Diabete Monogenico: che fare? Le domande del clinico

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UNIVERSITÀ DEGLI STUDI DELL'AQUILA

MESVA

Conflitto di Interessi

Negli ultimi due anni Marco G. Baroni ha ricevuto compensi per relazioni e/o consulenze da:

- Lilly, Novo Nordisk, Boheringer, Abbot, MSD, Viatris

La struttura di apparteneza di MG Baroni ha ricevuto:

- Compensi per studi clinici sponsorizzati da: Novo Nordisk

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.).

IL DIABETE IN ITALIA

Popolazione generale: ~ 60.000.000

Diabete ignoto: ~ 1.000.000

Diabete noto: ~ 4.000.000

Tipo 1: *~ 200.000 (5%)*

LADA: *~ 200.000 (5%)*

Tipo 2: *~ 3.500.000 (87%)*

Secondario: *~ 50.000 (1.5%)*

Monogenico: *~ 50.000-200.000*

BETE MONOGENICO
ei pazienti diagnosticati
0.5-5
T2D
5-6% dei pazienti pediatrici
3% delle donne con GDM

Stima dall'Osservatorio ARNO Diabete CINECA-SID

Diabete Monogenico

Un gruppo eterogeneo di disordini dovuti a
mutazioni in singoli geni
coinvolti nell'omeostasi del glucosio.

- Diabete mitocondriale
- Diabete neonatale (eventualmente sindromico)
- Maturity Onset Diabetes of the Young (MODY)

Maturity Onset Diabetes of the Young (MODY)

- 1-5% delle forme di diabete (Ledermann HM 1995)
- 5-43% di casi di bambini con iperglicemia asintomatica o occasionale (Lorini et al 2009)
- Comprende un gruppo eterogeneo di disordini monogenici caratterizzati da disfunzione beta-cellulare
- Causato da mutazioni in almeno 14 geni
- Si stima che l’80% dei casi non sia ancora diagnosticato

Diabete monogenico: che fare?
Le tre domande del clinico

1. Come sospettarlo
2. Come diagnosticarlo
3. Come monitorarlo e trattarlo

Caratteristiche (storiche) del MODY

- Esordio precoce (< 25 anni)

- Trasmissione autosomico-dominante
  il soggetto eterozigote sviluppa la malattia
  la metà dei figli di un affetto "sviluppa" la malattia

- Normopeso/sovrappeso (non obesità)

- Deficit secretorio

- Non segni di insulino-resistenza

Tattersall 1974

Caratteristiche storiche del MODY

Tattersall 1974

-Trasmissione autosomico-dominante
il soggetto eterozigote sviluppa la malattia
la metà dei figli di un affetto avrà la malattia

- Esordio precoce (< 25 anni)
- Normopeso
- deficit secretorio

Caratteristiche attuali del MODY

Clinical features	
Age at diagnosis of diabetes (Y)	13 (8 - 18)
Age at genetic diagnosis (Y)	17 (11 - 35)
Females	46 (68%)
BMI (Kg/m^2)	21 (19 - 24)
Extra-pancreatic features	2 (3%)
Parent(s) with diabetes	61 (90%)
HbA1c (%)	6.1 (5.8 -6.5)
Only diet	40 (59%)
Non-insulin therapy	12 (18%)
Insulin (+/- non-insulin therapy)	16 (23%)

Data are median value (25th – 75th percentile) or percentage

Marucci A et al, Acta Diabetologica 2022

Features of MODY

- A strong family history of diabetes (of any type)
- Early onset of diabetes (2-40 years)
- Impaired insulin secretion
- Insulin independence (although insulin may be needed for optimal control)
- Absence of features of insulin resistance
- Absence of β cell autoimmunity.
- The specific genetic subtype of MODY determines the clinical presentation, prognosis, and treatment response.

Diagnosi differenziale tra DM, DT1 e DT2

CARATTERISTICHE	DT1	DM	DT2
Insorgenza < 30 aa	Molto frequente	Molto frequente	Infrequente
Storia familiare	Infrequente	Molto frequente*	Frequente
Cheto-acidosi	Frequente	Molto infrequente	Molto infrequente
Ab pancreatici	Presenti	Assenti	Assenti
C-peptide sierico (ng/ml)	< 0,6	> 0,6	>> 0,6
Sovrappeso/obesità	Infrequente	Infrequente	Molto frequente
Dislipidemia aterogena)	Infrequente	Infrequente	Frequente
Caratteristiche sindromiche	Assenti	Possibili**	Assenti

* Particolarmente sospetta se coinvolge ≥ 3 generazioni e se interessa un solo ramo familiare (materno o paterno).
**cisti renali o altre malformazioni urogenitali, disturbi uditivi, disturbi visivi, lipodistrofia, anemia megaloblastica, acanthosis nigricans in soggetti magri, malformazioni cardiache o pancreatiche, diabete insipido.

SID 2022 -- Documento di orientamento clinico sul diabete monogenico. V. Trischitta et al.

Come sospettare il diabete monogenico

T1D?

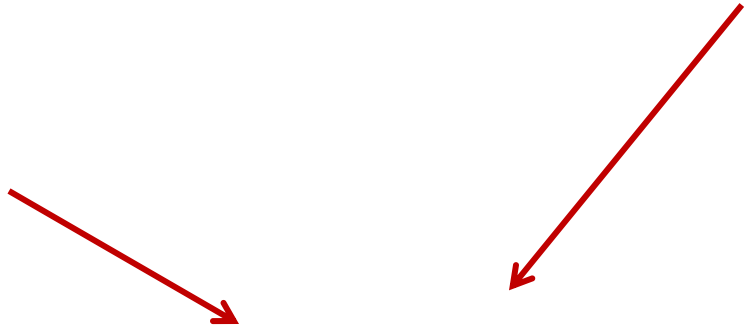
Family history of diabetes
No ketosis (modest hyperglycemia)
Extra-pancreatic features

T2D?

Early onset (<30 yrs)
No obesity (no dyslipidemia)
Extra-pancreatic features

No T1D-related Ab (GADA, IA-2A, IAA, ZnT8)

Preserved C peptide



Molecular diagnosis

C-peptide

- Livelli sierici di C-peptide «random» > 0.6 ng/ml (0.2 nmol/L; 200pmol/L): questo parametro è indice di buona capacità secretoria suggestiva di MODY o diabete tipo 2) (Hope et al.).
- C-peptide a digiuno: > 0.25 ng/ml (0.08 nmol/L; 80pmol/L)

- È importante sottolineare come i dati clinici in letteratura dimostrano l'equivalenza dei livelli di C-peptide misurati su prelievo random non a digiuno rispetto al prelievo dopo stimolo

(Hope SV, Knight BA, Shields BM, Hattersley AT, McDonald TJ, Jones AG. Random non-fasting C-peptide: bringing robust assessment of endogenous insulin secretion to the clinic. Diabet Med 2016;33:1554-1558)

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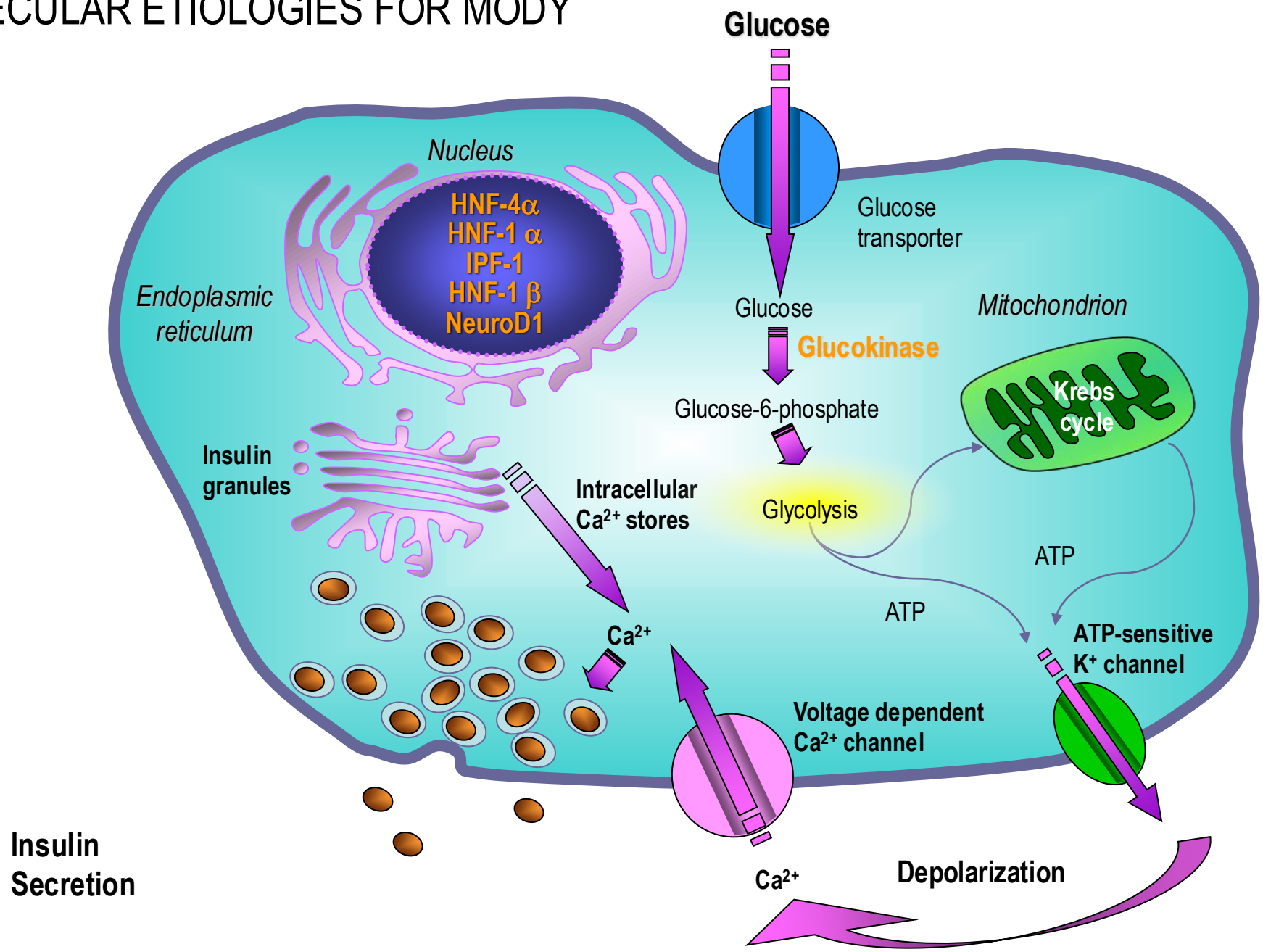
MOLECULAR ETIOLOGIES FOR MODY



Clinical features associated with mutations in genes that cause maturity onset diabetes of the young (MODY)

Gene	Relative prevalence	Other clinical features
HNF1A (MODY 3)	Common (16-33% of MODY)	Low renal threshold for glycosuria; **marked sensitivity to sulfonylureas**
GCK (MODY 2)	Common (30-70% of MODY)	Mild fasting hyperglycaemia throughout life; often detected during screening; small incremental glucose rise after carbohydrate load
HNF4A (MODY 1)	5-14% of MODY	Normal renal threshold; **marked sensitivity to sulfonylureas;** neonatal hyperinsulinaemia and hypoglycaemia with associated macrosomia;
HNF1B (MODY 5)	<5% of MODY	Malformations of the genitourinary tract (especially renal cysts and other renal developmental abnormalities); pancreatic atrophy; exocrine insufficiency

Clinical features associated with mutations in genes that cause maturity onset diabetes of the young (MODY)

Gene	Relative prevalence	Other clinical features
IPF1	Very rare	Pancreatic agenesis in homozygotes/compound heterozygotes
CEL	Very rare: fewer than 5 families reported	Exocrine pancreatic dysfunction
NEUROD1	Very rare: fewer than 5 families reported	
INS	Rare: <1% of MODY	More usually associated with neonatal diabetes
KCNJ11	Rare: <1% of MODY	More usually associated with neonatal diabetes; sulfonylurea responsive
ABCC8	Rare: <1% of MODY	More usually associated with neonatal diabetes; sulfonylurea responsive

Distribution of the most common MODY subtypes in Italy

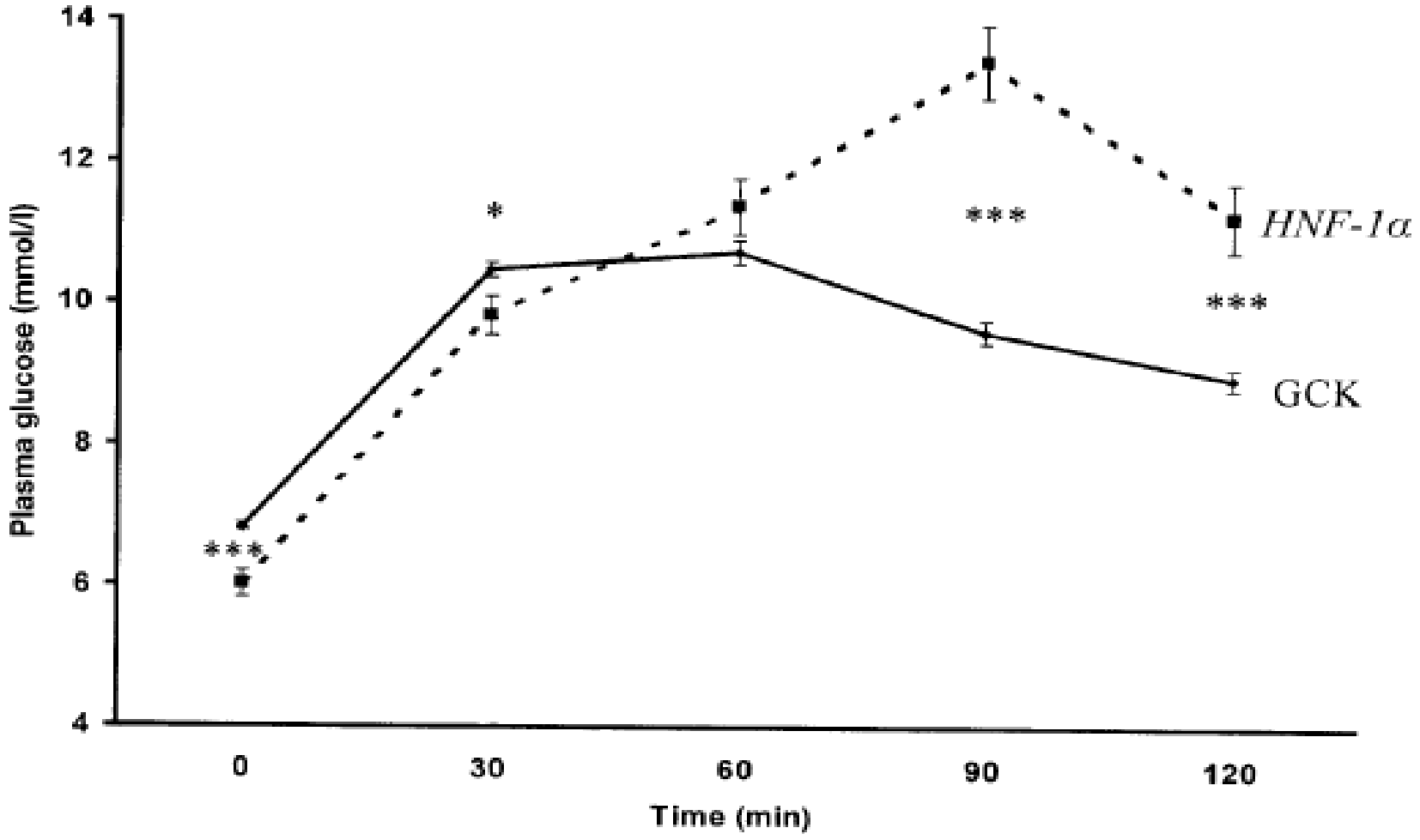
Gene	Subtype	Frequency (%)
HNF4A	MODY 1	5-14
GCK	MODY 2	30-70
HNF1A	MODY 3	16-33

Del Vecchio M et al, Diabetes Care 2014
Marucci A et al, Acta Diabetologica 2022

MUTAZIONI IN GLUCOKINASI (MODY2)

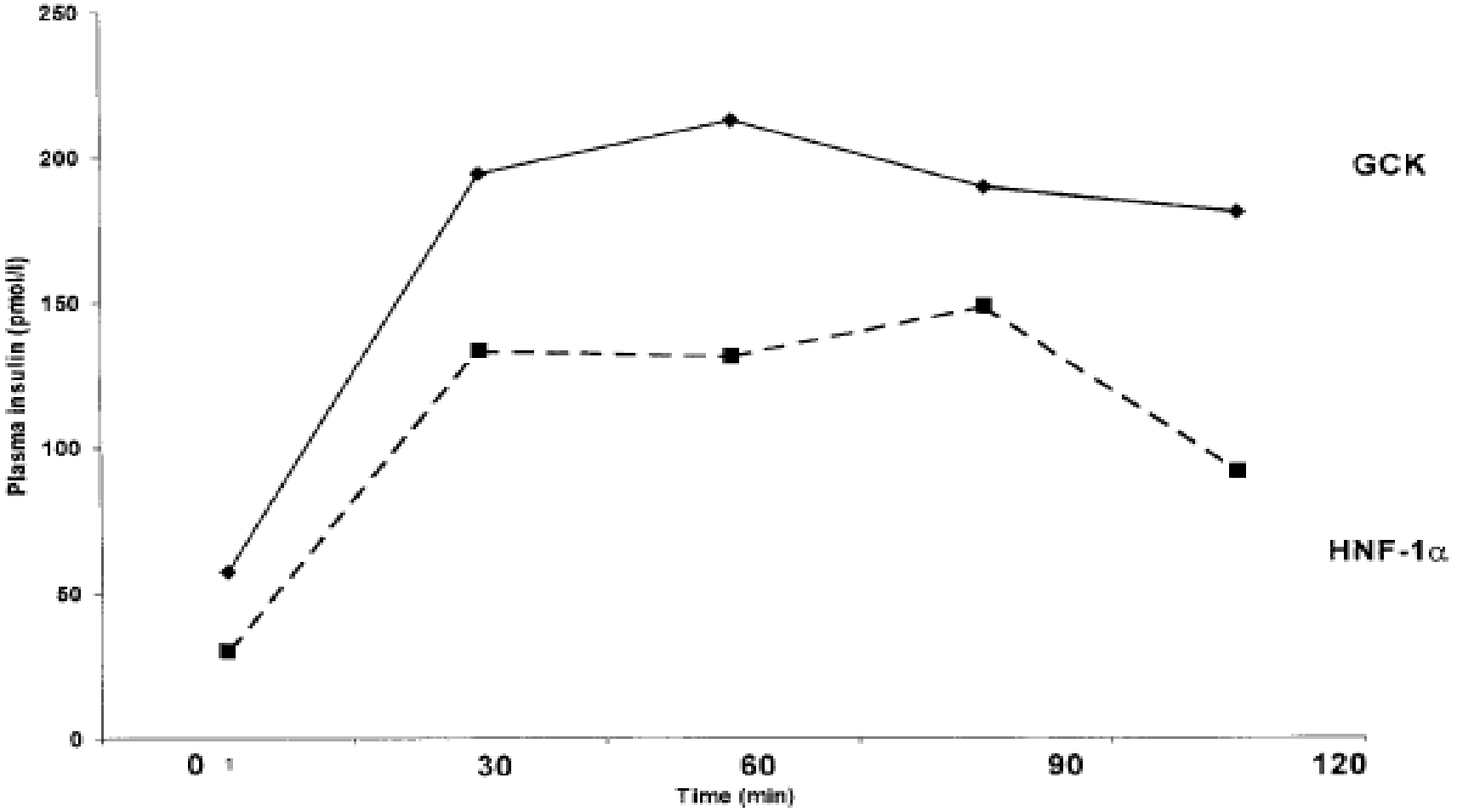
- Asintomatici per lunghi periodi ma alterazioni glicemiche evidenziabili già in età pediatrica. Diagnosi occasionale in gravidanza.
- Persistente iperglicemia a digiuno >100 mg/dl raramente >150)
- HbA1c raramente risulta >7,5%
- Incremento conseguente ad OGTT lieve, spesso < 54 mg/dl
- Follow-up di soggetti MODY2 esposti a iperglicemia per >50 anni dimostra che non sviluppano complicanze micro- e macro-vascolari
- Terapia quasi mai necessaria

Glucose concentrations during OGTT in subjects with GCK and HNF1a mutations



Stride A et al, Diabetologia 2002

Insulin concentrations during OGTT in subjects with GCK and HNF1a mutations



Stride A et al, Diabetologia 2002

Original Investigation

Prevalence of Vascular Complications Among Patients With Glucokinase Mutations and Prolonged, Mild Hyperglycemia

Characteristics	Median (IQR)			*P* Value	
	GCK Group (n = 99)	Control Group (n = 91)[a]	YT2D Group (n = 83)	*GCK* vs Control Groups	*GCK* vs YT2D Groups
Men, No. (%)	20 (20)	41 (45)	52 (63)	<.001	<.001
Current age, y	48.6 (40.1-62.7)	52.2 (42.3-64.8)	54.7 (49.2-62.0)	.49	.06
BMI	26.1 (22.3-29.3)	28.0 (25.3-31.2)	32.2 (28.3-37.0)	.004	<.001
Age hyperglycemia or diabetes diagnosis, y	33 (24-44)	NA	40 (35-42)	NA	.001
Duration hyperglycemia, y	48 (40-62)	NA	17 (9-23)	NA	<.001
Fasting plasma glucose, mg/dL	117 (126-135)	94 (86-101)	144 (112-187)	<.001	<.001
HbA_{1c}, %	6.9 (6.5-7.1)	5.8 (5.5-5.9)	7.8 (7.2-8.7)	<.001	<.001

Steele AM et al, JAMA 2014

Original Investigation

Prevalence of Vascular Complications Among Patients With Glucokinase Mutations and Prolonged, Mild Hyperglycemia

	No./Total (% [95% CI]) of Participants			*P* Value	
	GCK (n = 99)	Control (n = 91)	YT2D (n = 83)	*GCK* vs Control Groups	*GCK* vs YT2D Groups
Microvascular Complications					
Renal					
Persistent microalbuminuria	1/97 (1 [0.2-6])	2/89 (2 [0.2-8])	17/80 (21 [13-32])	.60	<.001
Proteinuria	0/97 (0 [0-4])	0/91 (0 [0-4])	8/80 (10 [4-19])	>.99	<.001
Retinal					
Any degree of retinopathy	27/90 (30 [21-41])	12/87 (14 [7-23])	52/83 (63 [51-73])	.007	<.001
Background retinopathy (all severities)	27/90 (30 [21-41])	12/87 (14 [7-23])	34/83 (41 [30-52])		
<5 Microaneurysms	22/27 (81 [62-94])	12/12 (100 [74-100])	13/34 (38 [22-56])	.02	.05
>5 Microaneurysms	5/27 (19 [6-38])	0/12 (0 [0-26])	21/34 (62 [44-78])		
Preproliferative retinopathy	0/90 (0 [0-4])	0/87 (0 [0-4])	7/83 (8 [3-17])	>.99	.005
Proliferative retinopathy	0/90 (0 [0-4])	0/87 (0 [0-4])	8/83 (10 [4-18])	>.99	.002
Maculopathy	0/90 (0 [0-4])	0/87 (0 [0-4])	17/83 (20 [12-31])	>.99	<.001
Advanced eye disease	0/90 (0 [0-4])	0/87 (0 [0-4])	3/83 (4 [1-10])	>.99	.005
Laser therapy for retinopathy	0/90 (0 [0-4])	0/87 (0 [0-4])	23/83 (28 [18-39])	>.99	<.001

Steele AM et al, JAMA 2014

Original Investigation

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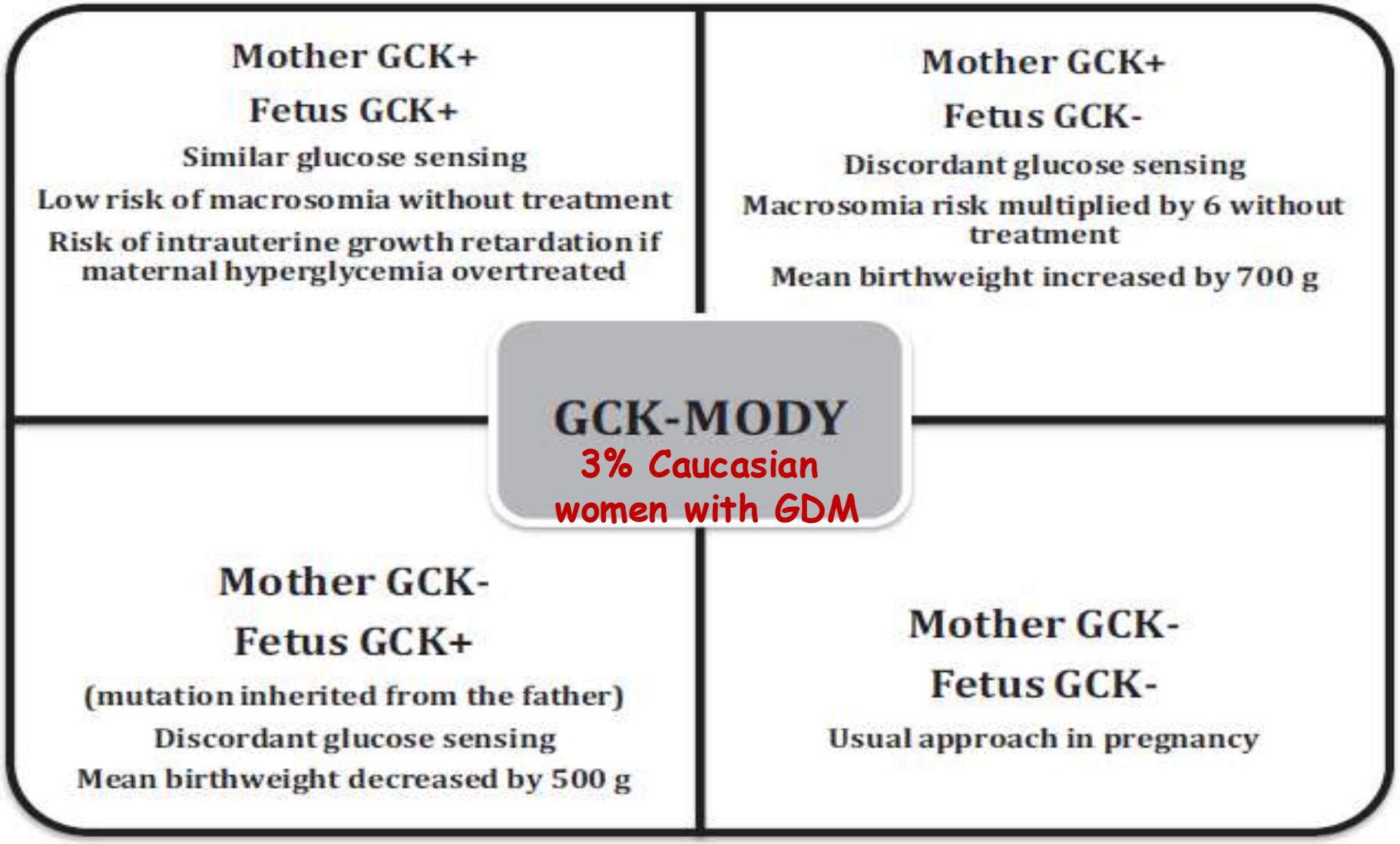
	No./Total (% [95% CI]) of Participants			*P* Value	
	GCK (n = 99)	Control (n = 91)	YT2D (n = 83)	*GCK* vs Control Groups	*GCK* vs YT2D Groups
Macrovascular Complications					
Vascular					
Significantly increased ABPI (ABPI≥1.40)	1/97 (1 [0.2-6])	3/91 (3 [0.7-9])	9/83 (11 [5-20])	.30	.006
Amputation	0/97 (0 [0-4])	0/91 (0 [0-4])	4/83 (5 [1-12])	.10	.04
Peripheral vascular disease[d]	1/93 (1 [0-5])	3/89 (3 [0-9])	13/83 (16 [8-25])	.30	<.001
Angina[e]	4/93 (4 [1-10])	10/89 (11 [5-19])	18/83 (22 [13-32])	.07	<.001
Myocardial infarction	2/89 (2 [0.2-7])	2/97 (2 [0.2-8])	5/83 (6 [2-14])	.99	.16
Ischemic heart disease[f]	2/99 (2 [0.2-7])	5/91 (5 [2-13])	13/83 (16 [10-29])	.32	.001
Cerebral vascular events					
Stroke	0/99 (0 [0-4])	0/91 (0 [0-4])	4/83 (5 [1-12])	>.99	.04

Steele AM et al, JAMA 2014

GCK In Pregancy

- Many patients with unkown *GCK* variants are identified initially when they present to an antenatal clinic for screening with an abnormal glucose tolerance. By conventional diagnostic criteria they would have GDM as they have glucose intolerance diagnosed for the first time in pregnancy.
- However, there are several important differences between GCK and the more conventional and common type of gestational diabetes;
  - Gestational diabetes is detected first during pregnancy (usually at the beginning of the 3rd trimester) and is usually not present on repeated OGTT after delivery of the baby.
  - GCK hyperglycaemia is always present from birth, and hence before conception (but is often unrecognised) and persists after delivery of the baby.
  - GCK hyperglycaemia is typified by a raised FPG and a small 2-hour increment on OGTT. In GDM FPG is often normal with a larger increment at 2 hours on OGTT. This means some criteria for hyperglycaemia in pregnancy (the 2-hour glucose value) may not detect *GCK* as abnormal.
  - GDM mothers are at very high risk of developing Type 2 diabetes years later, while GCK patients are likely to have stable glucose intolerance.
  - In GDM, offspring will almost certainly have normal glucose tolerance. In GCK hyperglycaemia, 50% of offspring will inherit the abnormal gene and therefore have abnormal glucose tolerance from birth.

Birth weight based on GCK genotype in mother vs. fetus

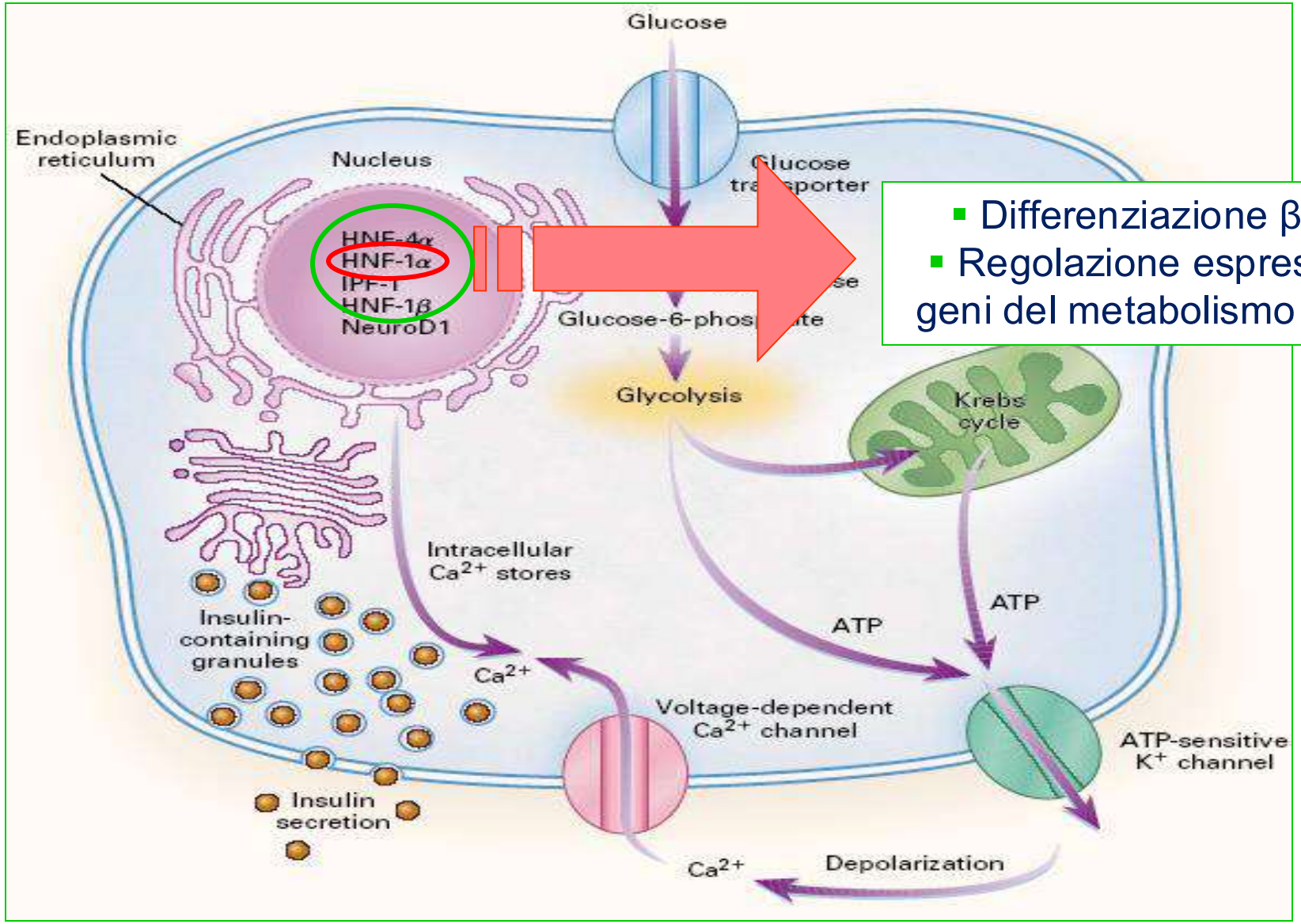


Lachance CH et al. Can J Diabetes 2016; 40:368–375

Hepatocyte Nuclear Factor 1a (MODY3) e HNF4a (MODY1)

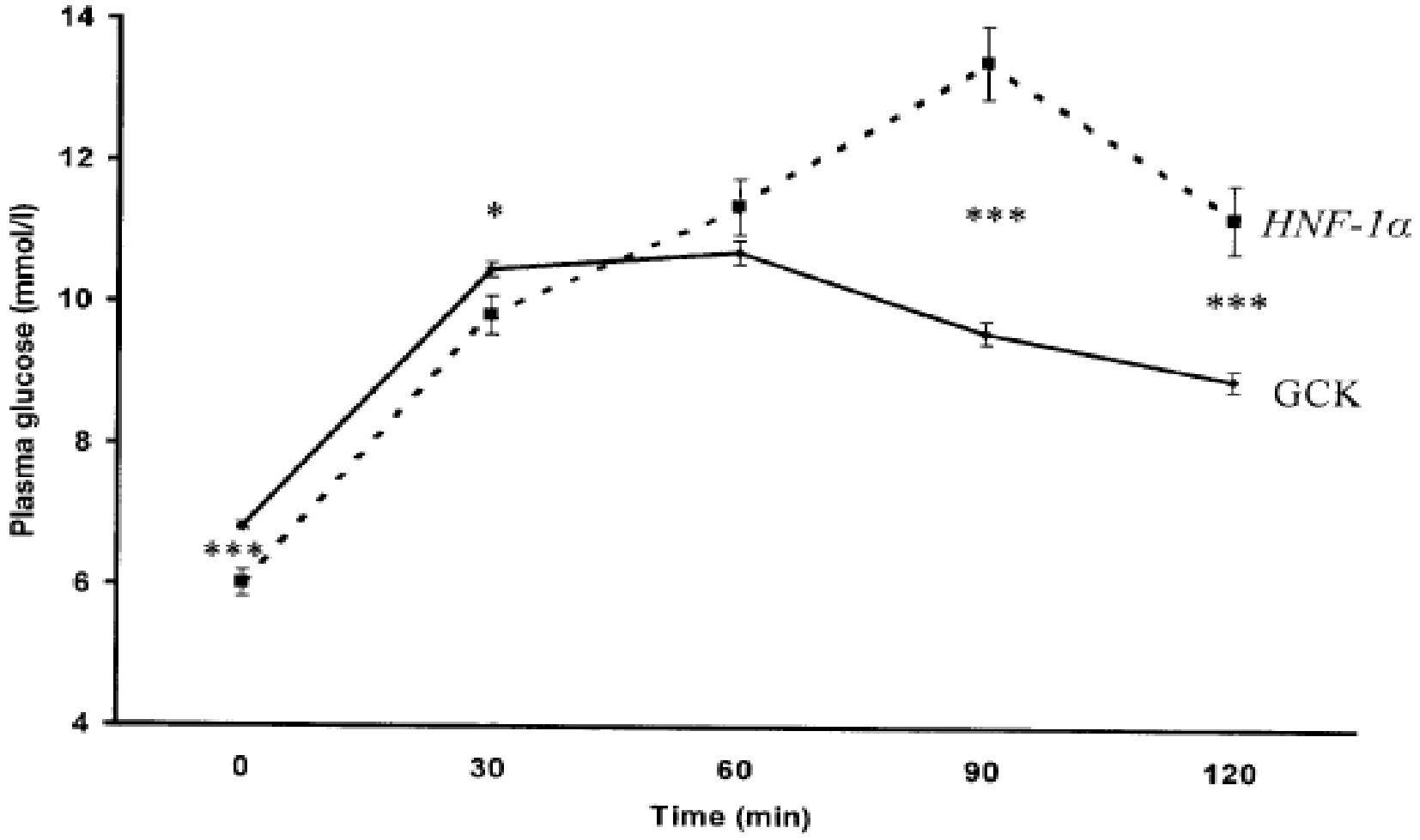
- Comparsa del diabete intorno ai 20 anni
- Storia familiare per diabete
- Progressivo peggioramento della tolleranza al glucosio
- Alla diagnosi: poliuria, polidipsia, dimagimento. spesso è presente glicosuria. Diagnosticati a volte come tipo 1 (controllare storia familiare e chetoni)
- Riscontro della produzione di insulina endogena dopo 3 anni dalla diagnosi
- Valori di c-peptide testabile
- Non presentano chetoacidosi in assenza di terapia insulinica
- Complicanze frequenti
- Terapia: 1/3 dieta, 1/3 OAD, 1/3 insulina (fabbisogno basso ~ 0.5 U/kg^{-1})

HNF1A-MODY (MODY 3)



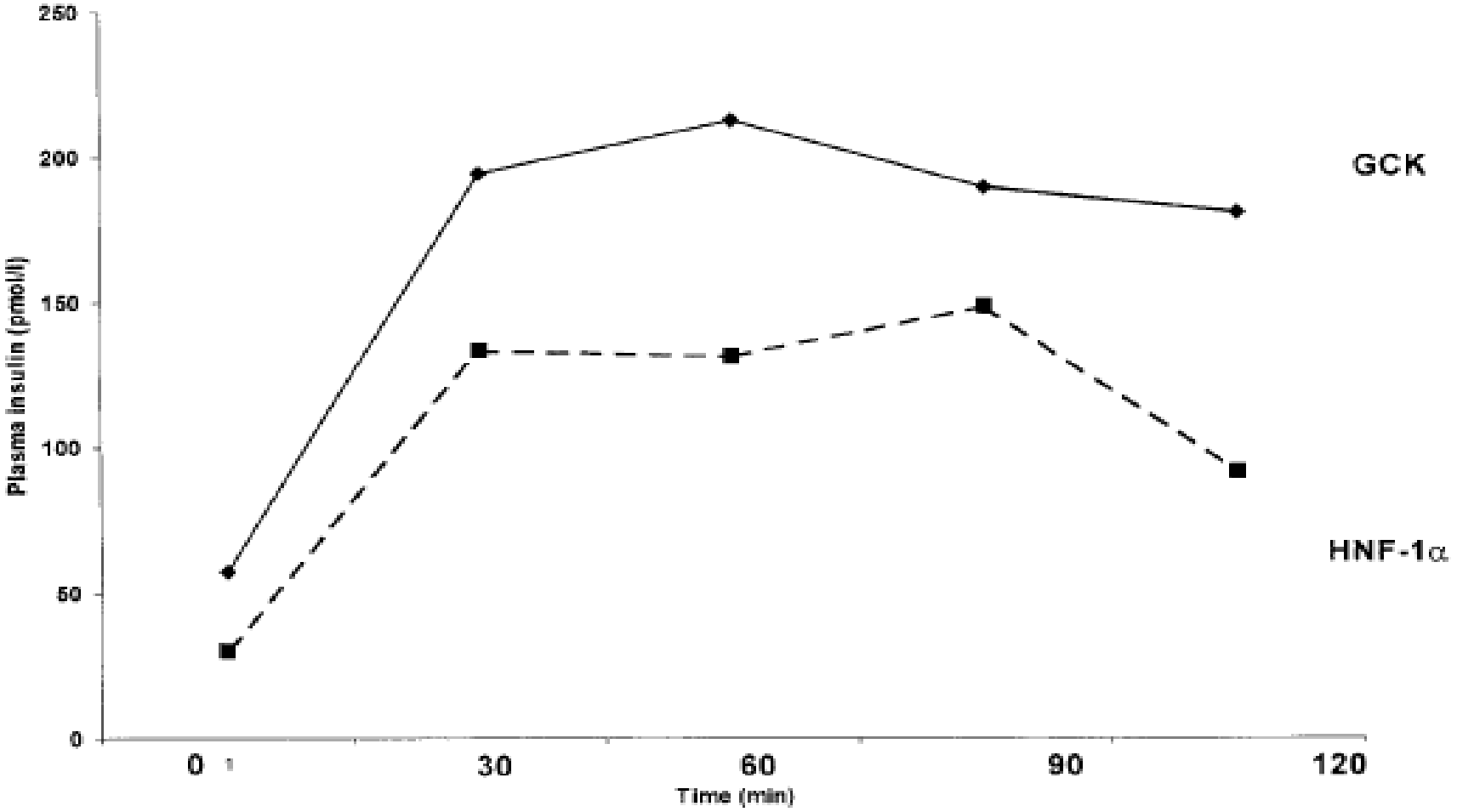
- Differenziazione β-cellule
- Regolazione espressione di geni del metabolismo glucidico

Glucose concentrations during OGTT in subjects with GCK and HNF1a mutations



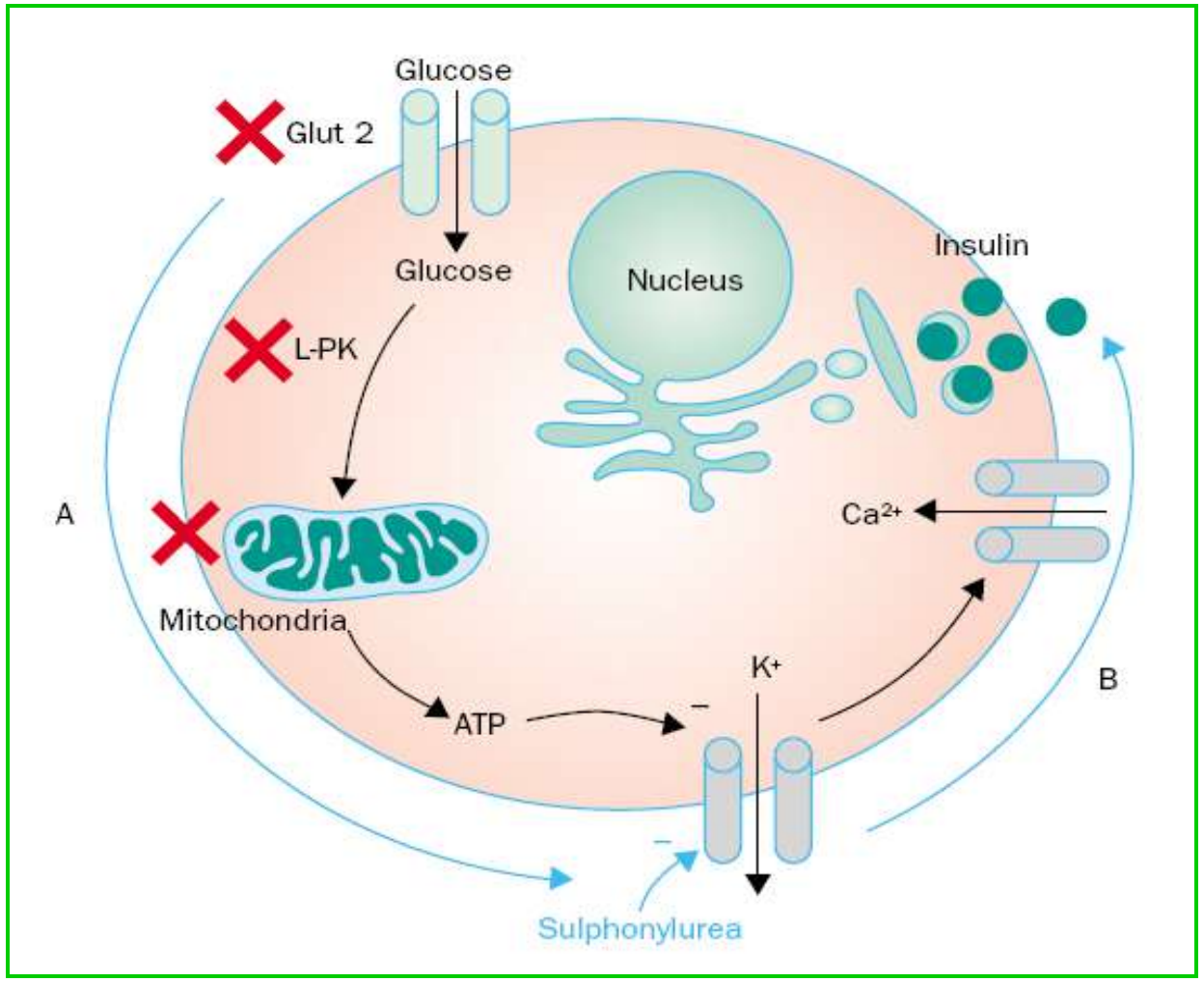
Stride A et al, Diabetologia 2002

Insulin concentrations during OGTT in subjects with GCK and HNF1a mutations



Stride A et al, Diabetologia 2002

Genetic cause of hyperglycaemia and response to treatment in diabetes



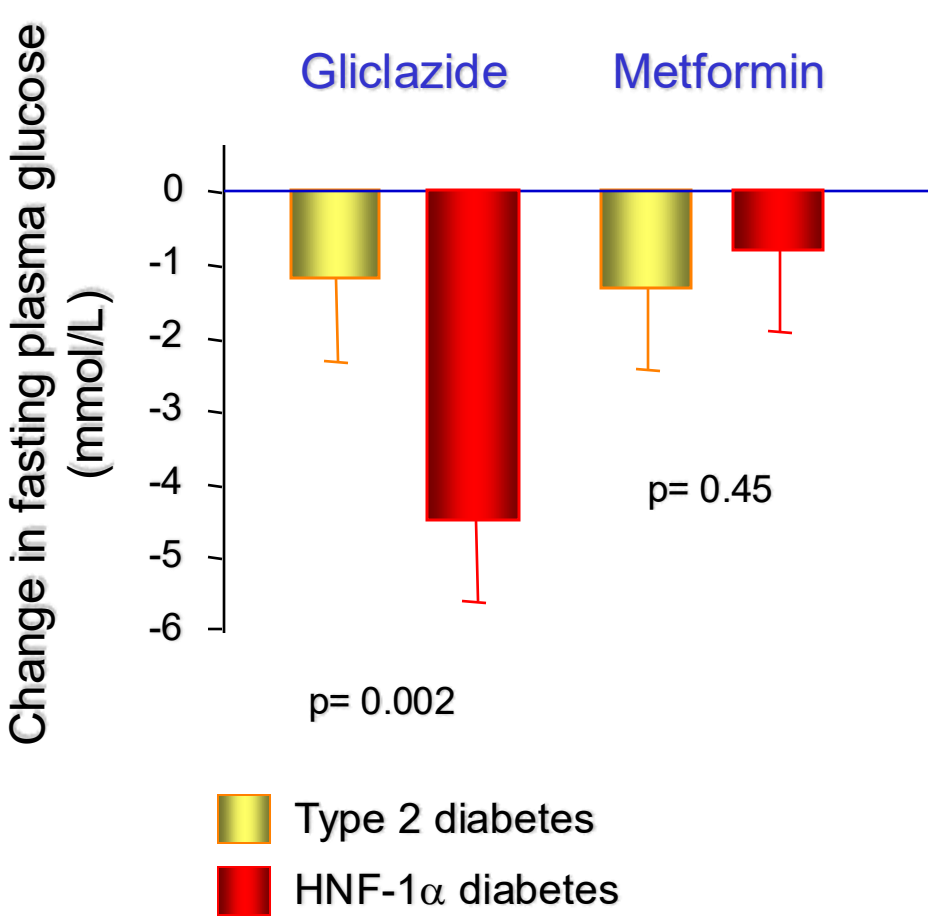
…HNF-1α mutations cause decreased transcription of Glut-2, insulin and decreased mitochondrial metabolism.

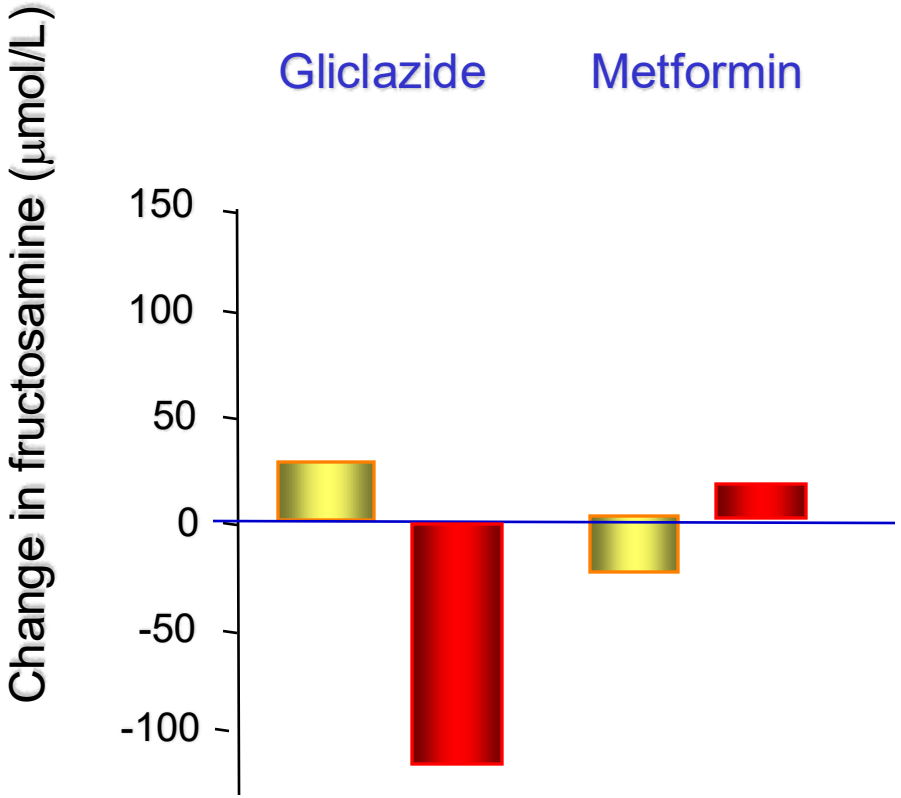
Sulphonylureas act to close the KATP channel thus triggering insulin release.

The predominant sites of action of HNF-1α (pathway A) are bypassed by sulphonylureas.

Pearson ER et al. Lancet 2003

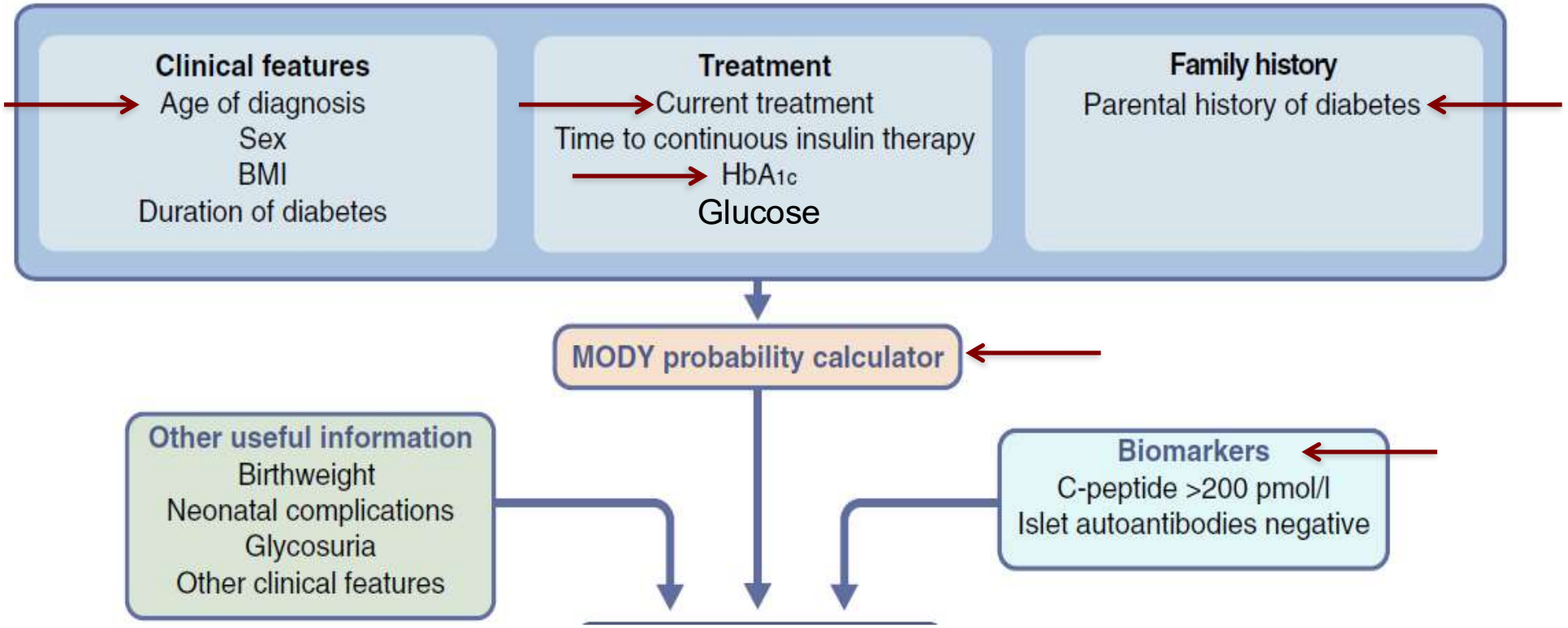
Response to Gliclazide vs. Metformin in Type 2 Diabetes and HNF-1α Diabetes (MODY3)





Pearson ER et al, *Lancet* 2003

How to procede to MODY genetic testing



MODY genetic testing

- *Yes or no?*
- *Which gene?*

Hattersley HA et al. Diabetologia 2017;60:769–777

MODY Probability Calculator

Please note work on this model is still in progress and further validation needs to be undertaken. **For regular phone use, please download the app here.**

This is for use in patients diagnosed with diabetes under the age of 35 and was developed on a European Caucasian cohort.
Strongly dependent on family history

https://www.diabetesgenes.org/mody-probability-calculator

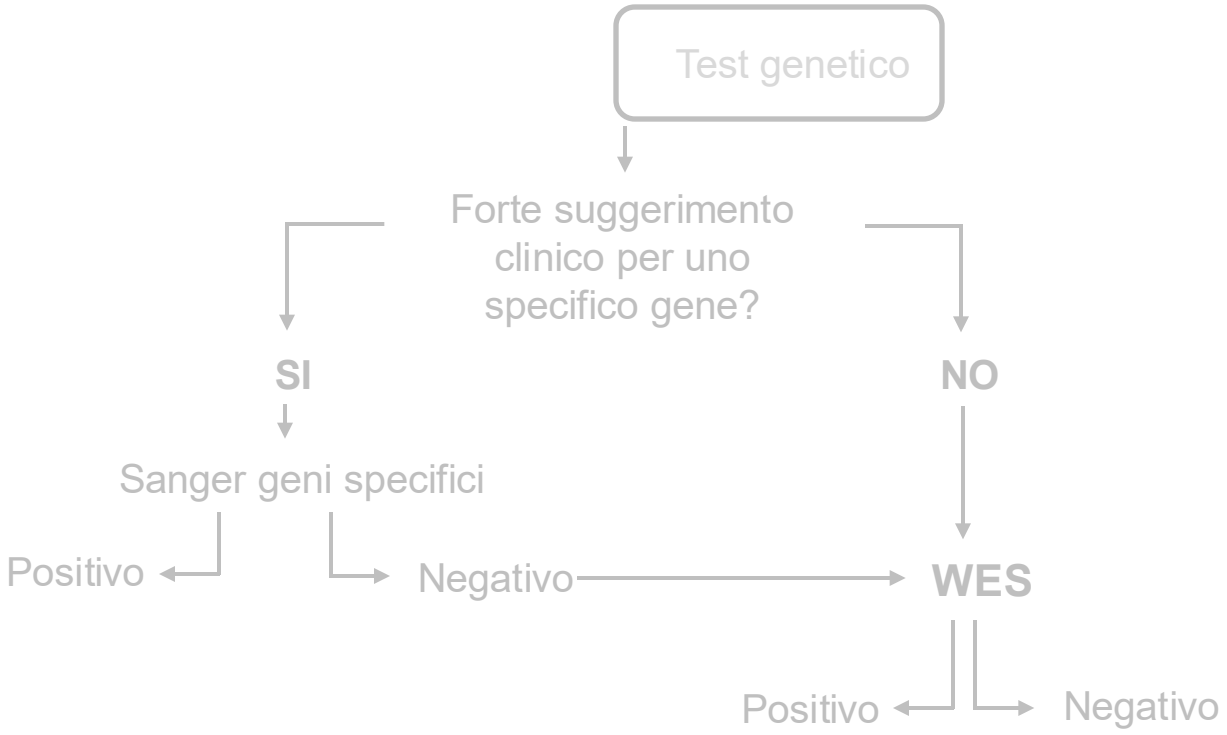
Enter clinical features of your patient in the form below and press the "Calculate Probability" button.

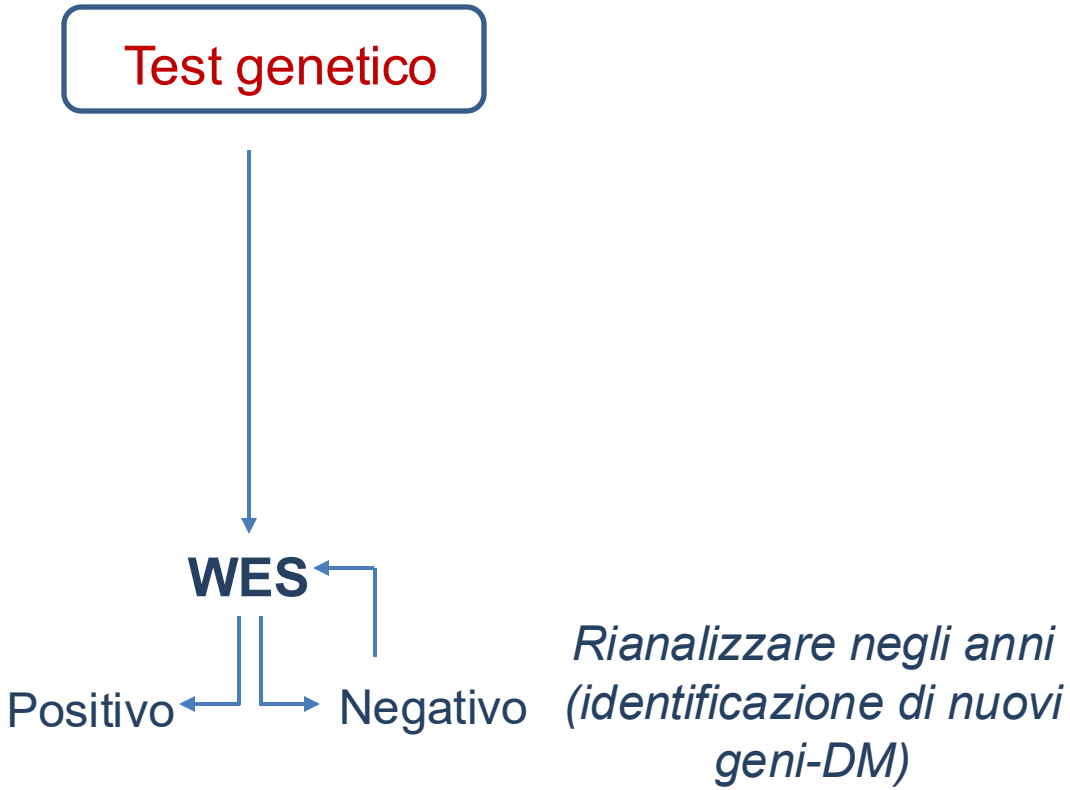
Age at diagnosis (years)	2.5	
Sex	◉ Male	○ Female
Currently treated with insulin *or* OHA?	○ Yes	◉ No
Time to Insulin Treatment (if currently treated with insulin)	◉ Not currently treated with insulin ○ Within 6 months of diagnosis ○ Over 6 months after diagnosis	
BMI (kg/m^2)	17.5	
HbA1c (%)	5.8	or mmol/mol
Current Age (yrs)	4	
Parent affected with diabetes?	◉ Yes	○ No

Calculate Reset

Probability of your patient having MODY is 75.5 %

Diagnosi molecolare del DM



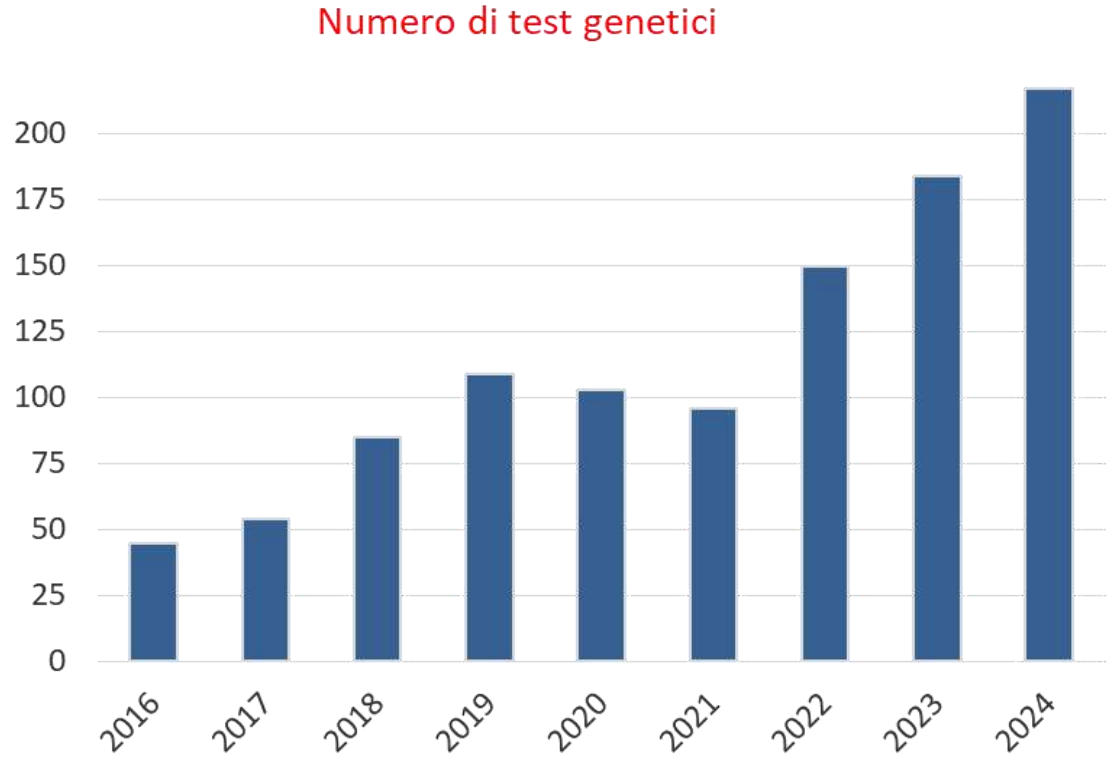


Diagnosi molecolare del DM

IRCCS Casa Sollievo della Sofferenza

Struttura dedicata al DM

- Stretto rapporto fra laboratorio e clinici
- Discussione casi clinici quindicinale
- Orientamento clinico per pediatri e diabetologi (consulenza telefoniche, video)
- Corsi di aggiornamento per medici e biologi
- Ritiro gratuito del prelievo alla fonte



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nature reviews disease primers https://doi.org/10.1038/s41572-023-00421-w

Primer Check for updates

Monogenic diabetes

Amélie Bonnefond[1,2,3], Ranjit Unnikrishnan[4], Alessandro Doria[5,6], Martine Vaxillaire[1,2], Rohit N. Kulkarni[5,6], Viswanathan Mohan[4], Vincenzo Trischitta[7,8] & Philippe Froguel[1,2,3]

Table 3 | Precision medicine approaches for management of some forms of monogenic diabetes

Form of diabetes	Precision medicine[a]	
	Treatment	Monitoring[b]
Dominant *GCK*-diabetes	Unnecessary	Relaxed
Dominant *HNF1A*-diabetes	Oral sulfonylureas and GLP1 analogues	Liver
Dominant *HNF4A*-diabetes	Oral sulfonylureas	NA
Dominant *HNF1B*-diabetes	Magnesium supplements 92% cases	Renal, urinary, genital, gonadal and exocrine pancreatic function
Dominant *CEL*-diabetes	NA	Exocrine pancreatic function
Dominant *ABCC8*-diabetes	Oral sulfonylureas	Neurodevelopment
Dominant *KCNJ11*-diabetes	Oral sulfonylureas	Neurodevelopment
Dominant *GATA4*-diabetes	NA	Cardiac function
Dominant *GATA6*-diabetes	NA	Cardiac function
m.3243A>G-diabetes	NA	Hearing and cardiac function

Treatment choices for HNF1A- and HNF4A-related MODY

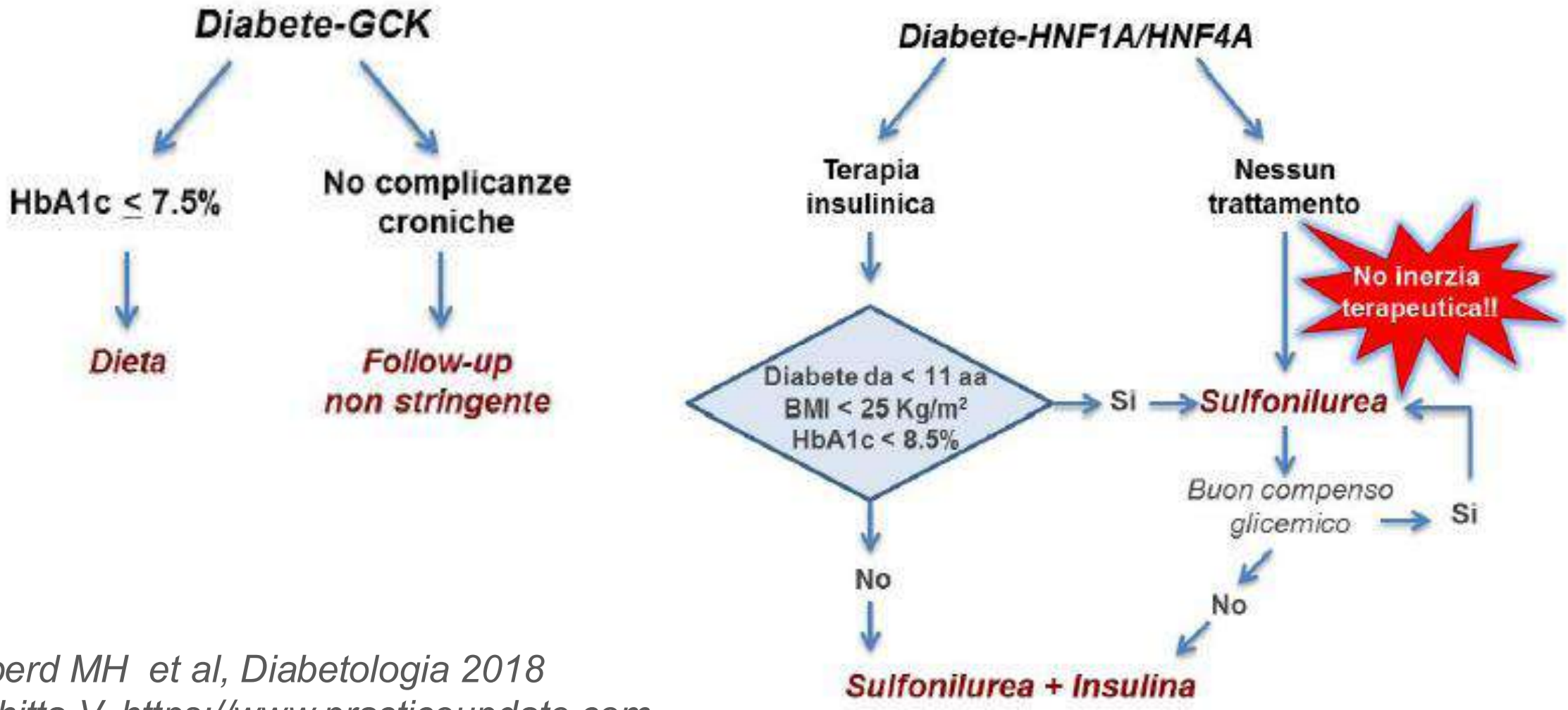
- Early diagnosis and no inertia in starting sulfonylurea is recommended
- Sulfonylurea is the treatment of choice and will be effective (A1c< 7.5%) in more than 1/3 patients.
- Long diabetes duration (11 years), A1c > 8.5% and BMI > 25 Kg/m^2 at genetic testing predict sulfonylurea failure (A1c > 7.5%)
- In individuals with long disease duration, especially if overweight/obese and with high HbA1c levels, sulfonylurea should be given in addition to pre-existing treatments

Sheperd MH et al, Diabetologia 2018
Trischitta V, https://www.practiceupdate.com

Sulphonylurea Transfer

- This approach would be appropriate for patients with a confirmed mutation in HNF1A or HNF4A.
- The patient should be advised this is a ‘trial’ off insulin and if unsuccessful, insulin will need to be recommenced. As HNF1A is progressive, insulin treatment is likely to be required again in the future.
- Transfer off insulin is likely to be most successful in younger patients
- Transfer from insulin to sulphonylureas:
  - Insulin should be stopped and Gliclazide 40mg commenced (20mg Gliclazied could be the starting dose for slim adolescents and 80mg Gliclazide could be the starting dose for those who have had diabetes >20 years).
  - The dose should be increased as necessary. Patients with HNF1A who have transferred from insulin successfully to date are currently managed on between **20mg and 320mg Gliclazide.**

Management of the most common MODY subtypes: a good example of precision medicine



Sheperd MH et al, Diabetologia 2018
Trischitta V, https://www.practiceupdate.com

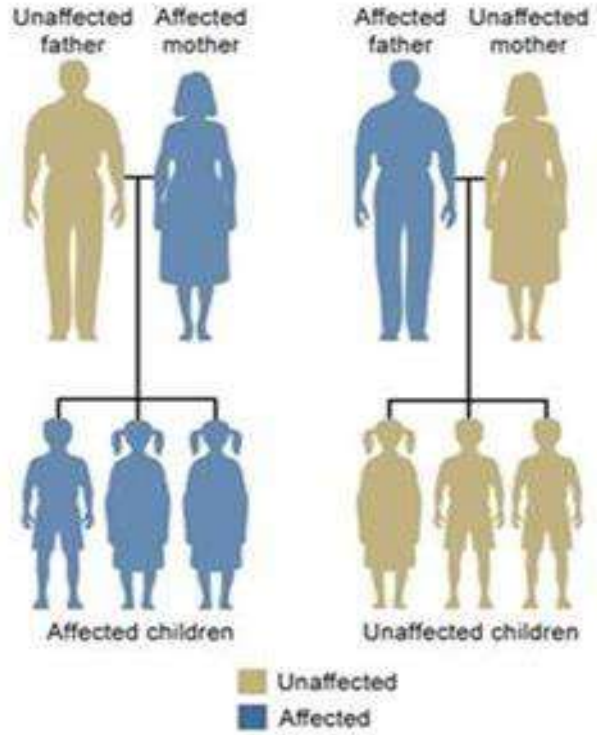
Diabete Monogenico

Un gruppo eterogeneo di disordini dovuti a
mutazioni in singoli geni
coinvolti nell'omeostasi del glucosio.

- Diabete mitocondriale
- Diabete neonatale (eventualmente sindromico)
- Maturity Onset Diabetes of the Young (MODY)

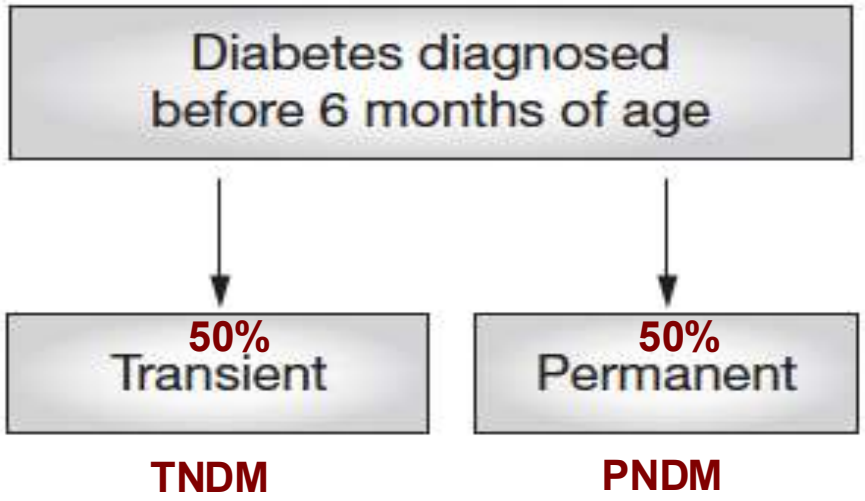
Diabete mitocondriale

- Diabete causato da mutazioni nel DNA mitocondriale
- Eredità mitocondriale, via materna
- Prevalenza: 0-8%
- La forma principale è rappresentata dalla "Maternally Inherited Diabetes and Deafness" **MIDD**, diagnosticata nella II decade di vita.
- La maggior parte dei casi è ascrivibile alla mutazione del DNA mitocondriale **A3243G**
- E' caratterizzata da progressiva perdita della funzione beta-cellulare, fino all'insulino-dipendenza
- Età media 38 anni, penetranza 100%



Neonatal diabetes mellitus

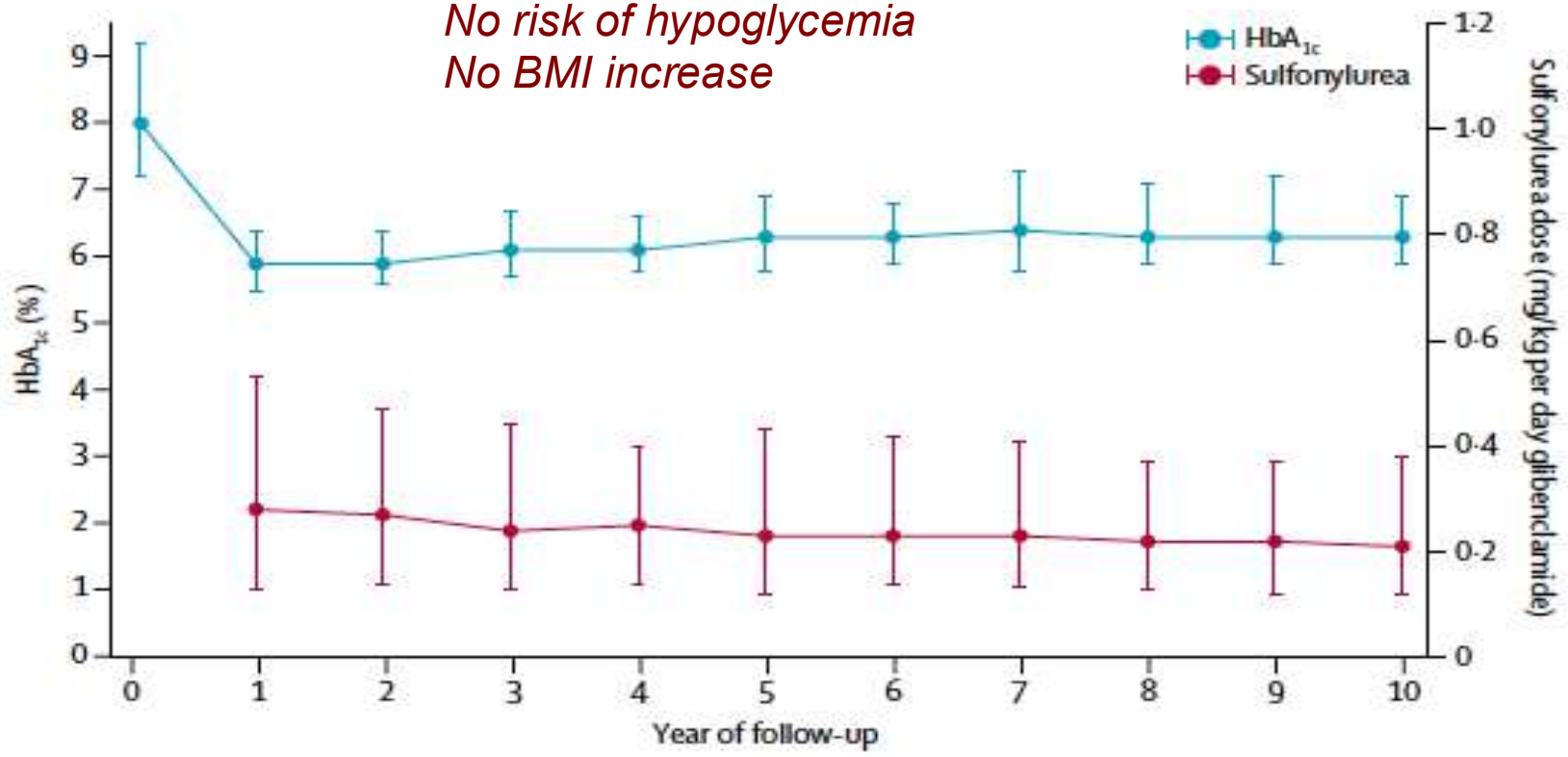
Prevalenza
1/300.000 nati vivi



Diabetes due to *KCNJ11* mutations: a perfect (and unique) example of pharmacogenetics

Closure K_{ATP} channel
K^+ efflux
Membrane depolarization
Ca^+ influx
Insulin secretion

No risk of hypoglycemia
No BMI increase



Bowman P et al, Lancet Diabetes Endocrinol 2018

Perchè è importante fare il test genetico diagnostico in caso di sospetto Diabete Monogenico

1. Pone diagnosi certa di Diabete Monogenico (a differenza di quanto possa fare la clinica, soprattutto nei casi sporadici) e ne definisce il sottotipo
2. Permette di definire la prognosi e ottimizzare lo screening/prevenzione delle complicanze croniche
3. Permette di estendere lo screening ai familiari ancora asintomatici per identificare precocemente i soggetti affetti e quelli a rischio
4. Ma soprattutto, offre la possibilità di individualizzare il trattamento evitando, incongrue terapie

Raccomandazioni su chi testare per diabete monogenico

1. Tutti i pazienti con diagnosi di **diabete prima dei 6 mesi** di età dovrebbero essere testati per le forme monogeniche di diabete neonatale con Whole Exome Sequencing (WES). **A**
2. Tutti i pazienti con **diagnosi tra i 6 e i 12 mesi** dovrebbero essere testati per le forme monogeniche di diabete neonatale con WES. Non vi è alcuna evidenza di una causa monogenica tale da giustificare direttamente test genetici nei pazienti con diagnosi tra i **12 e i 24 mesi. B**
3. Le donne con **diabete gestazionale** e glicemia a digiuno superiore a **100 mg/dl, in assenza di obesità**, dovrebbero essere testate per **etiologia GCK. B**
4. Le persone con **iperglicemia lieve persistente** (**HbA1c 38–62 mmol/mol** o glicemia a digiuno **100–140 mg/dl**) a qualsiasi età, **in assenza di obesità**, dovrebbero essere testate per **Diabete Monogenico. A**
5. Le persone **non obese** con età inferiore a **30 anni** che siano **negative agli autoanticorpi** e/o che abbiano **livelli di C-peptide conservati**, dovrebbero essere testate per **diabete monogenico** con WES.

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MISSIONE 6 - SALUTE

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