# Backgrounder

## The Role of Beta Cells in Diabetes

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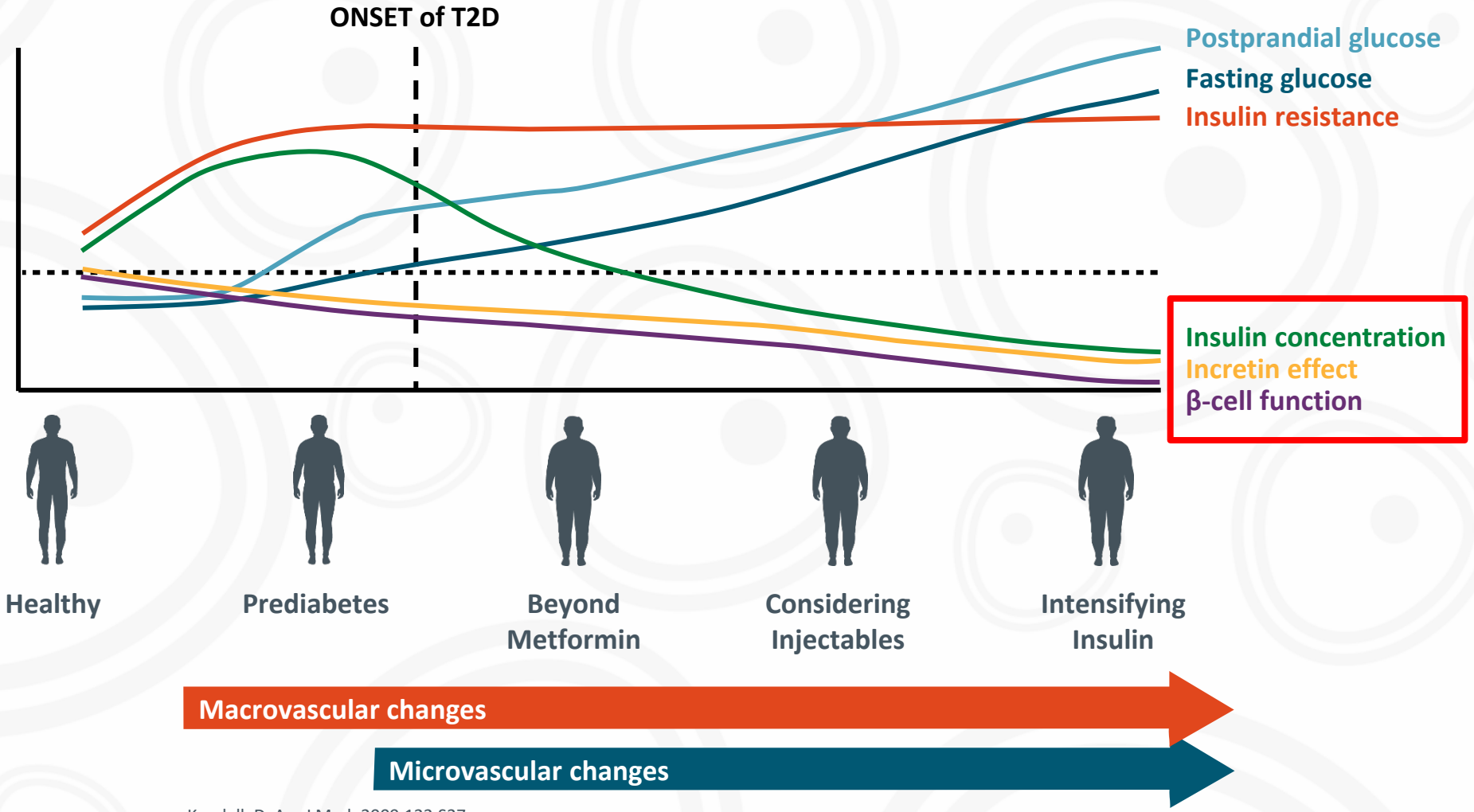
# What are Beta Cells?

**Beta Cells**

- The pancreas makes an important hormone: insulin. We all need insulin to help our bodies take glucose (sugar) we get from food and use it as energy. The cells that produce this hormone, insulin, are our beta cells.
- Beta cells unfortunately do not reproduce easily. Beta cells actually get exhausted over time, they die out and lose their function. We then end up with too little insulin production and too much glucose in our blood. That will cause side effects over time and depending on the severity will lead to diabetes.
- This condition can cause serious health problems and damage vital organs. Most people with diabetes have a shorter expectancy than people without the disease.

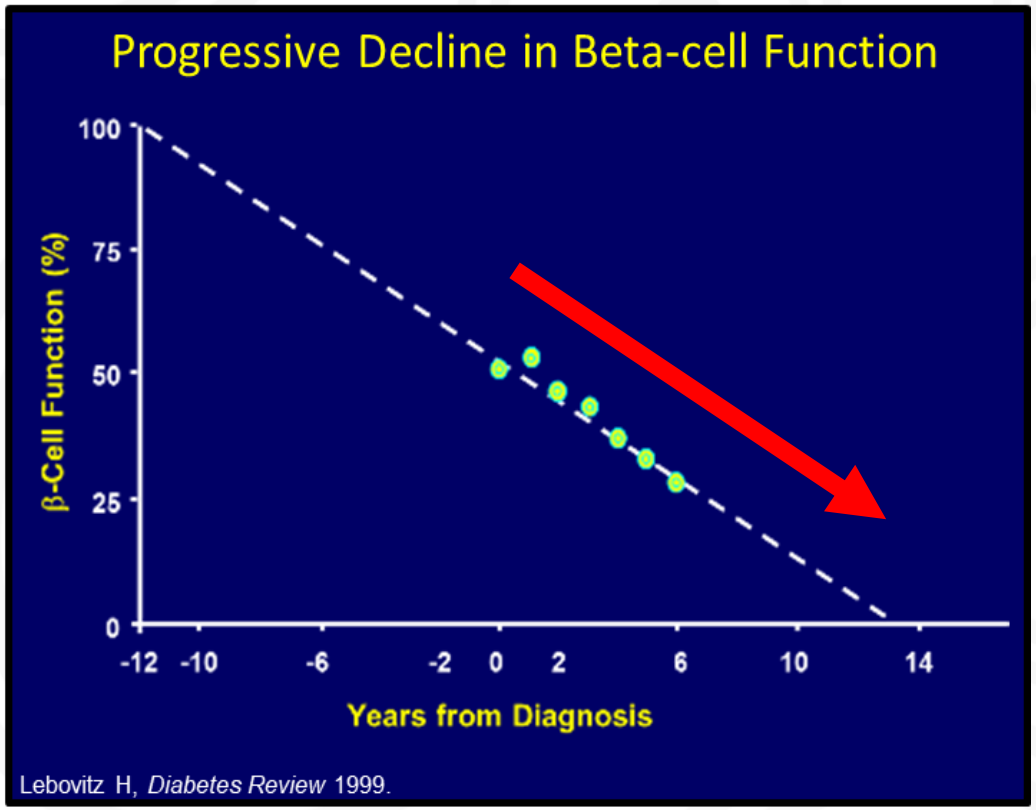
# Natural History of Types 2 Diabetes – A Progressive Decline in Beta Cell Function

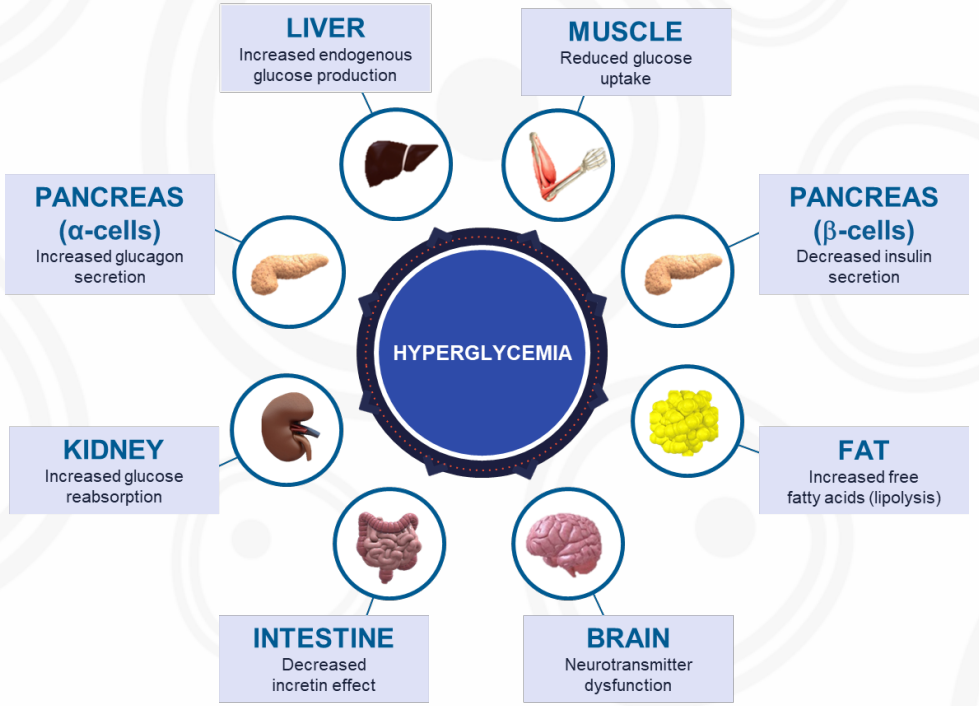



Kendall, D. Am J Med. 2009;122:S37.

# None of Today's T2D Agents Address the Root Cause of T2D

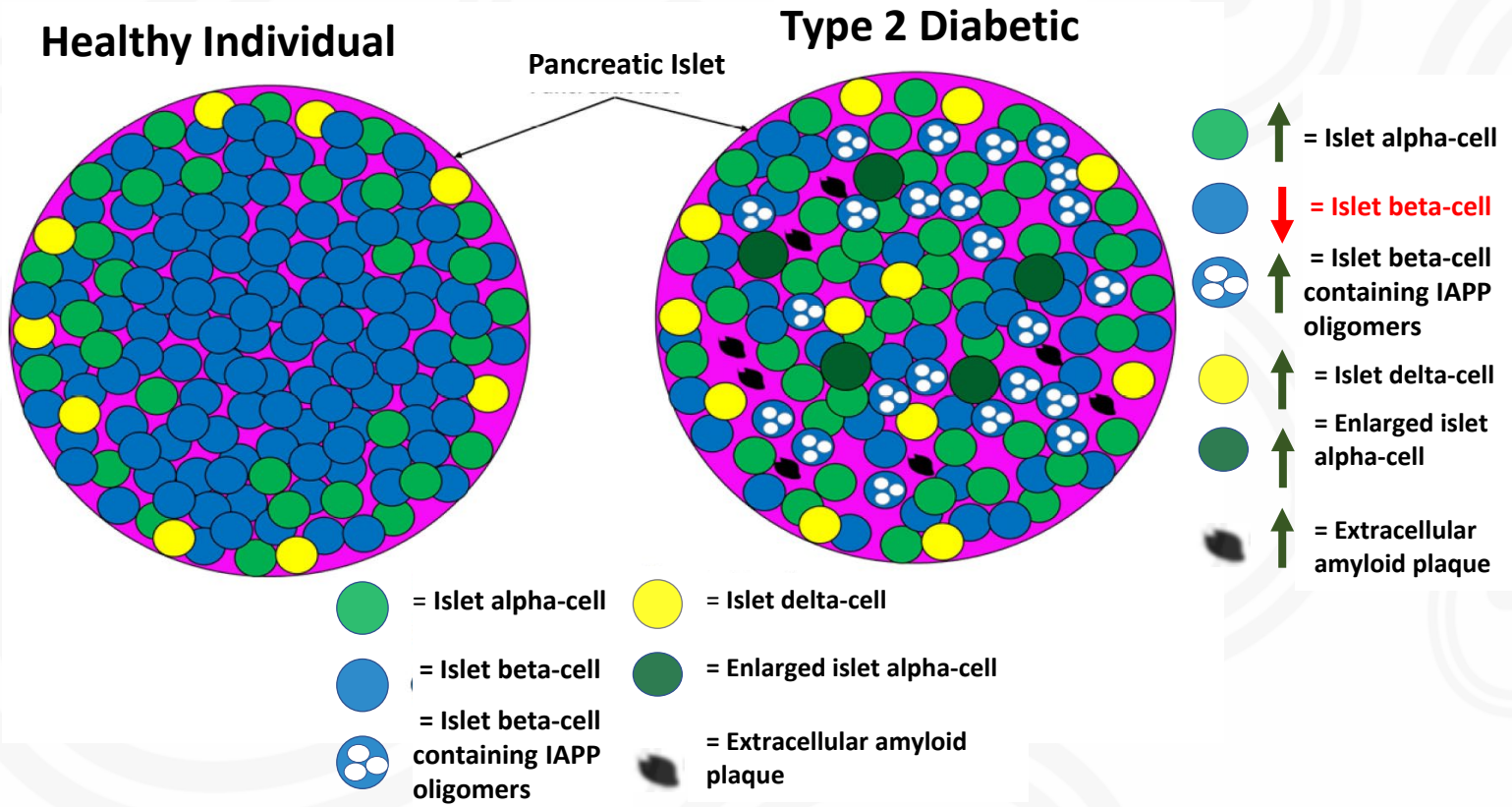
## - The Progressive Decline in Beta-Cell Mass and Function




Adapted from DeFronzo RA. *Diabetes.* 2009;58(4):773-795.

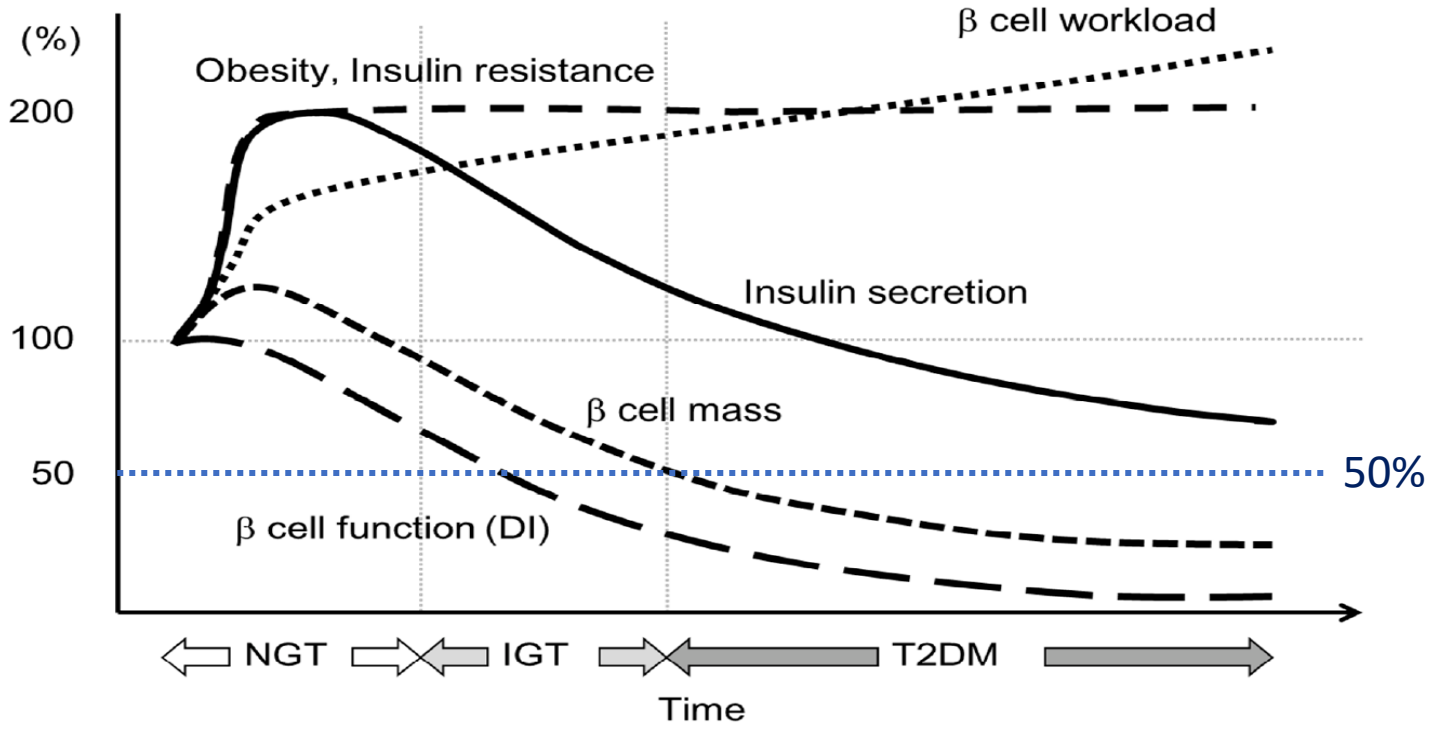
# Types 2 Diabetes Progression Results in Beta Cell Loss




- Beta cell mass is decreased by 50% to 90% in patients with T2D
- Glucose remains uncontrolled and beta cell function & number continues to deteriorate
- Standard of Care agents do not address the depleted pool of beta cells – the root cause of diabetes

*Int. J. Mol. Sci.* **2016**, *17*, 744; doi:10.3390/ijms17050744`

# Loss of Beta Cell Mass Drives the Progression of Type 1 and Type 2 Diabetes




Normal Glucose Tolerance (NGT) followed by Impaired Glucose Tolerance (IGT) followed by Type 2 Diabetes Mellitus (T2DM).
Insulin Resistance leads to an increase in Beta Cell Workload which ultimately leads to Beta Cell Failure and Death and the Progression of Type 2 Diabetes.

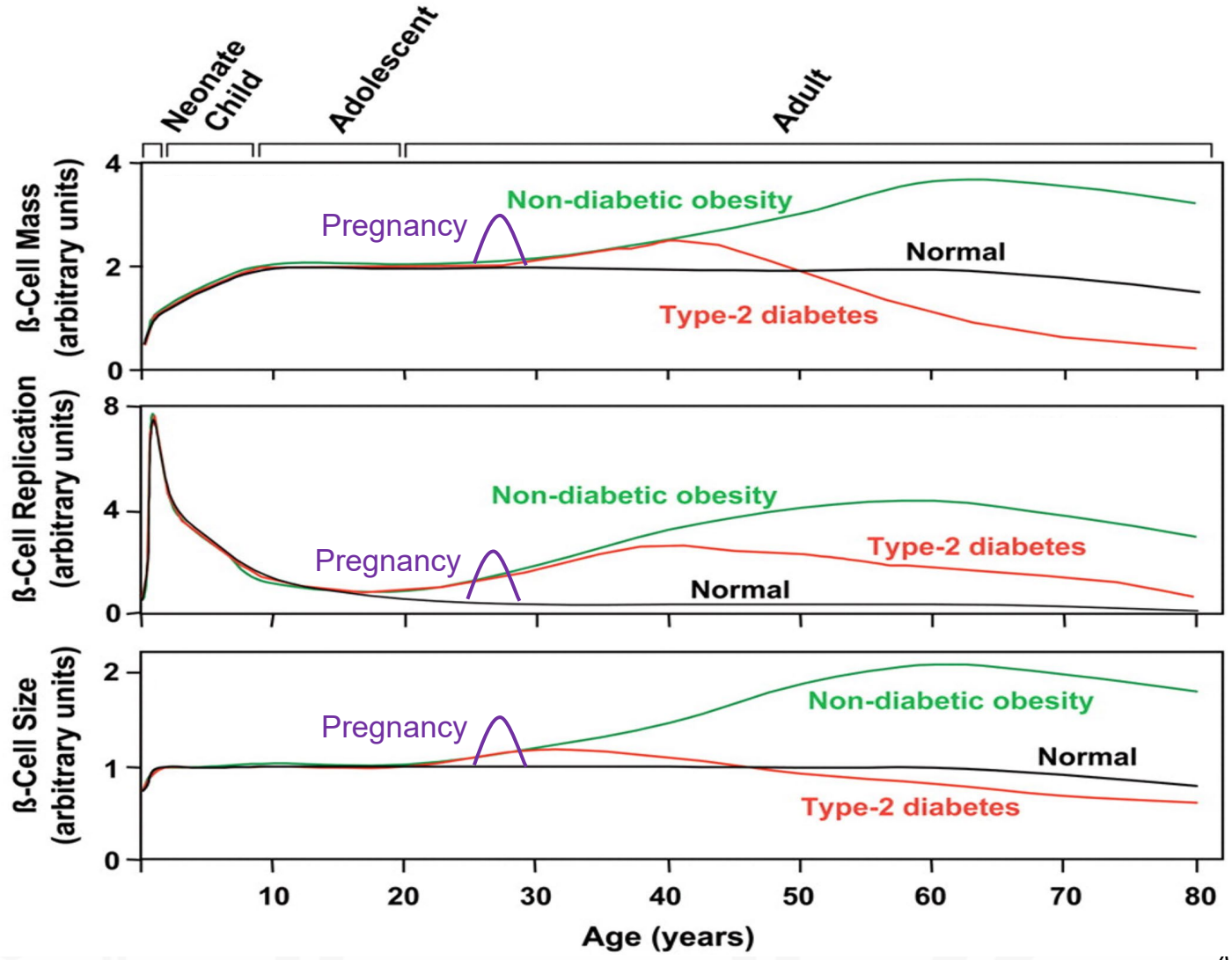
**Int. J. Mol. Sci.* **2016**, *17*, 744; doi:10.3390/ijms17050744

## Concepts of the Pathogenesis of Type 1 and Type 2 Diabetes

| | Type 1 diabetes | Type 2 diabetes |
|---|---|---|
| **Prior Paradigm** | β cell destruction<br>β cell mass ↓↓<br>Insulin secretion ↓↓ | Obesity<br>Insulin resistance<br>Hyperinsulinemia |
| **Current Paradigm** | β cell destruction<br>β cell mass ↓↓<br>Insulin secretion ↓↓ | β cell loss<br>β cell mass ↓<br>Insulin secretion ↓ |
| **Causes** | Autoimmune | Insulin resistance<br>β cell overwork |

**Type 1 and Type 2 Diabetes results in Loss of Beta Cell Mass**

# Beta Cell Compensation in Physiological and Pathophysiological States in Mammals




**β-Cell Mass**

**β-Cell Replication**

**β-Cell Size**

*Adapted from Science 2005*

# Beta Cells Adapt to Metabolic Demands

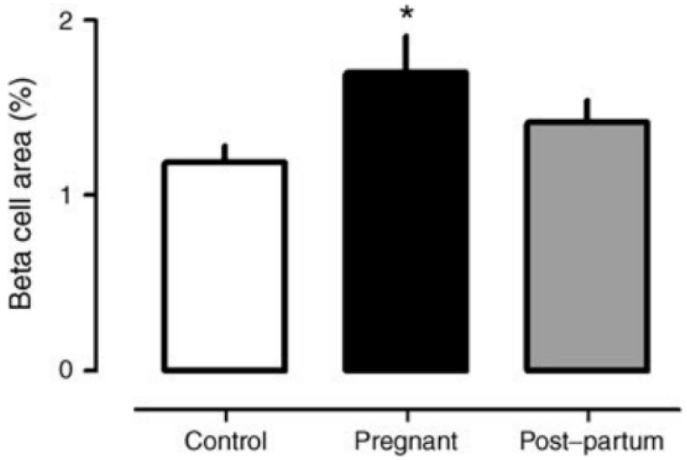
TABLE II

*The endocrine pancreas in non-pregnant and pregnant women*

| | Endocrine tissue (per cent) | β cells (per cent) |
|---|---|---|
| *Non-pregnant women* | | |
| 1 | 1·6 | 75 |
| 2 | 1·5 | 68 |
| 3 | 2·0 | 78 |
| 4 | 1·4 | 69 |
| 5 | 1·3 | 74 |
| Mean ± SD | 1·56 ± 0·27 | 72·8 ± 4·2 |
| *Pregnant women* | | |
| 1 | 3·2 | 81 |
| 2 | 3·1 | 83 |
| 3 | 2·9 | 79 |
| 4 | 3·6 | 84 |
| 5 | 3·7 | 83 |
| Mean ± SD | 3·3 ± 0·3 | 82·0 ± 1·8 |
| P | <0·001 | <0·005 |

**Assche and Aerts.**
***British Journal of Obstetrics and Gynaecology*. 1978**

"This quantitative morphological study shows a **marked enlargement of the islets of Langerhans in pregnant women**."
*F. A. Van Assche et al. British Jornal of Obstetrics and Gynaecology, 1978 November*




**Butler et al. Diabetologia. 2010**


British Journal of Obstetrics and Gynaecology
November 1978. Vol. 85. pp 818–820

A MORPHOLOGICAL STUDY OF THE ENDOCRINE PANCREAS IN HUMAN PREGNANCY

BY

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**Summary**

During human pregnancy an enlargement of the islets of Langerhans and hyperplasia of the β cells is present. These morphological changes indicate that the endocrine pancreas is able to adapt to the metabolic changes of pregnancy.

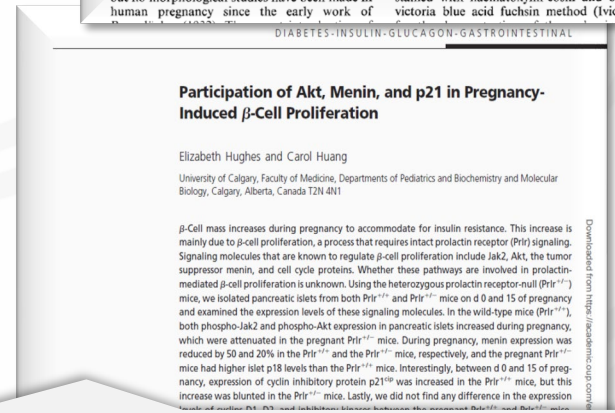
THERE is evidence that in normal human pregnancy hyperinsulinism develops (Spellacy and Goetz, 1963; Spellacy, 1971; Nitzan *et al*, 1975), perhaps as a response to the increased anabolic requirements of the developing conceptus (Nitzan *et al*, 1975; Saudek *et al*, 1975). In the pregnant rat it has been shown that the number of insulin producing β cells is increased and that the islets have an increased sensitivity to secretagogues (Green and Taylor, 1972; Van Assche, 1974; Aerts and Van Assche, 1975), but no morphological studies have been made in human pregnancy since the early work of

five women of comparable age, who died in car accidents and were not using oral contraceptives, were used as controls.

A sixth case is included, for interest, of a woman who died of post-molar choriocarcinoma.

The clinical data are shown in Table I. A biopsy of the pancreatic tail was taken within 24 hours of death and fixed in Bouin's solution for 48 hours.

Sections of 3 μm thickness were made from paraffin embedded tissue. The slides were stained with haematoxylin-eosin and by Ivic's victoria blue acid fuchsin method (Ivic, 1959)


DIABETES-INSULIN-GLUCAGON-GASTROINTESTINAL

**Participation of Akt, Menin, and p21 in Pregnancy-Induced β-Cell Proliferation**

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University of Calgary, Faculty of Medicine, Departments of Pediatrics and Biochemistry and Molecular Biology, Calgary, Alberta, Canada T2N 4N1

β-Cell mass increases during pregnancy to accommodate for insulin resistance. This increase is mainly due to β-cell proliferation, a process that requires intact prolactin receptor (Prlr) signaling. Signaling molecules that are known to regulate β-cell proliferation include Jak2, Akt, the tumor suppressor menin, and cell cycle proteins. Whether these pathways are involved in prolactin-mediated β-cell proliferation is unknown. Using the heterozygous prolactin receptor-null ($Prlr^{+/-}$) mice, we isolated pancreatic islets from both $Prlr^{+/+}$ and $Prlr^{+/-}$ mice on d 0 and 15 of pregnancy and examined the expression levels of these signaling molecules. In the wild-type mice ($Prlr^{+/+}$), both phospho-Jak2 and phospho-Akt expression in pancreatic islets increased during pregnancy, which were attenuated in the pregnant $Prlr^{+/-}$ mice. During pregnancy, menin expression was reduced by 50 and 20% in the $Prlr^{+/+}$ and the $Prlr^{+/-}$ mice, respectively, and the pregnant $Prlr^{+/-}$ mice had higher islet p18 levels than the $Prlr^{+/+}$ mice. Interestingly, between d 0 and 15 of pregnancy, expression of cyclin inhibitory protein $p21^{Cip}$ was increased in the $Prlr^{+/+}$ mice, but this increase was blunted in the $Prlr^{+/-}$ mice. Lastly, we did not find any difference in the expression

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"We conclude that **during pregnancy**, placental hormones act through the prolactin receptor to increase beta cell mass by **up regulating beta cell proliferation** by engaging Jak2, Akt, **menin**/p18, and p21."
*Hughs et al. Endocrinology, March 2011, 152(3):847–855*

# The Role of Beta Cells in Diabetes - Literature References

# Relevant Literature

**Type 2 diabetes-a matter of beta-cell life and death?** Christopher J. Rhodes Science – 2005 Jan 21, 307(5708):380-4. doi: 10.1126/science.1104345. PMID: 15662003.
**Diabetes Invest_Beta-cell failure in diabetes – Common susceptibility and mechanisms shared between type 1 and type 2 diabetes 1** Hiroshi Ikegami, Naru Babaya, and Shinsuke Noso Journal of Diabetes Investigation – 2021 Sep; 12(9): 1526–1539. Published online 2021 Jun 16. doi: 10.1111/jdi.13576
**Not control but conquest – Strategies for the remission of Type 2 diabetes mellitus** Jinyoung Kim, Hyuk-Sang Kwon Diabetes and Metabolism Journal – 2022 Mar;46(2):165-180. doi: 10.4093/dmj.2021.0377.
**Increased beta-cell proliferation before immune cell invasion prevents progression of Type 1 diabetes** Dirice E et al., 2019 Nature Metabolism Nat Metab – 2019 May; 1(5): 509–518. Published online 2019 May 6. doi: 10.1038/s42255-019-0061-8
**Importance of beta cell mass for glycaemic control in people with Type 1 diabetes** Theodorus J P Jansen, et. al., Diabetologia, 2023 Feb; 66(2):367-375. doi: 10.1007/s00125-022-05830-2. Epub 2022 Nov 17.
**Postprandial C-Peptide to Glucose Ratio as a Marker of β Cell Function: Implication for the Management of Type 2 Diabetes** Yoshifumi Saisho International Journal of Molecular Science – 2016 May 17; 17(5):744. doi: 10.3390/ijms17050744. PMID: 27196896; PMCID: PMC4881566.
**Remission of human Type 2 diabetes requires decrease on liver and pancreas fat content, but is dependent upon capacity for beta cell recovery**Taylor R et al. Cell Metabolism, 2018 Oct 2; 28(4):547-556.e3. doi: 10.1016/j.cmet.2018.07.003.
**Intervention with therapeutic agents, Understanding the path to remission in Type 2 Diabetes: Part 1** Shuai Hao et al.Endocrinology Metabolism Clinics of North America – 2023 Mar; 52(1):27-38. doi: 10.1016/j.ecl.2022.07.003. Epub 2022 Nov 14.
**Intervention with therapeutic agents, Understanding the path to remission in Type 2 diabetes – Part 2** Shuai Hao et al.Endocrinology Metabolism Clinics of North America – 2023 Mar; 52(1):39-47. doi: 10.1016/j.ecl.2022.07.004. Epub 2022 Nov 18.

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# THANK YOU

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