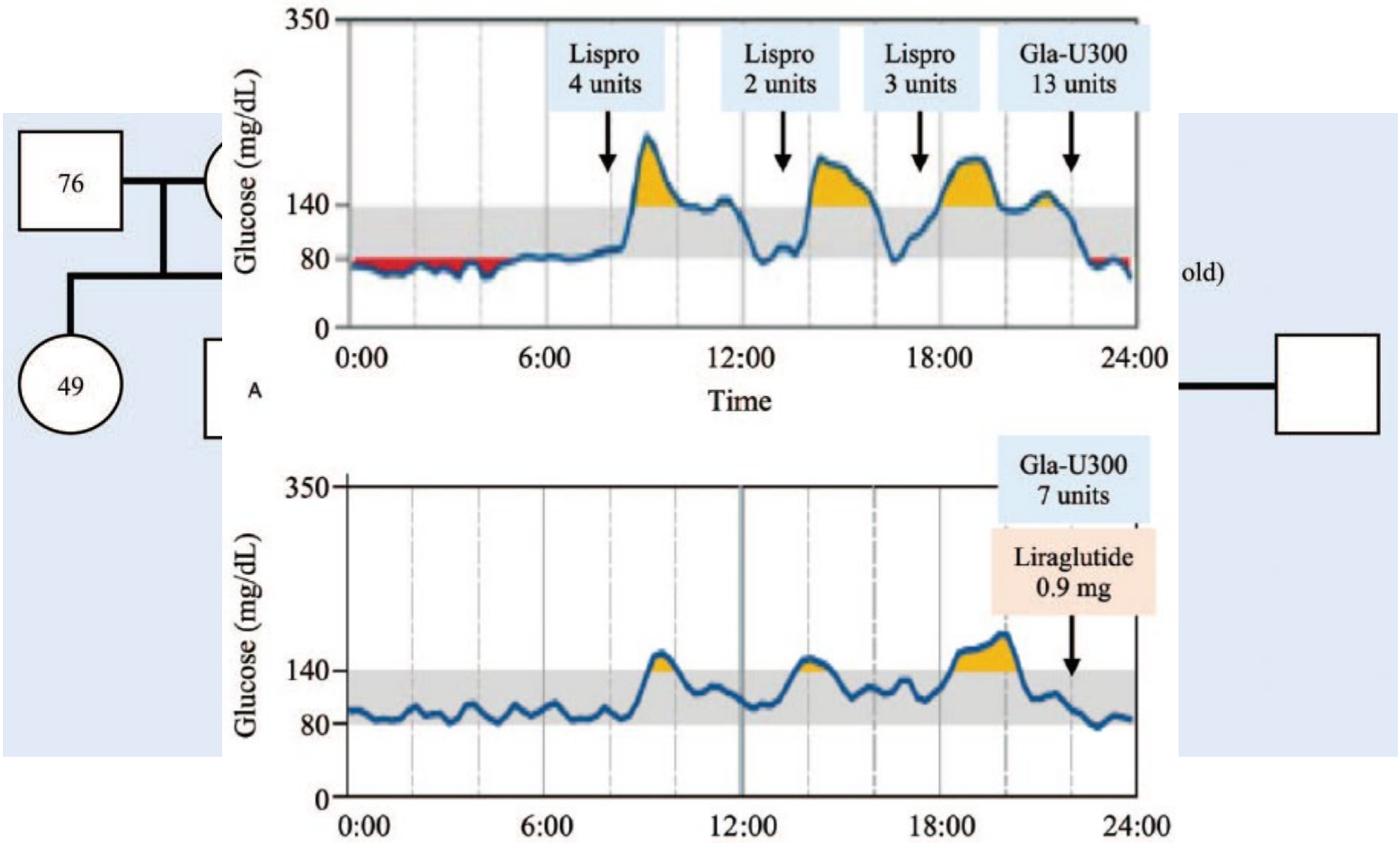
GLP-1R Agonist vs. Sulfonylurea in MODY3 *Diabetes Care* Volume 37, July 2014

GLP1RA effects on SU dose, HbA1c, Weight

	Age	Adjunctive GLP1-RA	SU dose reduction	HbA1c reduction	Weight Loss
HNF1A (MODY3)	47, F	oral semaglutide, 7 mg once daily, 22 mos	glimepiride 6 mg/day reduction	1.3 ± 0.4%	7.1 ± 4.8 Kg
HNF1A (MODY3)	55, F	subcutaneous dulaglutide, 1.5 mg once weekly, 21.5 mos	glipizide 5 mg/day reduction		
HNF1A (MODY3)	56, F	subcutaneous semaglutide, 0.5 mg once weekly, 24 mos	glipizide 10 mg/day reduction		
HNF4A (MODY1)	43, F	subcutaneous dulaglutide, 1.5 mg once weekly, 47.5 mos	glipizide 10 mg/day reduction		

ADA 2024 poster 1875-LB: Adjuvant Glucagon-Like Peptide 1 Receptor Agonist (GLP-1 RA) Use in HNF1A- and HNF4A-MODY

HNF1β-MODY

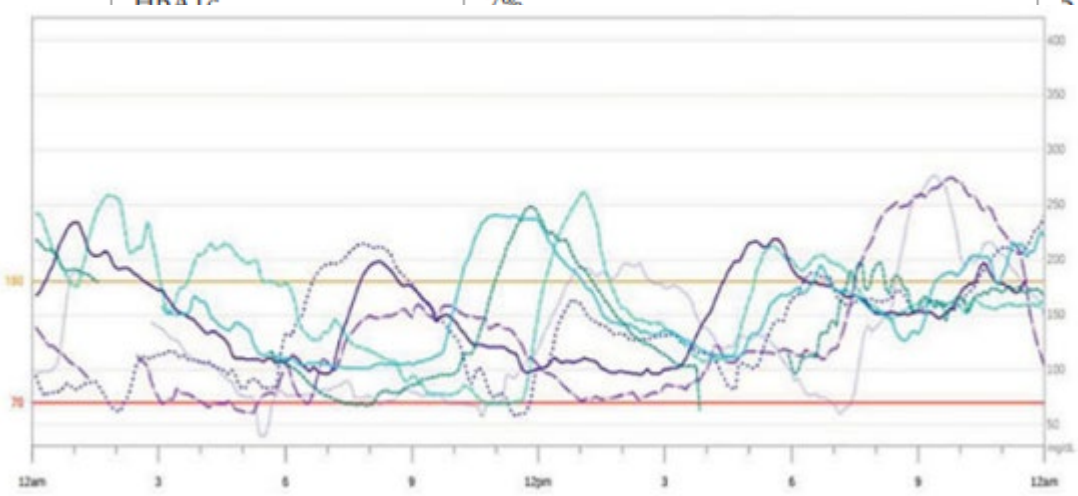


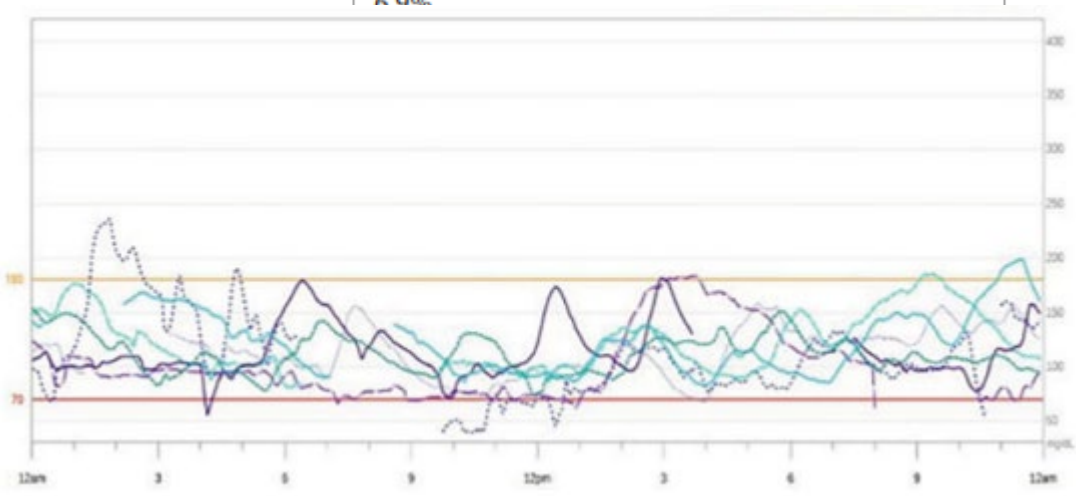
Terakawa A, et Al. *Medicine* 2020;99:35(e21939)

HNF1β-MODY

- 18-year-old, nonobese female patient diagnosed with HNF1B-MODY

Parameters	Before semaglutide therapy (insulin 0.7 units/kg/day)	During semaglutide therapy (O.5 mg weekly)	3 months off semaglutide therapy (insulin 0.7 units/kg/day)
BMI kg/m^2	24.1 (75th-85th percentile)	20.1 (25th-50th percentile)	24.9 (75th-85th percentile)
HbA1c	7%	5.6 %	6.9%
TIR in best days	77%	100%	-



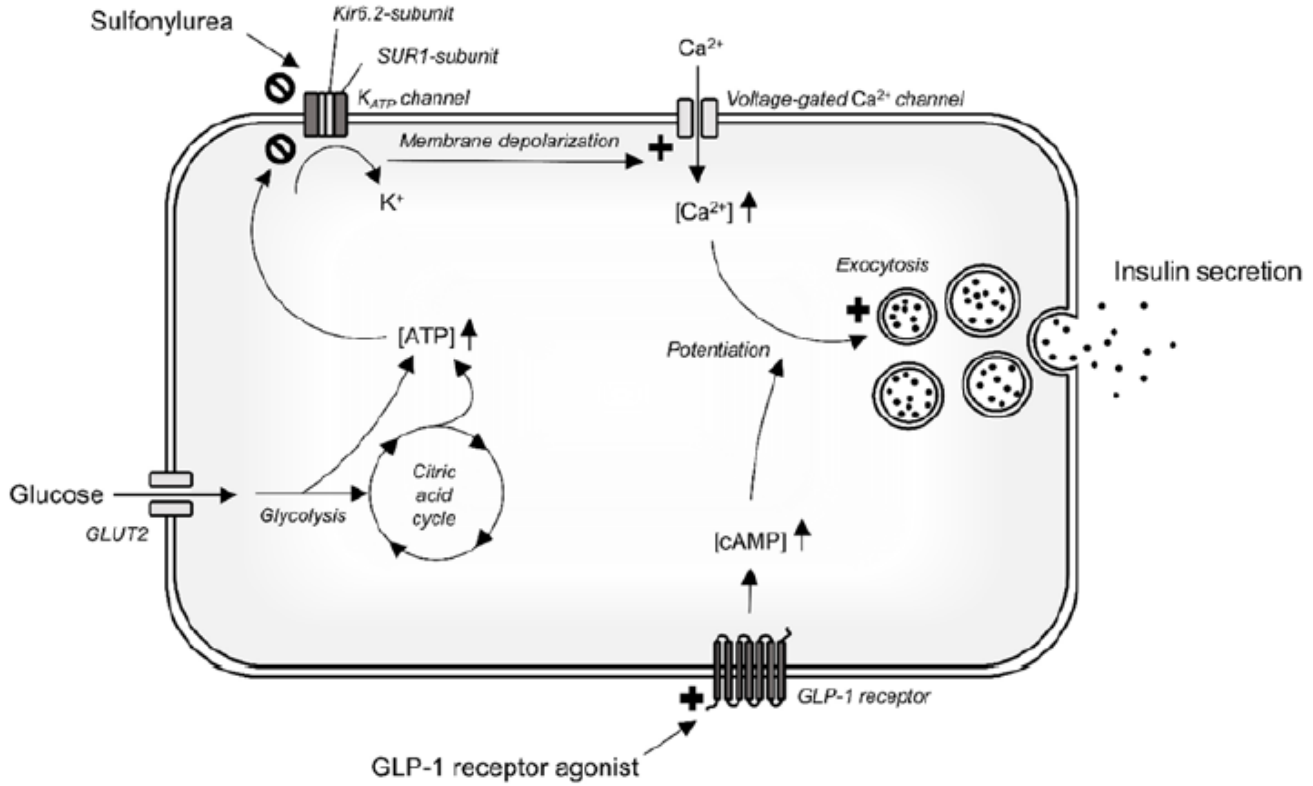


TIR, time-in-range (glucose level 80–180 mg/dL); TAR1, time-above-range 1 (glucose level 181–250 mg/dL); TAR2, time-above-range 2 (glucose level above 250 mg/dL); TBR1, time-below-range 1 (glucose level below 70 mg/dL); TBR2, time-below-range 2 (glucose level below 54 mg/dL); CV, coefficient of variation.

Almutair A and Almulhem B *Front. Endocrinol* 2024

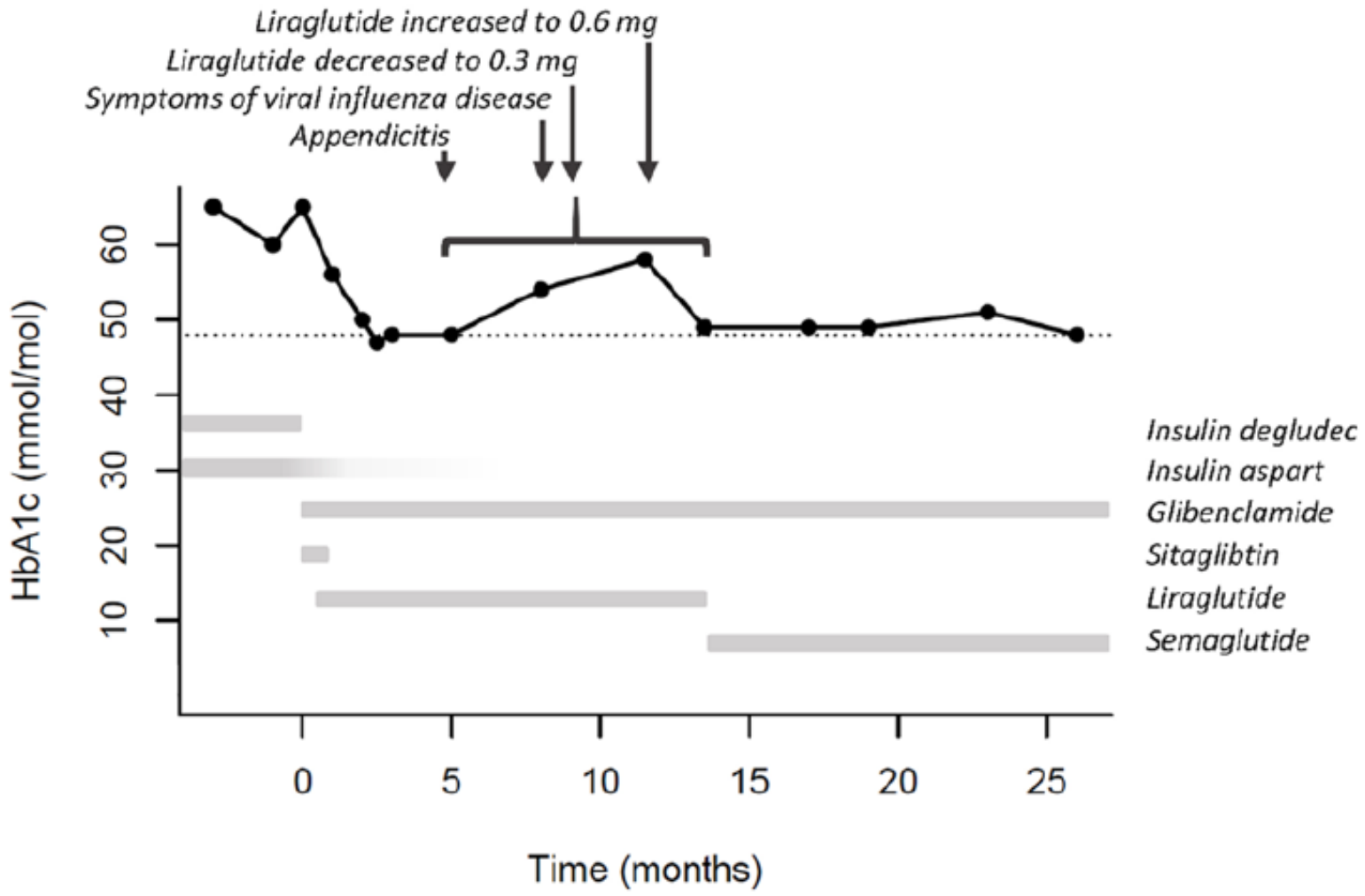
Diabete neonatale

- Permanente (40-50%)
  - La mutazione puntiforme *KCNJ11* (gene Kir 6.2) è presente nel 30-58% di tutti i casi di NDM *(80% de novo)*
  - Mutazione *ABCC8* (gene SUR1)
  - Delezione *IPF1* → agenesia pancreas
  - Mutazione *EIF2AK3* → Ipoplasia β-cellule (sindrome di Wolcott-Rallison)
- Transitorio (50-60%)
  - Mutazioni in eterozigosi di *ABCC8* (SUR1)



Diabete neonatale

A 40-year-old lean man (body mass index 22.6 kg/m2) with insulin-treated diabetes mellitus since the neonatal period



Hindsø M, et al. *EJCRIM* 2021;8

Marta, 38 anni

- Familiarità negativa per diabete
- Diabete mellito insorto all'età di 10 anni. Fin dalla diagnosi negatività degli anticorpi anti-ICA, anti-GAD, anti-IA2
- In terapia con microinfusore insulinico associato a sensore per il monitoraggio glicemico continuo

- Nel corso di una visita oculistica di controllo: «non segni di retinopatia diabetica, segni sfumati di atrofia del n.ottico»
- Completamento del panel anticorpale: AAZNT8 e IAA entrambi negativi, peptide C < 0,02 ng/mL.

➔ Riscontro di mutazione del gene WS1 (c.2099G>A in eterozigosi)

Sindrome di Wolfram

Genetica

- Gene WFS1 (4p 16.1) che codifica per una proteina transmembrana del reticolo endoplasmatico (wolframina) espressa nelle cellule beta pancreatiche, nei neuroni, nel polmoni, nella placenta. Le mutazioni sono prevalentemente recessive.

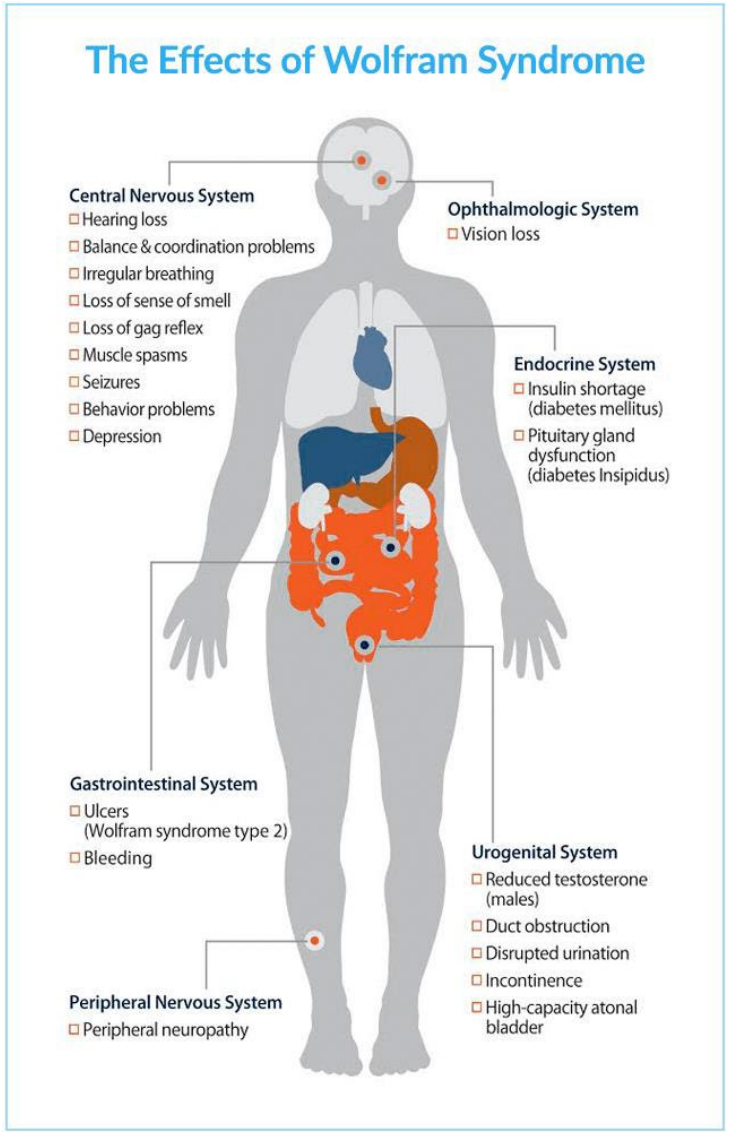
- WFS1 loss of function causes an increase in the cytosolic concentration of Ca2+ ions, resulting in the establishment of chronic ER stress and the inappropriate activation of the unfolded protein response (UPR) signaling pathway

Panfili E et al. *Front. Clin. Diabetes Healthc*. 4:1171091

Sindrome di Wolfram

Caratteristiche cliniche

- D.I. diabete insipido
- D.M. diabete mellito
- O.A. atrofia del nervo ottico
- D. sordità



Sindrome di Wolfram

GLP1-RA in WS

Species	GLP1-RA	Effects in WFS1-SD	Reference
mouse	exenatide	improving of glycaemic control	Sedman et al. (74)
	exenatide	improving of glycaemic control	Kondo et al. (75)
rat	liraglutide	preventing development of glucose intolerance, improving insulin and glucagon secretion control, reducing ER stress in Langerhans islets	Toots et al. (78)
	liraglutide	delaying onset of diabetes, protecting against optic nerve atrophy and vision loss	Jagomäe et al. (79)
	liraglutide	delaying progression of hyperglycaemia and neuroprotective effects	Seppa et al. (80)
	liraglutide	neuroprotective effect	Seppa et al. (81)
human	dulaglutide	improving of glycaemic control	Scully et al. (76)
	liraglutide	improving of glycaemic control	Kondo et al. (75)
	liraglutide	decreasing of insulin requirement, stabilizating neuro-ophthalmological and neurophysiological disease parameters	Frontino et al. (18)
	liraglutide	improving of the glycaemic control	Png et al. (82)

Panfili E et al. *Front. Clin. Diabetes Healthc*. 4:1171091

GLP1-RA nel diabete monogenico

- Dalle esperienze preliminari presenti in letteratura, i GLP1-RA sembrano dei buoni candidati alla terapia del diabete monogenico, in particolare nelle forme con deficit di secrezione insulinica grazie sia agli effetti incretinici e sia agli effetti antiapoptotici sulla beta cellula.
- La maggiore esperienza è stata fatta sul HNF1α-MODY, la forma più frequente di diabete monogenico
- Le SU e la terapia insulinica restano i farmaci di scelta nelle forme caratterizzate da deficit di secrezione insulinica, ma i GLP1RA possono avere un ruolo come terapie aggiuntive
- Rispetto alle SU, sono stati documentati vantaggi a breve termine in termini di riduzione del rischio ipoglicemico e possibilità di utilizzare le SU a dosaggi ridotti
- I vantaggi eventuali dei GLP1-RA sulla apoptosi beta-cellulare andranno valutati a lungo termine

Effects of single dapagliflozin 10 mg in HNF1α-MODY

- *HNF1A* is a weak transactivator of the insulin gene in beta cells and its variants can lead to abnormal insulin secretion. Some genetic variants also result in a low renal threshold for glucose because of lower expression of SGLT2
- *CGK-MODY* presents higher threshold for glucose-stimulated insulin secretion. The resulting hyperglycemia is often stable and mild

Table 1 Clinical characteristic and biochemical measurements of the study group

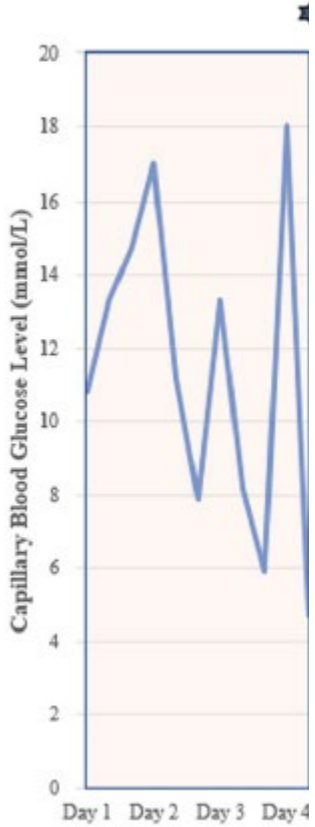
Characteristic	HNF1A-MODY	GCK-MODY	T2DM	*p*-value
N	14	19	12	NA
Male/female (*n*)	7/7	7/12	8/4	0.17[a]
Age at examination (years)	34.1 ± 11.0	40.3 ± 10.8	61.8 ± 5.6	0.0000[b]
Time from diabetes diagnosis (years)	11.4 ± 6.8	8.7 ± 7.1	5.8 ± 4.2	0.10[b]
BMI (kg/m^2)	24.4 ± 4.9	23.4 ± 2.8	31.3 ± 5.3	0.0000[b]
eGFR CKD-EPI (ml/min/1.73 m^2)	98.1 ± 15.1	99.9 ± 15.6	87.7 ± 15.9	0.10[b]
HbA1c (%, mmol/mol)	6.0 ± 0.7, 42.0 ± 5.3	6.4 ± 0.4, 46.0 ± 2.0	6.9 ± 0.9, 52.0 ± 7.5	0.03[c]
hsCRP (mg/l)	0.52 ± 0.30	1.12 ± 1.57	1.60 ± 1.15	0.09[b]
GCR (*Day 0*)—patients with positive urinary glucose only (mmol/mmol, *n*)	0.15, 1	0.17 ± 0.18, 2	2.01, 1	NA
GCR change (8–12 h after dapagliflozin administration) (mmol/mmol)	35.64 ± 14.10	38.72 ± 9.65	19.37 ± 18.76	0.001[b]
GCR change (*Day +1—Day 0*) (mmol/mmol)	20.51 ± 12.08	23.19 ± 8.10	9.84 ± 6.68	0.001[b]
1,5-AG (Day 0) (mg/ml)	8.75 ± 8.43	19.61 ± 9.22	26.72 ± 9.03	0.0000[b]
1,5-AG change (Day +1 −Day 0) (mg/ml)	−0.09 ± 4.21	−0.86 ± 4.16	−6.57 ± 7.34	0.02[b]
FPG (Day 0) (mmol/l)	5.60 ± 1.02	6.82 ± 0.71	7.73 ± 2.25	0.005[c]
FPG change (Day +1—Day 0) (mmol/l)	−0.14 ± 0.90	−0.50 ± 0.72	−0.23 ± 1.20	0.51[b]
Average daily glucose in SMBG (Day −1) (mmol/l)	6.02 ± 1.03	6.99 ± 0.50	7.60 ± 1.77	0.008[c]
Average daily glucose in SMBG (Day 0) (mmol/l)	5.81 ± 0.87	6.90 ± 0.59	7.32 ± 1.58	0.002[c]
Average daily glucose change in SMBG (Day 0—Day −1) (mmol/l)	−0.21 ± 0.61	−0.09 ± 0.51	−0.27 ± 1.27	0.84[c]

Data are presented as mean ± standard deviation

Hohendorff J et al. *Endocrine* (2017) 57:272–279

Empagliflozin in HNF1α-MODY

- 30-year-old woman with MODY3 with poor glycaemic control despite the treatment with supramaximal doses of sulfonylurea and metformin



Sriravindrarajah A et al. *Endocrinol Diab Metab Case Reports* Dec 2021

Empagliflozin in HNF1α-MODY

- In a randomized, double-blind, crossover study, 11 persons with MODY3 and 10 T2D underwent two three-step hyperglycemic clamps targeted at 10, 14, and 18 mmol/L (1h each) with and without 25 mg empagliflozin

The similar effects of SGLT2 inhibition in persons with MODY3 and T2D observed here, point to SGLT2 inhibition as a relevant glucose-lowering treatment strategy in persons with MODY3 despite the potentially lower SGLT2 expression

Table. Plasma glucose, urinary glucose excretion, infused glucose, and urine volume during three-hour, three-step hyperglycemic clamp (10, 14, 18 mmol/L) with SGLT2 inhibition and placebo, respectively, in persons with MODY3 and type 2 diabetes, respectively.

	MODY3		Type 2 Diabetes		MODY3 vs. Type 2 Diabetes
	Placebo	SGLT2i	Placebo	SGLT2i	
Plasma Glucose (AUC, 5-180 min), mmol/L × min	2486 (2460; 2513)	2451 (2424; 2477)	2450 (2414; 2487)	2430 (2393; 2466)	
SGLT2i effect, ETD	-35 (-53; -18)*		-20 (-38; -3)*		-15 (-36; 6)
Urinary Glucose Excretion, g/3h	9.7 (5.2; 14.2)	34.2 (29.1; 39.3)	5.6 (3.7; 7.6)	29.1 (24.5; 33.7)	
SGLT2i effect, ETD	24.5 (20.7; 28.4)*		23.5 (20.5; 26.5)*		1.0 (-3.2; 5.3)
Infused Glucose[#], g/3h	52.0 (45.7; 58.2)	80.3 (69.3; 91.3)	75.3 (51.3; 99.4)	94.4 (74.5; 114.3)	
SGLT2i effect, ETD	28.4 (21.9; 34.8)*		19.0 (10.1; 27.9)*		9.4 (-0.2; 18.9)
Urine Volume, mL/3h	500 (384; 616)	908 (784; 1031)	393 (263; 522)	883 (652; 1113)	
SGLT2i effect, ETD	407 (292; 522)*		490 (358; 622)*		-83 (-235; 70)

Data presented as means with 95% confidence intervals. *P<0.05. [#]Amount of glucose infused to maintain plasma glucose concentrations during the clamp. ETD, Estimated treatment difference. MODY3, maturity-onset diabetes of the young type 3 (HNF1A-MODY). SGLT2i, Sodium-glucose cotransporter-2 inhibitor.

ADA 2024 poster 909-P: Impact of SGLT2 Inhibition on Glucosuria in HNF1A-MODY

Empagliflozin in HNF1α-MODY

	Baseline	4 months
HbA1c, mmol/mol	52 (42–84)	43 (38–62)
Change from baseline		−12 (−22 to 7)
HbA1c, %	6.9 (6.0–9.8)	6.1 (5.6–7.8)
Change from baseline		−1.1 (−2.0 to 0.7)
BMI, kg/m^2	27.1 (23.6–29.0)	24.7 (22.5–28.3)
Change from baseline		−1.1 (−4.9 to −0.3)
On insulin treatment, *n*	4	1
Daily dose, units/day	20 (6–28)	2

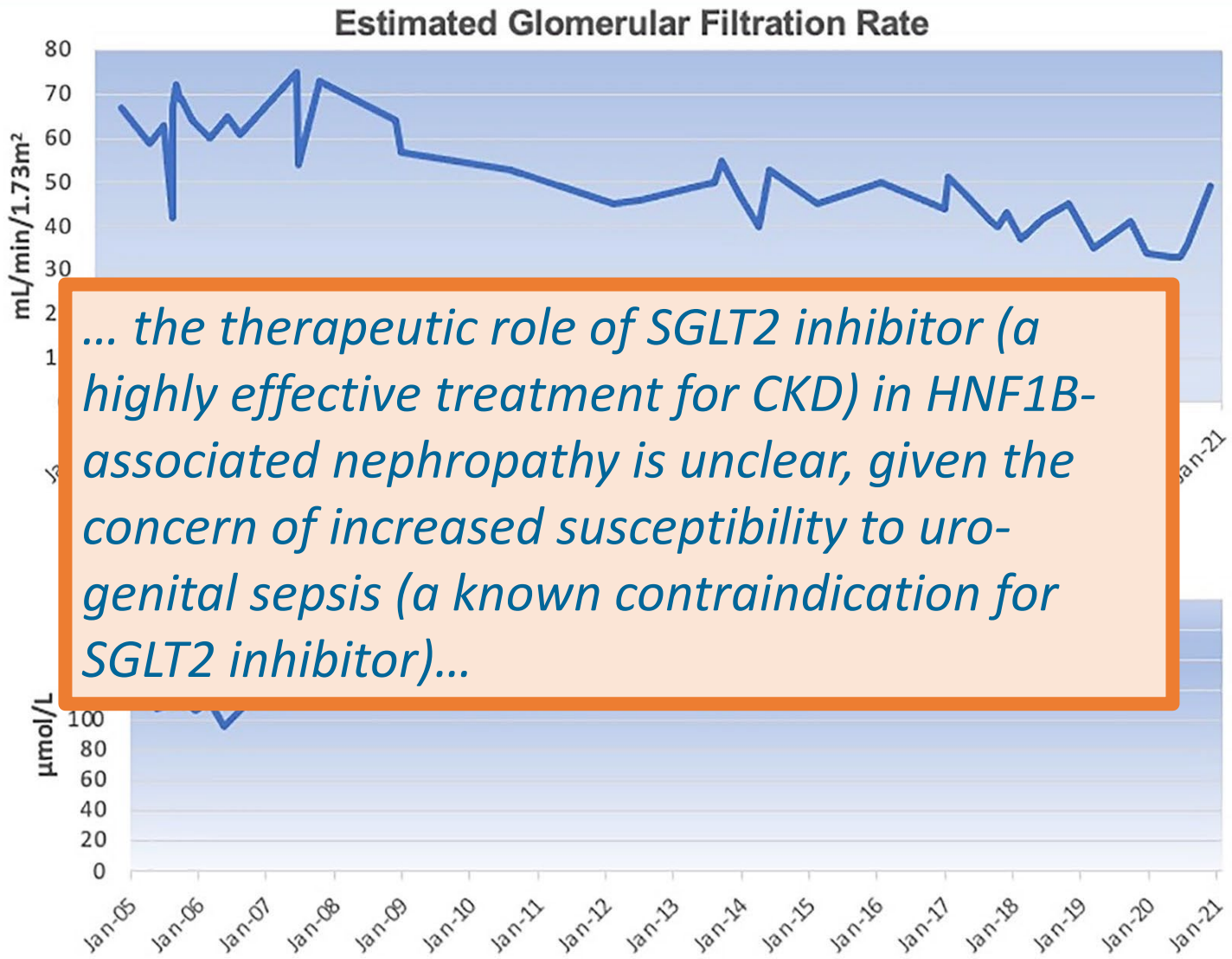
Note: Data presented as median with range in brackets or numbers (%).

Abbreviations: BMI, body mass index; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide 1 receptor agonist; HbA1c, glycated haemoglobin A1c.

Treatment combinations, *n* (%)	
Glimepiride + Insulin + DPP-4 inhibitor	3 (43%)
Glimepiride + Insulin + GLP-1RA	1 (14%)
Glimepiride + GLP-1RA + Metformin	1 (14%)
Glimepiride + GLP-1RA	1 (14%)
Glimepiride + DPP-4 inhibitor	1 (14%)

Maagensen E *Diabetic Medicine.* 2024;41:e15387

HNF1β-MODY



… the therapeutic role of SGLT2 inhibitor (a highly effective treatment for CKD) in HNF1B-associated nephropathy is unclear, given the concern of increased susceptibility to uro-genital sepsis (a known contraindication for SGLT2 inhibitor)…

SGLT2-i nel diabete monogenico

- Dalle esperienze preliminari presenti in letteratura, le gliflozine sembrano dei discreti candidati candidati alla terapia del diabete monogenico, in particolare per l'accentuazione della glicosuria nel HNF1α-MODY
- L'effetto glicosurico nel HNF1α-MODY sembra maggiore che nel T2D, nonostante sia caratterizzato da ridotta espressione del recettore a livello renale

- Il ruolo delle gliflozine nel diabete monogenico resta di tipo «aggiuntivo» a SU o insulina, che restano le terapie di prima scelta in particolare nelle forma caratterizzate da deficit parziale di secrezione insulinica