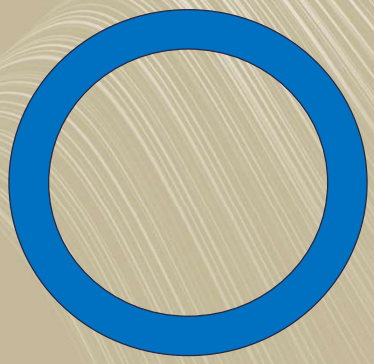
OPTOMETRY WA WAVE CONFERENCE 2025

DIABETES: MORE THAN 1 OR 2

The blue circle is the universal symbol for diabetes.
United Nations Resolution 61/225



Greg Ong MBBS PhD FRACP

Department of Endocrinology and Diabetes, Fiona Stanley Hospital
Diabetes WA

1

DISCLOSURES

Honoraria and Educational grants:

AstraZeneca
Eli Lilly & Co.
Novo Nordisk

2

LEARNING OBJECTIVES

1.Appreciate the pathophysiology of different causes of diabetes and their classification

2.Understand the clinical importance of appropriate aetiological classification of diabetes

3

AGENDA

What is diabetes?

How does diabetes mellitus occur?

Why is diabetes mellitus important?

4

AGENDA

What **is diabetes?**

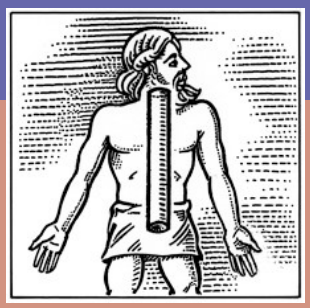
How does diabetes mellitus occur?

Why is diabetes mellitus important?

5

ΔΙΑΒΑΙΝΩ *diabaino*

Demetrius of Apameia (c.150BC)



Ionic language term - "to pass or run through," as in a

siphon

Aretaeus of Cappadocia (c.AD150)

The patient never stops making water, but the flow is incessant, as if from the opening of aqueducts…

Hence, the disease appears to me to have got the name diabetes (siphon), because the fluid does not remain in the body, but uses the man's body as a ladder, whereby to leave it.

HORMONES 2012, 11(1):109-113
AM J KID DIS 2010;56:1175

6

Sweet Honey

John Rollo (1797) added ***mellitus*** *(honey)* to diabetes as a descriptor

XXVII. *Experiments and Obſervations on the Urine in a* Diabetes, *by* Matthew Dobſon, *M. D. of* Liverpool; *communicated by Dr.* Fothergill.

SOME authors, eſpecially the Engliſh, have remarked, that the urine in the diabetes is ſweet. Others, on the contrary, deny the exiſtence of this quality, and conſequently exclude it from being a characteriſtic of the diſeaſe. So far as my own experience has extended, and I have met with nine perſons who were afflicted with the diabetes, the urine has always been ſweet in a greater or leſs degree, and particularly ſo in the caſe of the following patient.

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DIABETES

Manneken-Pis (Brussels)

On the other hand, a learned and justly celebrated professor, the very ingenious [William Cullen (1710-1790)], assures me, that he has met some cases of the diabetes, in which the urine was not sweet, agreeable to what has been observed by foreign writers

Matthew Dobson (1732-1784)

AM J KID DIS 2010;56:1175

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DIABETES

EXCESS URINATION
EXCESS THIRST
DEHYDRATION

MELLITUS

INSIPIDUS

9

DIABETES

EXCESS URINATION
EXCESS THIRST
DEHYDRATION

METABOLIC

NEUROHORMONAL

Radiopedia

MELLITUS

INSIPIDUS

10

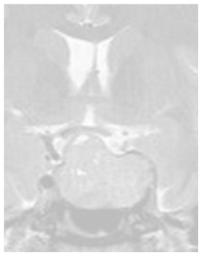
DIABETES

EXCESS URINATION
EXCESS THIRST
DEHYDRATION

METABOLIC

MELLITUS

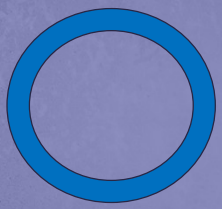
NEUROHORMONAL



INSIPIDUS

11

AGENDA



What is diabetes?

How does diabetes mellitus occur?

Why is diabetes mellitus important?

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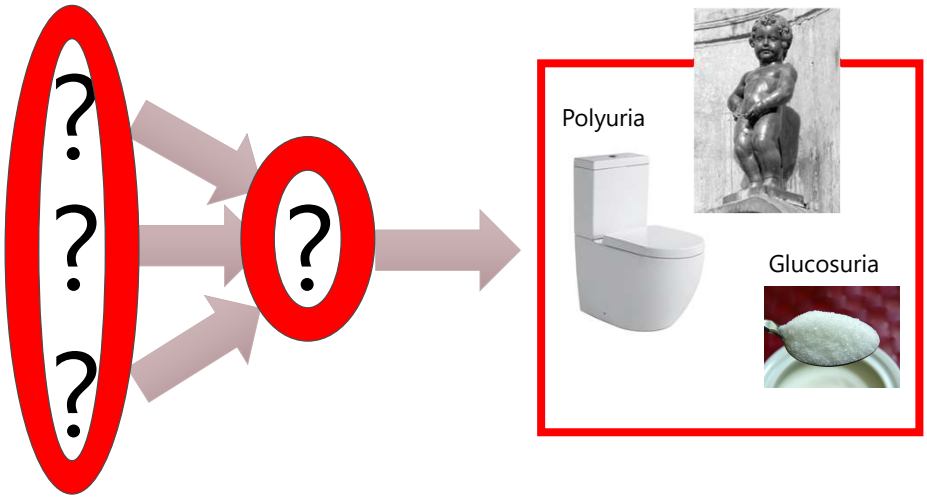
Diabetes MELLITUS: HOW?



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Polyuria

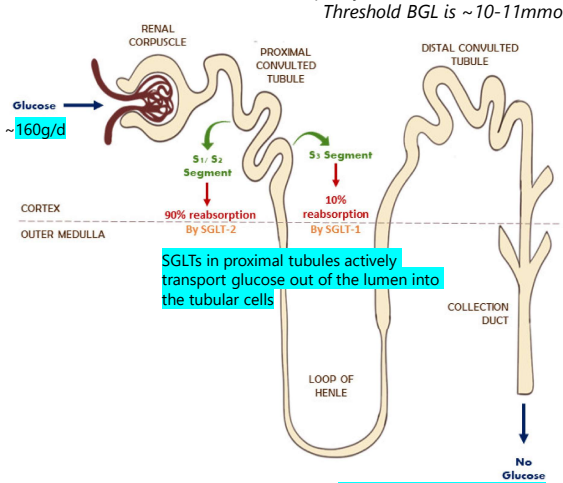
Physiological Role of the Kidney

- Contribute to maintaining:
  - intravascular volume
  - electrolytes
  - acid-base balance
  - glucose homeostasis
- How?
  - Filtration
  - Secretion
  - Selective reabsorption

Glucose appears in urine when tubular resorption capacity is exceeded.

- *Basal capacity is 19.5mmol/min*
- *Can increase capacity to max of ~23.3mmol/min*

Threshold BGL is ~10-11mmol/L

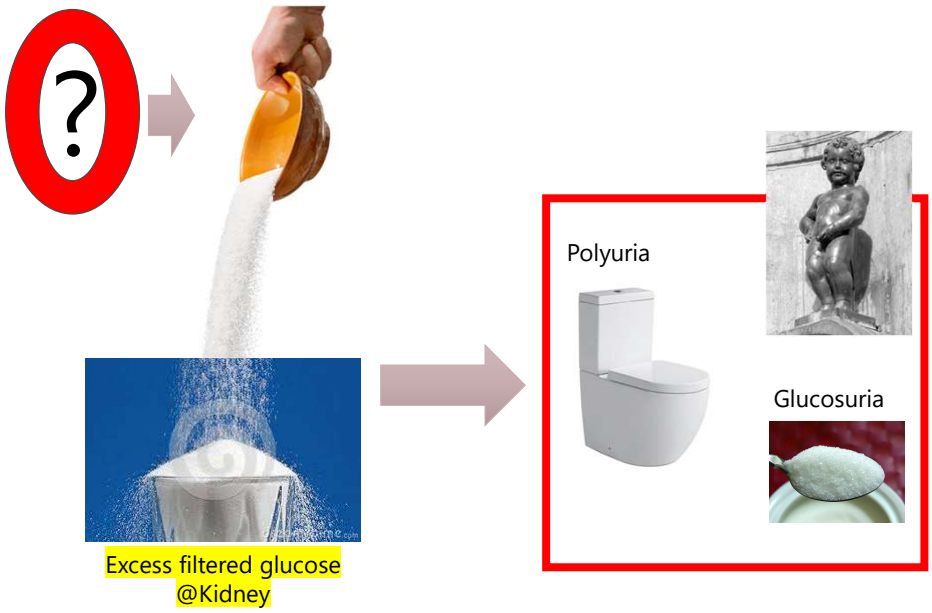


SGLTs in proximal tubules actively transport glucose out of the lumen into the tubular cells

<<1% of filtered load in urine (~0.25mg/mL)

Washington University
Kidney International 2011; 79(S120):S1
Int. J. Mol. Sci. **2021**, *22*(23), 12677

14



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Insulin is a master regulator of metabolism.

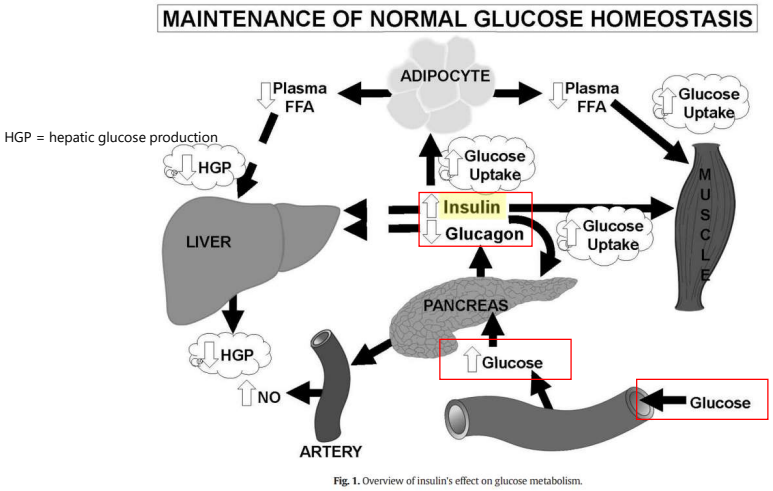

Fig. 1. Overview of insulin's effect on glucose metabolism.

Metabolism Clinical and Experimental 129 (2022) 155142

16

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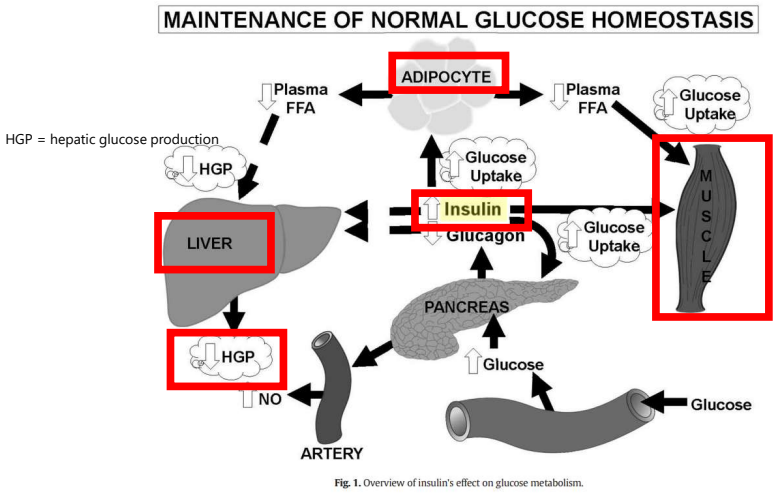

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17

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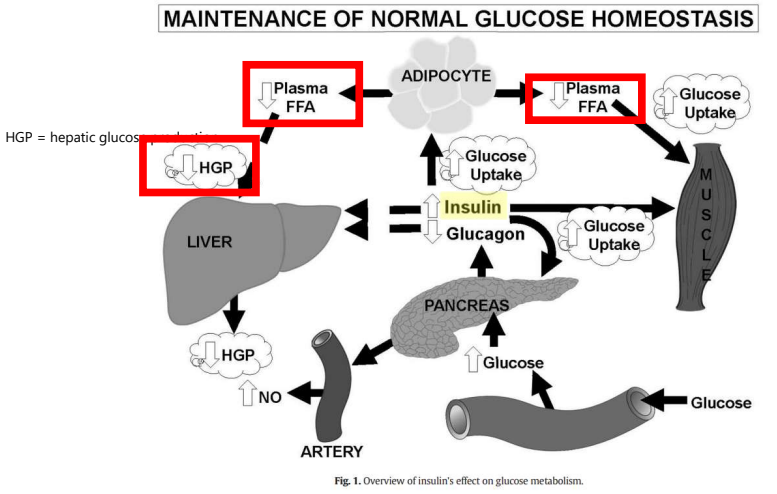

Fig. 1. Overview of insulin's effect on glucose metabolism.

Metabolism Clinical and Experimental 129 (2022) 155142

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Diabetes MELLITUS: HOW?

Defect in Insulin Production/Secretion
Defect in Insulin Action
Defect in Insulin

Excess glucose in blood

Clinical Syndrome

Excess filtered glucose@Kidney

Tubular Defect

Polyuria

Glucosuria

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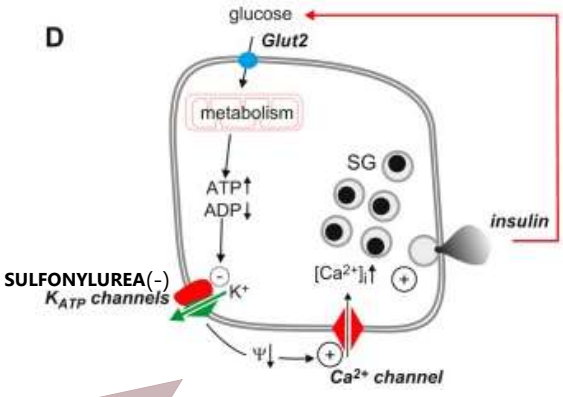
Beta-Islet Cells and Insulin Release



KATP (ATP-sensitive potassium) channel comprises:
4 x Kir6.2 subunits + 1 x SUR1 (ATP/ADP sensing) regulatory unit.
- High ATP/ADP closes channel → No K efflux → depolarisation
- Voltage dependent Ca channels open → calcium influx

Physiol Rev. 2018 Jan 1; 98(1): 117–214.
Diabetes Obes Metab. 2013 Jan; 15(1): 15–27.
Nutr Rev. 2010 May; 68(5): 270–279.

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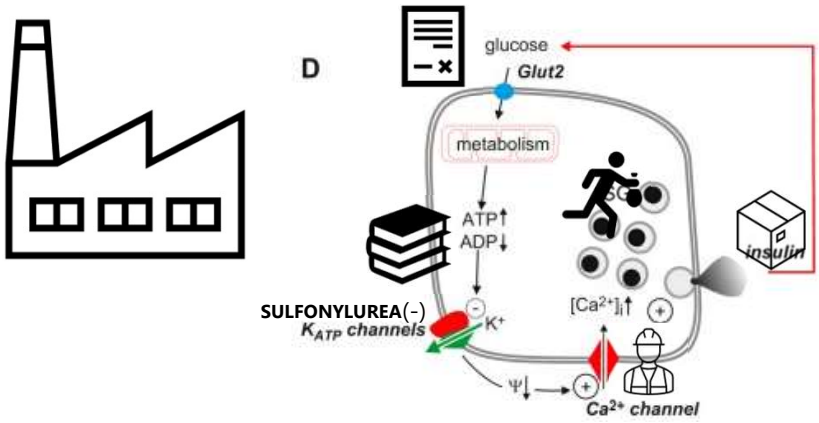
Beta-Islet Cells and Insulin Release



Physiol Rev. 2018 Jan 1; 98(1): 117–214.
Diabetes Obes Metab. 2013 Jan; 15(1): 15–27.
Nutr Rev. 2010 May; 68(5): 270–279.

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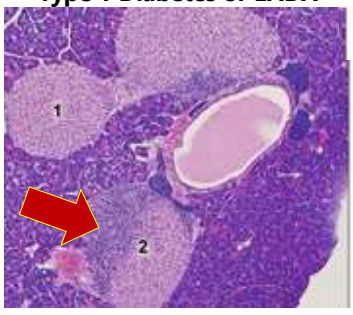
Defect in insulin production

Destruction of beta-islet cells will result in absolute insulin deficiency

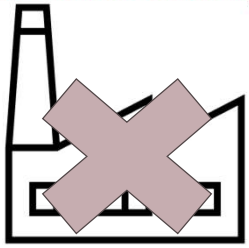
Type

1

Autoimmune attack =
Type 1 Diabetes or LADA



John Hopkins University



Type

3c

Any generally destructive process

Pancreatitis, cancer, surgery, cystic fibrosis, iron deposition

Academic Forensic Pathology, 06 Jun 2018, 8(2):311-323

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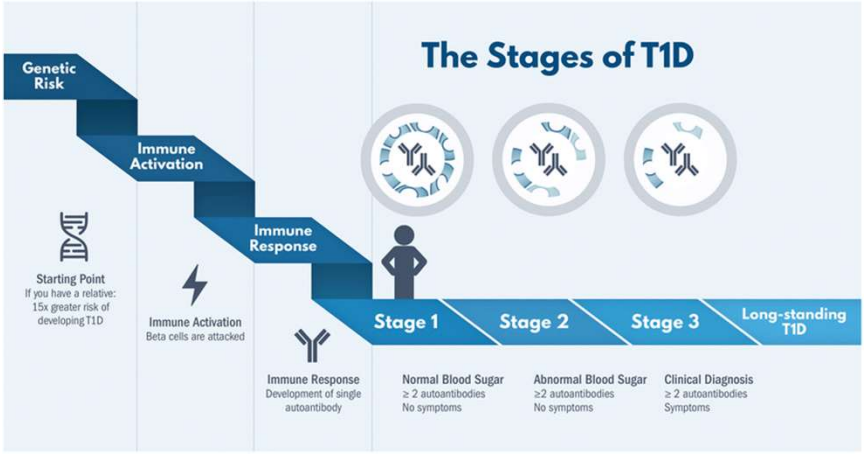
Type 1 Diabetes mellitus

- Autoimmune-mediated (95%) or idiopathic (5%) beta-islet cell specific destruction.



Diabetes Care 2015;38(6):979–988
Curr Diab Rep (2017) 17: 119
Curr Diabetes Rev. 2017 ; 13(3): 322–329
Curr Diab Rep. 2013 doi:10.1007/s11892-013-0405-9.

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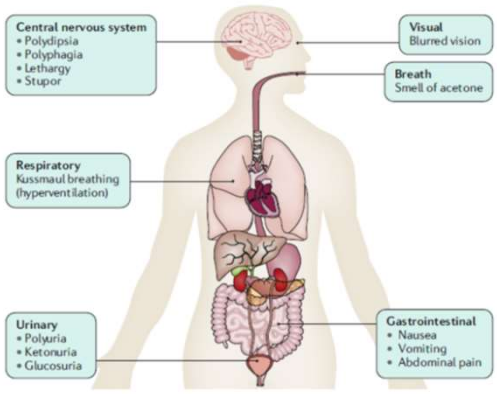
Total System Failure: *No insulin or no insulin effect*



the patient is **short-lived**…

for the **melting is rapid, the death speedy**.

Moreover, **life is disgusting and painful**; thirst, unquenchable; excessive drinking, which, however, is disproportionate to the large quantity of urine, for more urine is passed; and **one cannot stop them either from drinking or making water**.

they are **affected with nausea, restlessness, and a burning thirst**; and **at no distant term they expire.**

Aretaeus of Cappadocia (c.AD150)

HORMONES 2012, 11(1):109-113
Nature Reviews Disease Primers 2020; 6:40

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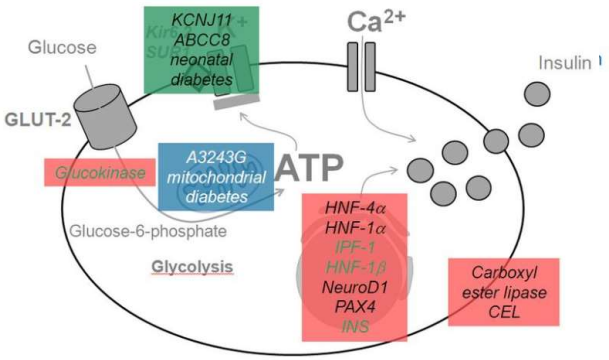
Defect in insulin secretion

A single gene mutation can impair any of the pathways controlling glucose sensing or secretion

- 2-5% of all cases of diabetes may have a monogenic cause.
- "MODY" (maturity onset diabetes of the young)
  - heterogeneous set of conditions due to mutations in glucose sensing or transcription factors. *Strong family history usually present.*
- Mitochondrial Diabetes (mutated mtDNA)
  - Typically occurs as part of a syndrome (e.g. deafness, ocular problems, lactic acidosis, cardiac, stroke-like episodes, myopathies, encephalopathies)
- Neonatal (present from birth)
  - defective pancreatic organogenesis or key functional elements of beta-cell function



NEJM 2001; 345: 971
Swiss Med Wkly. 2012;142:w13690

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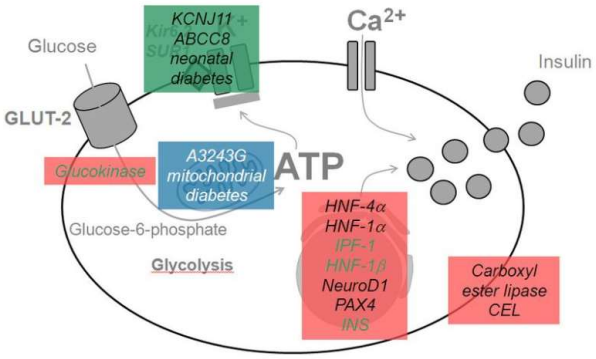
MODY

SUSPICIOUS CLINICAL FEATURES

- **Not classically T2DM:**
  - Early onset (typically <25yo)
  - Slimmer than expected for Type 2 diabetes
  - Strong family history (**autosomal dominant**)
  - Excessive response to sulfonylurea treatment
  - No signs of insulin resistance, including reasonably normal lipid profile
- **Not classically T1DM:**
  - No autoantibodies
  - Persistent internal insulin production
  - No history of diabetic ketoacidosis
- **Atypical features:**
  - Organ malformations
  - Neonatally abnormal glucose (high or low)



EXETER DIABETES

MODY Probability Calculator

>25% post test probability → genetic testing

J Clin Endocrinol Metabol 2021;106:237

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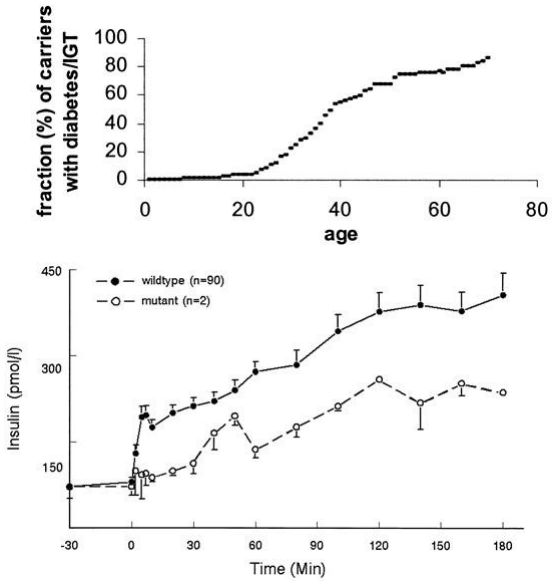
Mitochondrial Diabetes

SUSPICIOUS CLINICAL FEATURES

- Early Onset (Age<25)
- Maternally inherited A3243G mutation
- Altered lactate production → hepatic gluconeogenesis
- Progressive failure of insulin secretion rather than insulin resistance.
  - Mitochondrial dysfunction → beta cell death
- Specific features
  - Sensorineural hearing loss (usually before diabetes onset)
  - Unusual retinal pigmentation
  - Myopathy
  - Encephalopathy
    - Stroke-like symptoms
    - Epilepsy
  - Lactic acidosis (MUST AVOID METFORMIN)



Diabetes 2004;53(suppl_1):S103–S109

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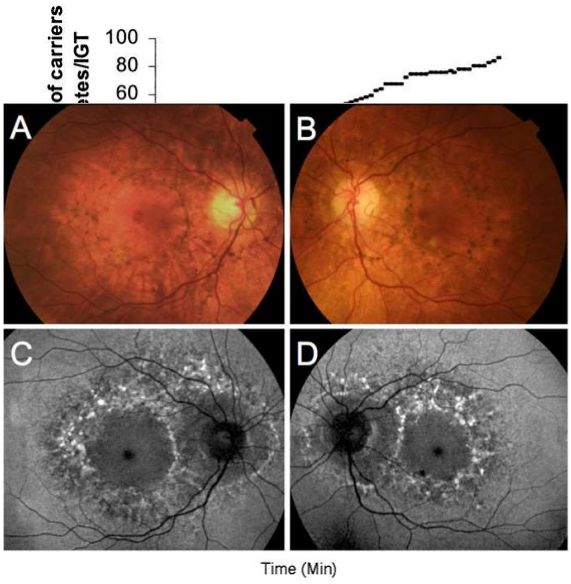

BMC Ophthalmology 2014;14:77
Diabetes 2004;53(suppl_1):S103–S109

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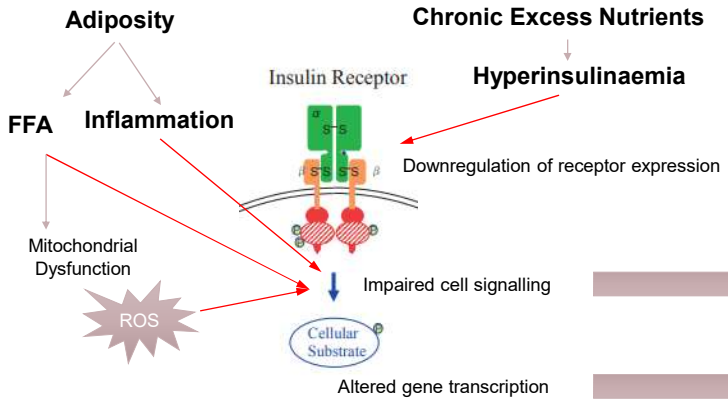
Defect in insulin signalling: Type 2 Diabetes mellitus

(common)



Diabetologia (2021) 64:994–1006
Molecular Metabolism 2021; doi:10.1016/j.molmet.2021.101304

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AGENDA

What is diabetes?

How does diabetes mellitus occur?

Why is diabetes mellitus important?

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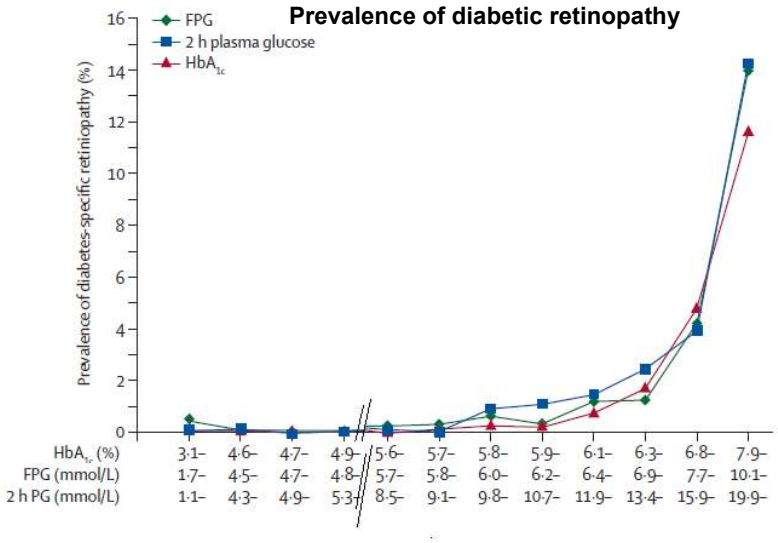
Relationship between markers of glycaemia and microvascular complications



Diabetes Care 2011; 34:145-150.

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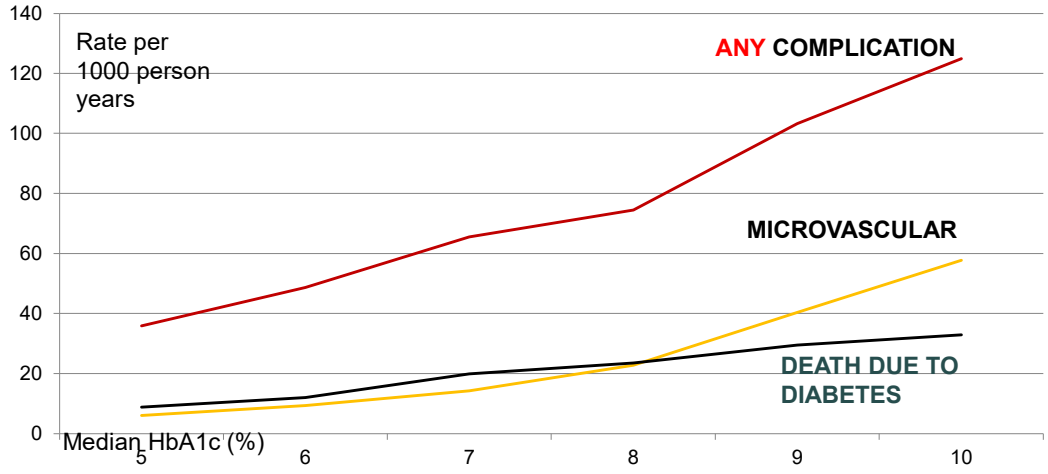
Relationship between glucose and adverse events in Type 2 Diabetes (UKPDS 35)



BMJ. 2000 Aug 12; 321(7258): 405–412

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Summary

Defect in Insulin *(rare)*
Defective secretion of insulin
(MODY, mitochondrial)
Lack of insulin
(commonly T1DM or pancreatic DM)
Defect in Insulin Action
(commonly T2DM)

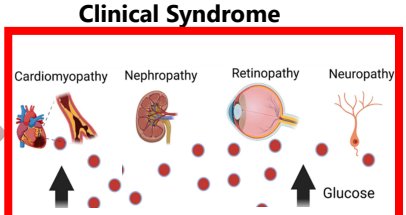
Absolute insulin deficiency or severe defect in the system

Diabetic Ketoacidosis

Excess glucose in blood

Excess filtered glucose@Kidney

Clinical Syndrome



Vascular Disease

Polyuria

Glucosuria

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SUMMARY

Diabetes mellitus is a clinical syndrome of **hyperglycaemia with numerous causes.**

Understanding underlying pathophysiology is important as **clinical risk and treatments are not identical**

Specific clinical features may hint at an unusual form of diabetes.

Awareness is poor in the general clinical community

Multidisciplinary support remains crucial for diabetes care irrespective of cause.

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THANK YOU

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