

**Supplementary information**

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# Models of hyperglycaemia in diabetes mellitus and its complications

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## Supplementary Material

**Supplementary Table 1. Criteria for diagnosis of diabetes<sup>1</sup>.**

| <b>Criteria for Diagnosis</b> | <b>Prediabetes</b>               | <b>Diabetes</b>        |
|-------------------------------|----------------------------------|------------------------|
| <b>HbA1c</b>                  | 5.7 - 6.4%                       | ≥ 6.5%                 |
| <b>Fasting plasma glucose</b> | 100 -125mg/dL<br>(5.6 - 6.9 mM)  | ≥ 126mg/dL<br>(≥7mM)   |
| <b>2-hour plasma glucose</b>  | 140 – 199 mg/dL<br>(7.8 – 11 mM) | ≥ 200mg/dL<br>(11.1mM) |

*Supplementary Table 1 was adapted with permission from ref. 1, American Diabetes Association.*

**Supplementary Table 2. Strengths and limitations of commonly adopted *in vivo* models of diabetes<sup>2</sup>.**

| Model Category                              | Obese                                                                                                                                                                                                                | Non-Obese                                                                                                                                                                                                                                                                                                                                  | Advantage                                                                                                                                                                                                                                                                                           | Disadvantage                                                                                                                                                                                                                                                                                                            |
|---------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Spontaneous/<br/>Genetically-derived</b> | ob/ob mouse<br>db/db mouse<br>KK mouse<br>KK/Ay mouse<br>NZO mouse<br>NONcNZO10 mouse<br>TSOD mouse<br>M16 mouse<br>Zucker fatty rat<br>ZDF rat<br>SHR/N-cp rat<br>JCR/LA-cp rat<br>OLETF rat<br>Obese rhesus monkey | Cohen<br>diabetic rats<br>GK rat<br>Torri rat<br>Non obese<br>C57BL/6<br>Akita mutant mouse<br>ALS/Lt mouse                                                                                                                                                                                                                                | Type 2 diabetes in these animals occurs naturally, influenced by genetic factors, and mirrors the disease in humans.<br>Consistent genetics and controlled environments make it easier to study the genetic causes of type 2 diabetes.<br>Consistent results and require fewer animals for testing. | Highly inbred, with diabetes mainly caused by single genes, which differs from the complex genetics seen in humans.<br>Costly and hard to obtain for diabetes research.<br>Some, like the db/db mouse, have high mortality rates due to ketosis and require insulin treatment to survive.<br>Requires specialized care. |
| <b>Transgenic/<br/>Knockout</b>             | b3 receptor knockout mouse<br>Uncoupling protein ( <i>Ucp1</i> ) knockout mouse                                                                                                                                      | Transgenic or knock out mice involving genes of insulin, insulin receptor and its components of downstream insulin signaling e.g., IRS-1, IRS-2, GLUT-4, PTP-1B and others.<br><i>Pparg</i> tissue-specific knockout mouse.<br>Glucokinase or <i>Glut2</i> gene knockout mice. Human islet amyloid polypeptide overexpressed rat (HIP rat) | Single gene mutations can be studied in live animals to understand how they affect diabetes.<br>Complex genetic factors in type 2 diabetes can be studied more easily in these models.                                                                                                              | Complex and expensive to develop and maintain.<br>Costly for routine drug screening.                                                                                                                                                                                                                                    |

|                           |                                           |                                   |                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                          |
|---------------------------|-------------------------------------------|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Surgically-induced</b> | VMH lesioned dietary obese                | Partial pancreatectomized animals | Avoid the harmful side effects of chemical diabetes treatments. Mimic human type 2 diabetes by reducing $\beta$ -cell mass.                                                                                                                                                                    | Technically complex. May cause other digestive issues due to pancreas damage. Can disrupt glucagon secretion, leading to poor blood sugar regulation. Mortality rates are higher.                                                                                                                        |
| <b>Chemically-induced</b> | GTG-treated obese mice                    | Low dose ALX or STZ               | Selectively destroys pancreatic $\beta$ -cells, sparing other cell types in the islet such as alpha or delta cells. Residual insulin production allows the animals to survive without long-term insulin treatment. Lower risks of ketosis and death. Generally cheaper and easier to maintain. | Hyperglycemia in these models is due to direct $\beta$ -cell damage, not insulin resistance. Chemically-induced diabetes is often unstable and can reverse, requiring careful monitoring of $\beta$ -cell function. Chemicals can harm other organs besides $\beta$ -cells. More variability in results. |
| <b>Diet-induced</b>       | Sand rat<br>C57/BL6J mouse<br>Spiny mouse |                                   | They develop obesity-related diabetes, similar to "diabesity" in humans. Avoids harming other vital organs.                                                                                                                                                                                    | Dietary treatments in some models take a long time to work. Normal animals do not develop full diabetes from diet alone, making them unsuitable for testing certain diabetes drugs.                                                                                                                      |

**Abbreviations:** ALX: alloxan; STZ: streptozotocin; GTG: Gold thioglucose; VMH: Ventromedial hypothalamic; GK: Goto-Kawazaki.

## Supplementary References

1. ElSayed, N. A. *et al.* 2. Classification and Diagnosis of Diabetes: Standards of Care in Diabetes—2023. *Diabetes Care* **46**, S19–S40 (2022).
2. Srinivasan, K. & Poduri, R. Animal models in type 2 diabetes research: an overview. *Indian J. Med. Res.* **125**, 451–472 (2007).