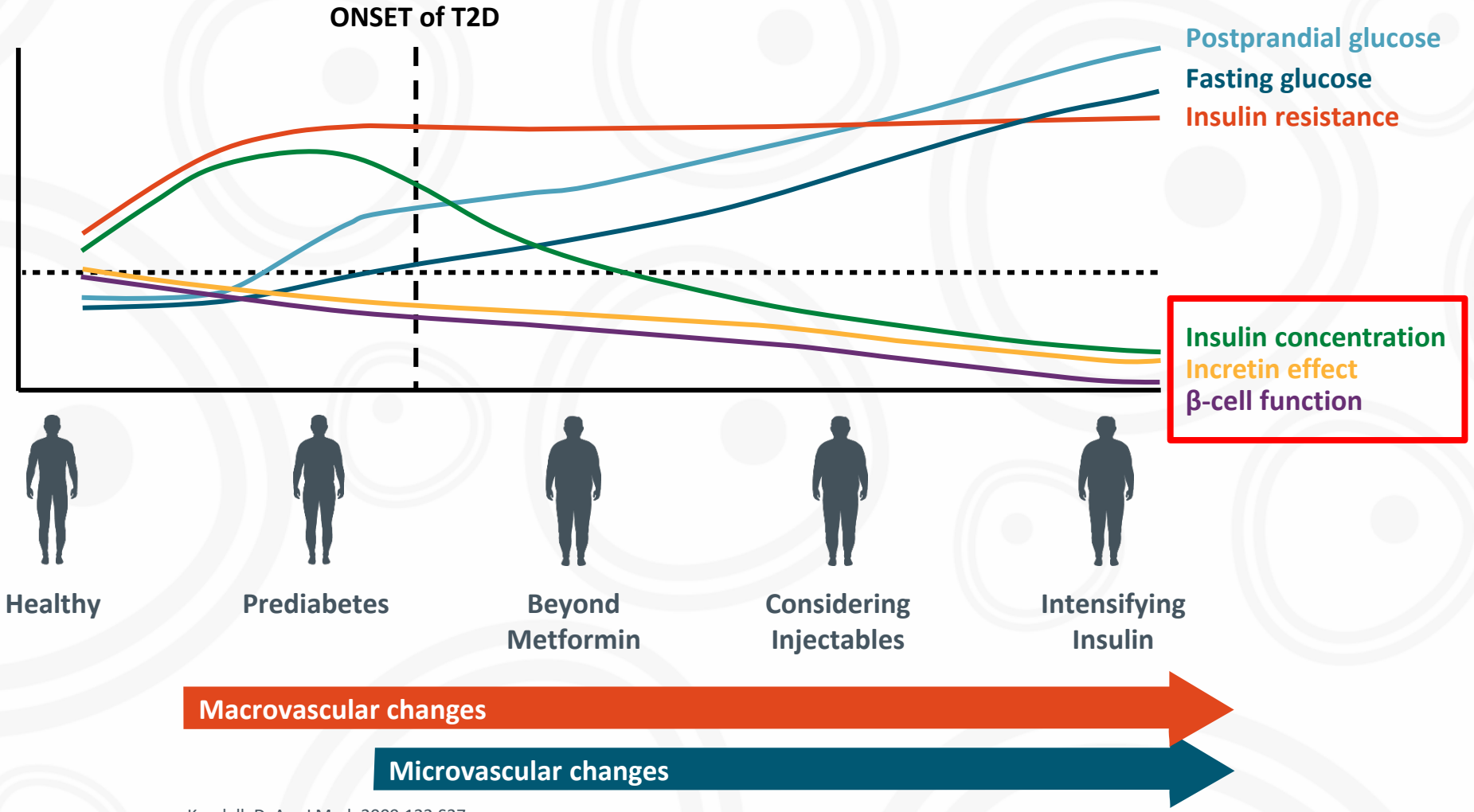
Backgrounder

Beta Cell Proliferation

biomea FUSION

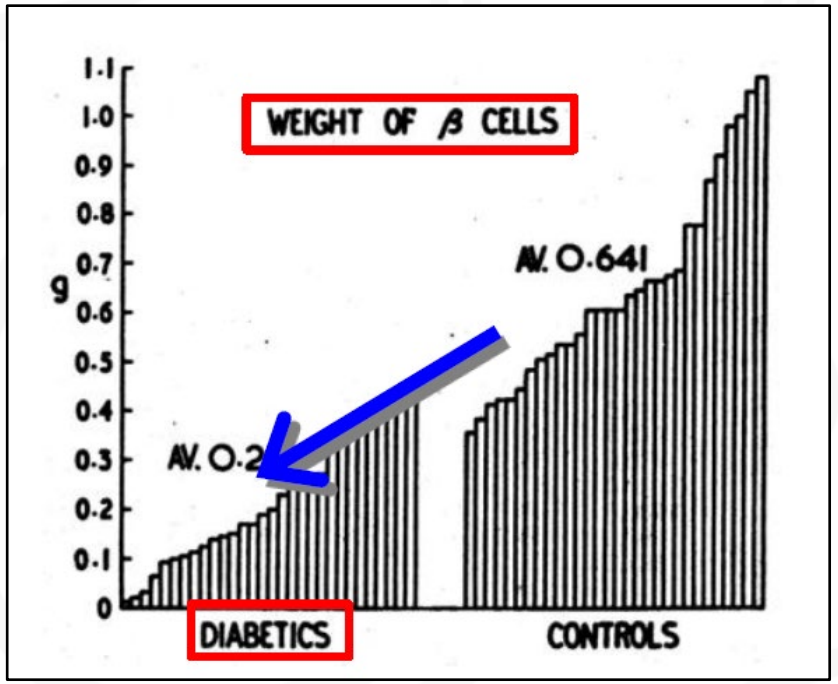
Beta Cell Proliferation
- Natural Occurrences of Proliferation

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



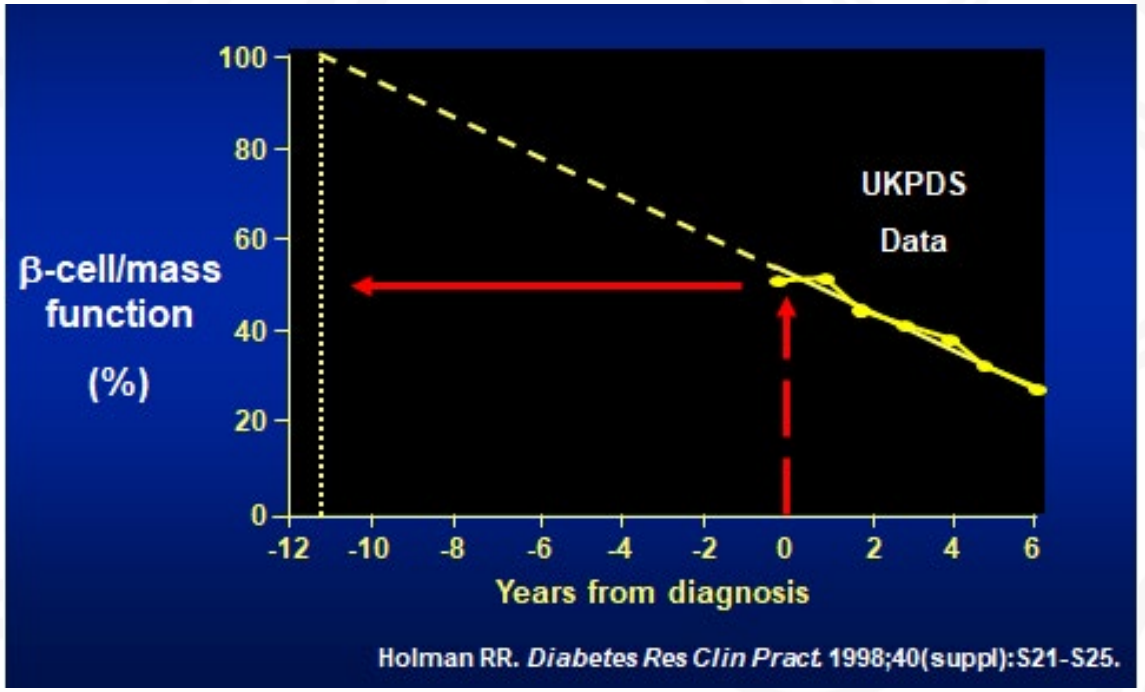
Kendall, D. Am J Med. 2009;122:S37.

Key Historic Findings Support the Presence of Beta-Cell Defects in T2D



Maclean and Ogilvie, ***Diabetes*** 4:,1955

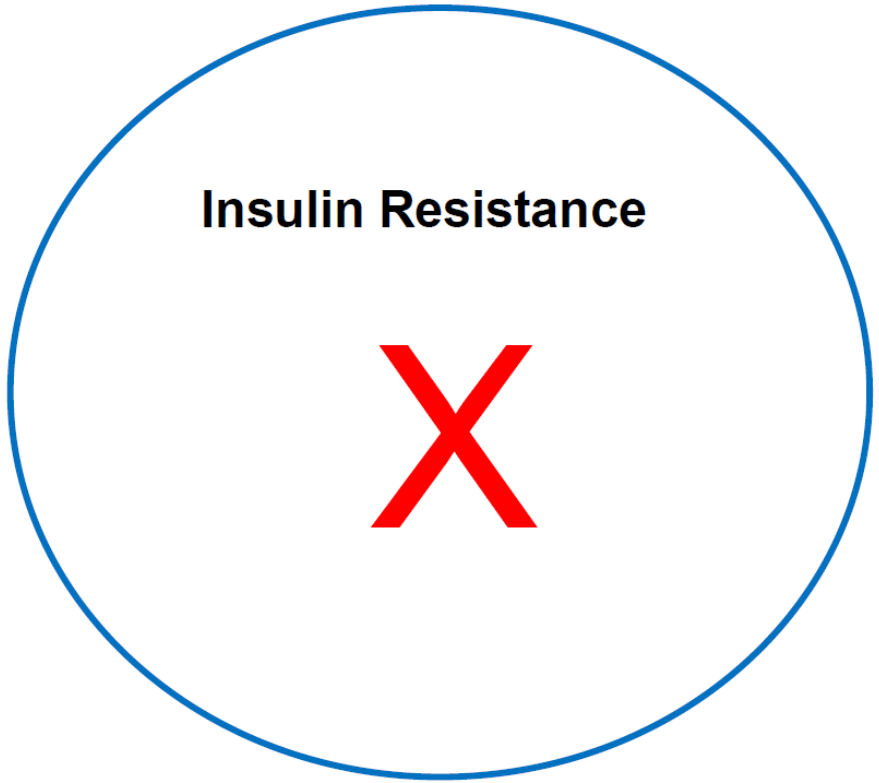
Reduced beta cell volume in T2D



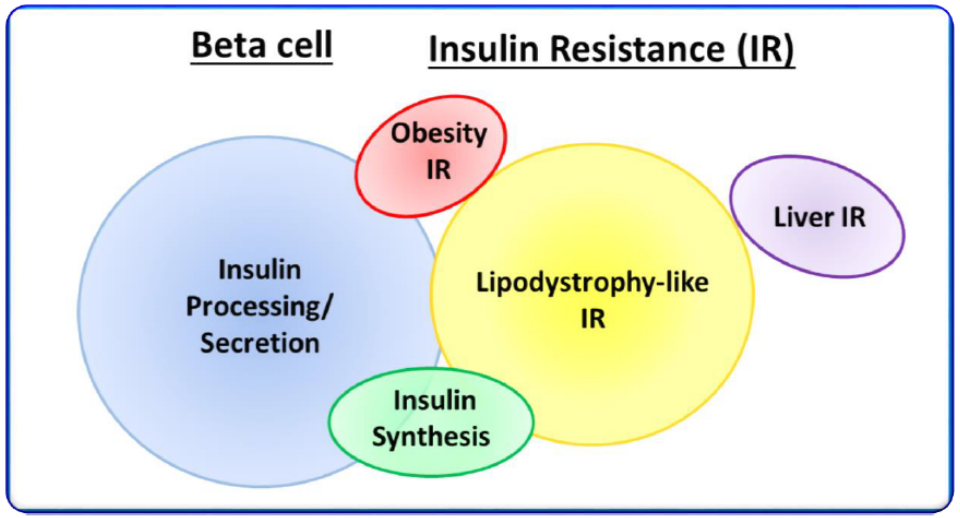
Beta cell mass/function decline with increasing year since diagnosis

Recent Concepts Have Shown Beta Cell Failure is Essential for Development of T2D

Traditional View

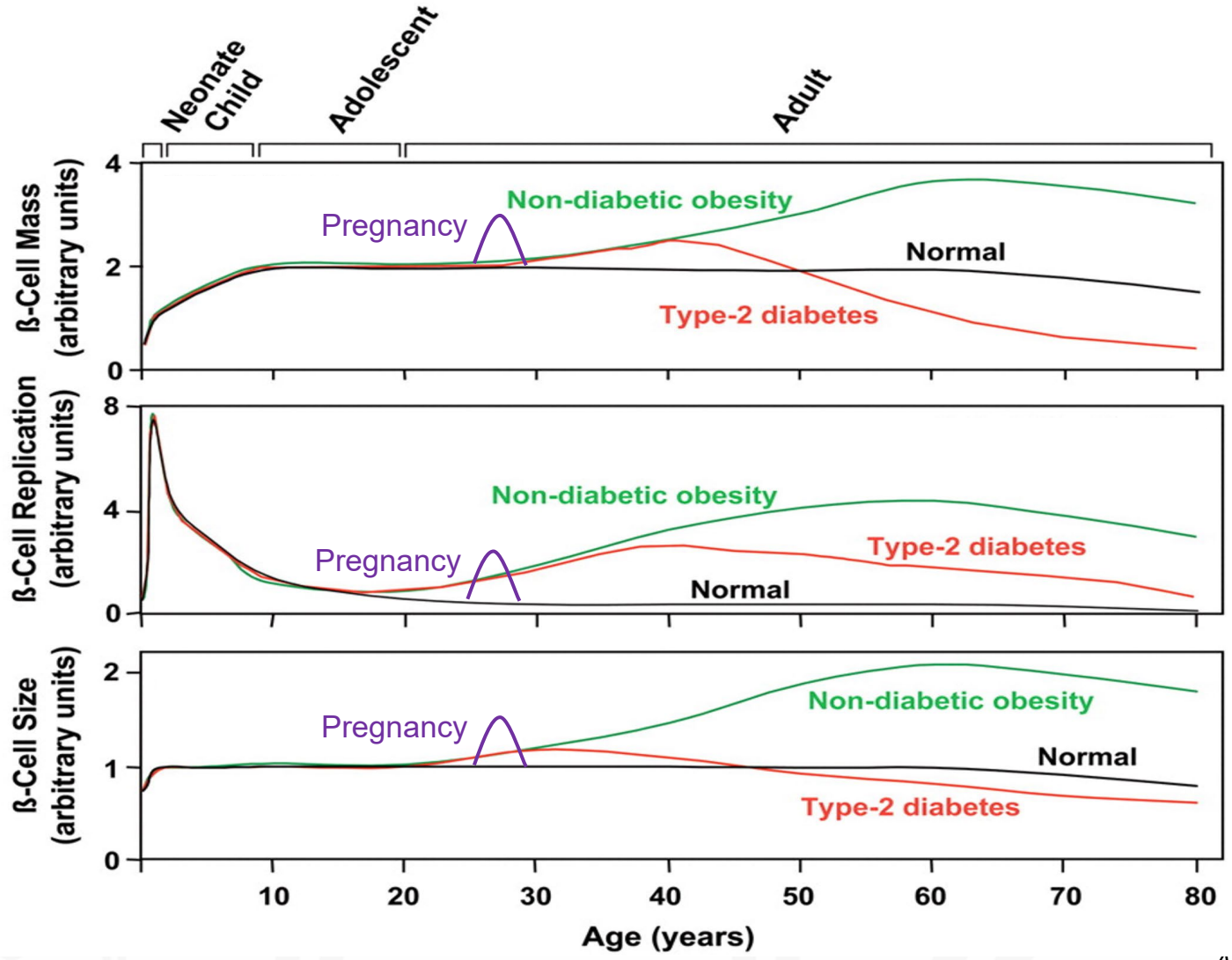


Recent concepts



β-cell failure is essential (*sine qua non*) for development of T2D

Beta Cell Compensation in Physiological and Pathophysiological States in Mammals



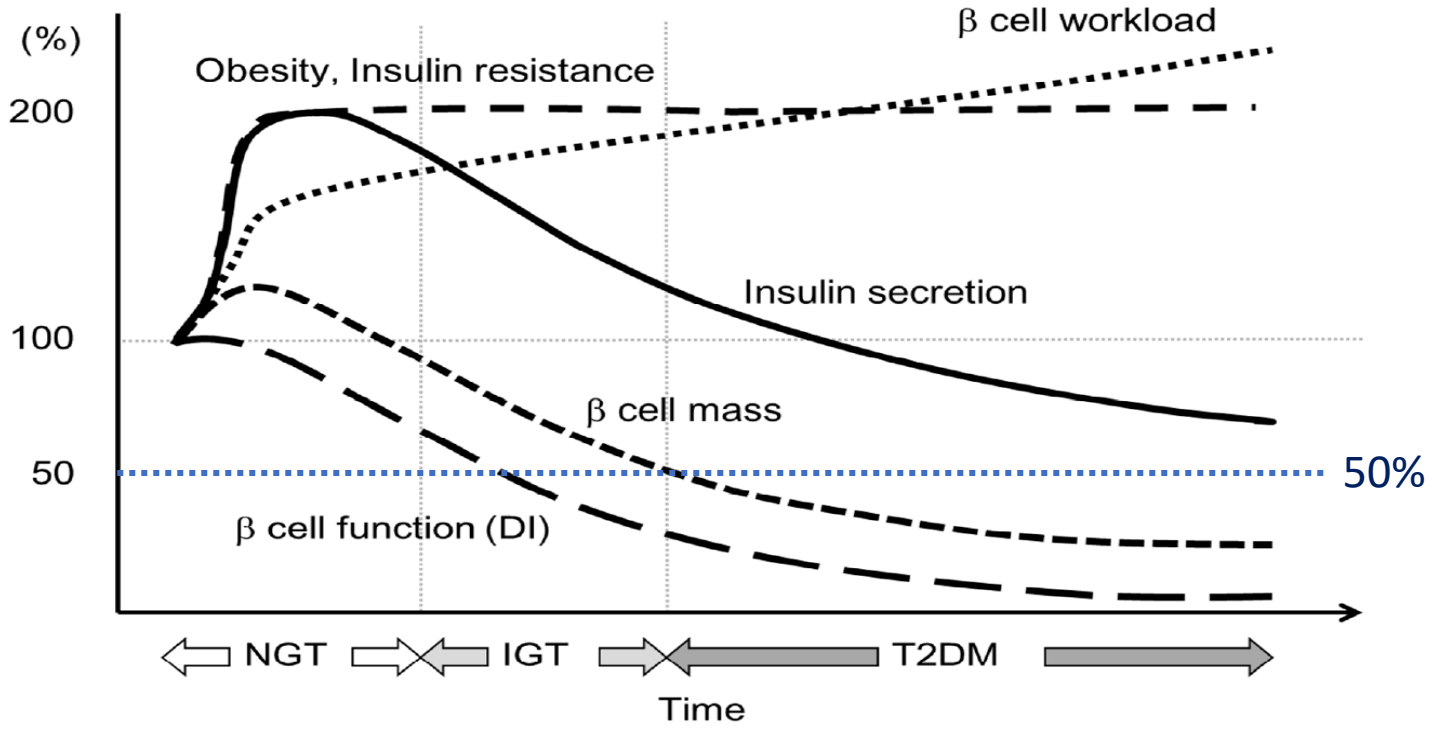
β-Cell Mass

β-Cell Replication

β-Cell Size

Adapted from Science 2005

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 β cell mass ↓↓ Insulin secretion ↓↓	Obesity Insulin resistance Hyperinsulinemia
Current Paradigm	β cell destruction β cell mass ↓↓ Insulin secretion ↓↓	β cell loss β cell mass ↓ Insulin secretion ↓
Causes	Autoimmune	Insulin resistance β cell overwork

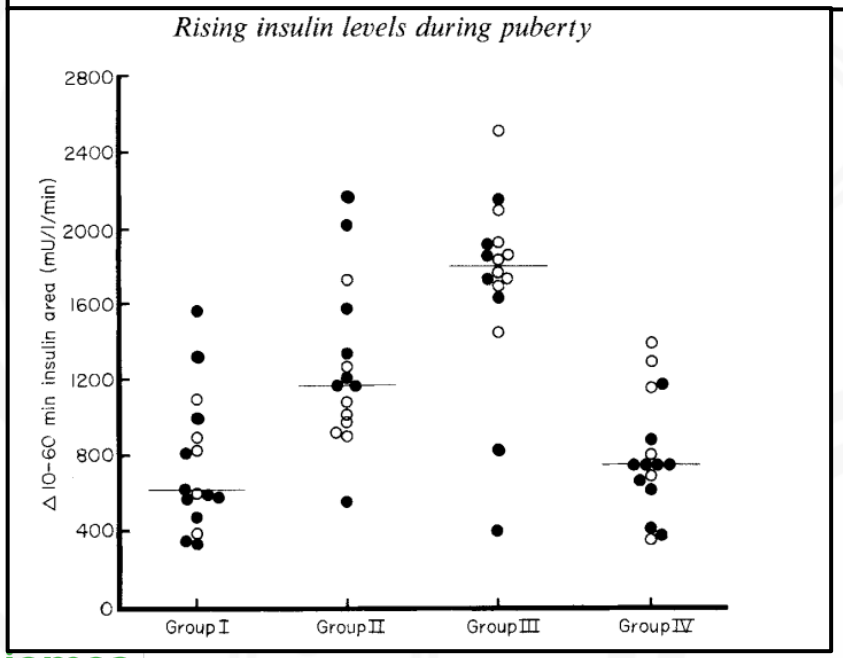
Type 1 and Type 2 Diabetes results in Loss of Beta Cell Mass

Beta Cells Can Adapt to Metabolic Demand during Puberty

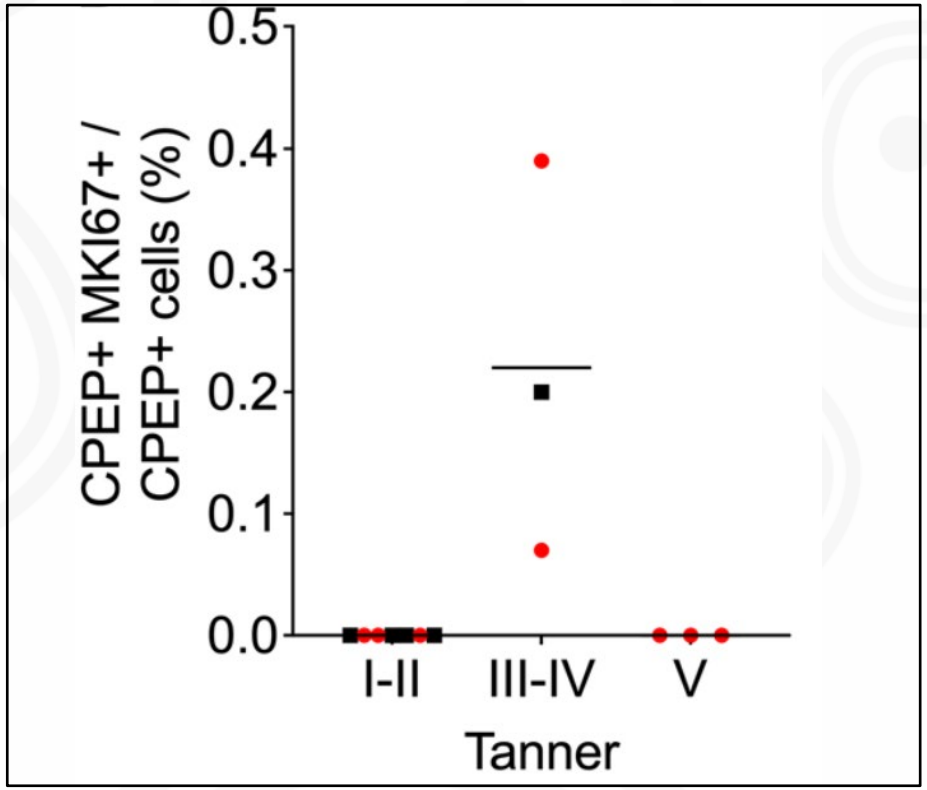
Table 1. Clinical details of subjects

	Group I (stage 1)	Group II (stage 2&3)	Group III (stage 4&5)	Group IV (adult)
Sex ratio (M/F)	11/5	8/7	7/9	10/6
Mean age (years) ± SD	9·1 ± 1·8	12·4 ± 2·3	15·2 ± 1·3	30 ± 5·1
Mean WLI (%) ± SD	106 ± 13	101 ± 13	107 ± 16	104 ± 14
HLA identical (%)	4 (25%)	3 (20%)	5 (31%)	—

WLI Weight-for-length index.



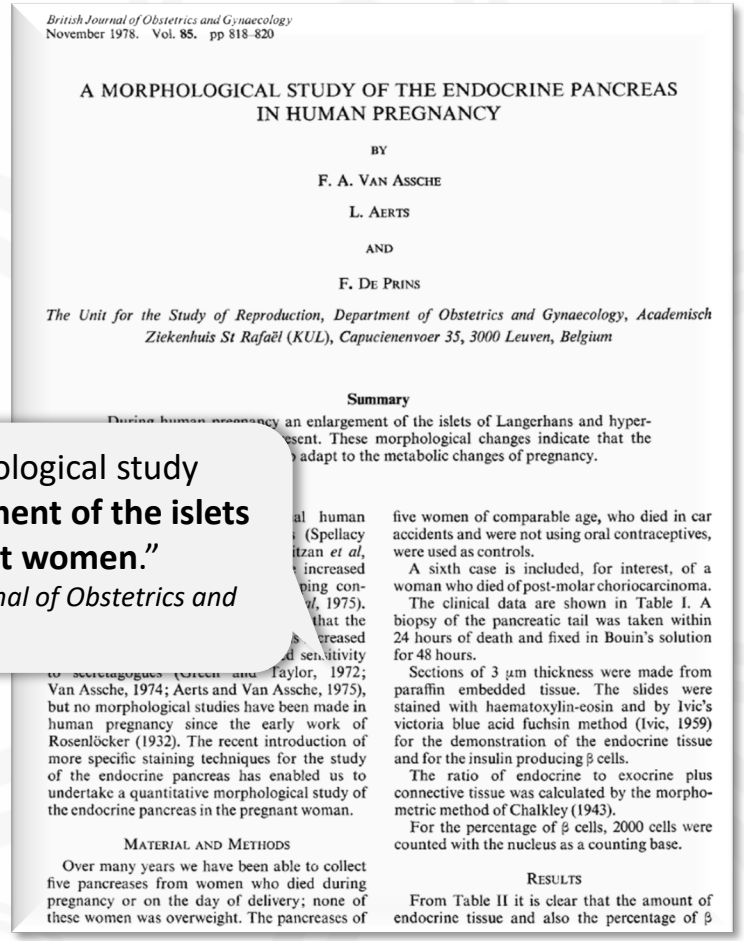
Tanner stages / sexual maturity rating (SMR)



Smith et al. Clinical Endocrinology. 1988

Laura-Castel et al. JCI Insight. 2022

Beta Cells Proliferate during Pregnancy



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 hyper- esent. These morphological changes indicate that the adapt to the metabolic changes of pregnancy.

al human (Spellacy itzan *et al*, increased ping con- l, 1975). that the creased d sensitivity 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 Rosenlöcker (1932). The recent introduction of more specific staining techniques for the study of the endocrine pancreas has enabled us to undertake a quantitative morphological study of the endocrine pancreas in the pregnant woman.

MATERIAL AND METHODS

Over many years we have been able to collect five pancreases from women who died during pregnancy or on the day of delivery; none of these women was overweight. The pancreases 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) for the demonstration of the endocrine tissue and for the insulin producing β cells.

The ratio of endocrine to exocrine plus connective tissue was calculated by the morphometric method of Chalkley (1943).

For the percentage of β cells, 2000 cells were counted with the nucleus as a counting base.

RESULTS

From Table II it is clear that the amount of endocrine tissue and also the percentage of β

"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

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

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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 [illegible] mice. Interestingly, between d 0 and 15 of pregnancy, [illegible] mice, but this

Pancreatic β-cell mass and f plasticity so that in time of ment, such as obesity and preg insulin secretory capacity can inc this metabolic demand (1, 2). Several lines of evidence sug- gest that prolactin and/or placental lactogens are responsible for the pregnancy-associated changes in β-cell mass and function. First, during pregnancy, the increase in serum prolactin and placental lactogen levels parallels the increase in β-cell mass (3). Second, prolactin receptor, the receptor for both prolactin and placental lactogens, is present on pancreatic β-cells (4), and its expression increases during pregnancy (5). Furthermore, *in vitro* exposure of isolated islets to prolactin/placental lactogen showed that these hormones can increase insulin secretion and β-cell proliferation and lowers the prolactin receptor ($Prlr^{+/-}$) have impaired glucose tolerance during pregnancy but normal glucose homeostasis during the nonpregnant state. In addition, the pregnant $Prlr^{+/-}$ mice have lower serum insulin levels in comparison with the $Prlr^{+/+}$ mice, which correlated with a reduced β-cell mass and a decreased β-cell proliferation rate in the pregnant $Prlr^{+/-}$ mice. These results suggest that during pregnancy, the action of pregnancy hormones is essential for maintaining adequate insulin responses by enhancing β-cell proliferation, thereby increasing β-cell mass.

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doi: 10.1210/en.2010-1250 Received November 3, 2010. Accepted December 9, 2010.
First Published Online January 14, 2011

Abbreviations: CDK, Cyclin-dependent kinase; CIP, cyclin inhibitory protein; IR, insulin receptor; IRS, IR substrate; PI3K, phosphoinositol-3-kinase.

"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."
Hughes et al. Endocrinology, March 2011, 152(3):847–855

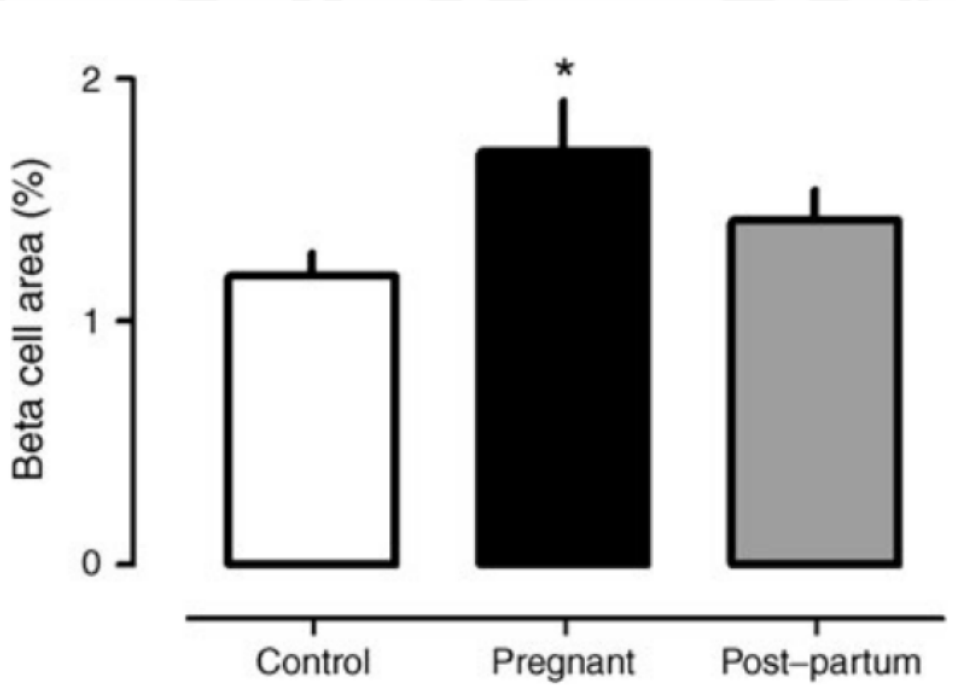
Beta Cells Proliferate During Pregnancy and Stay Elevated Thereafter

TABLE II

The endocrine pancreas in non-pregnant and pregnant women

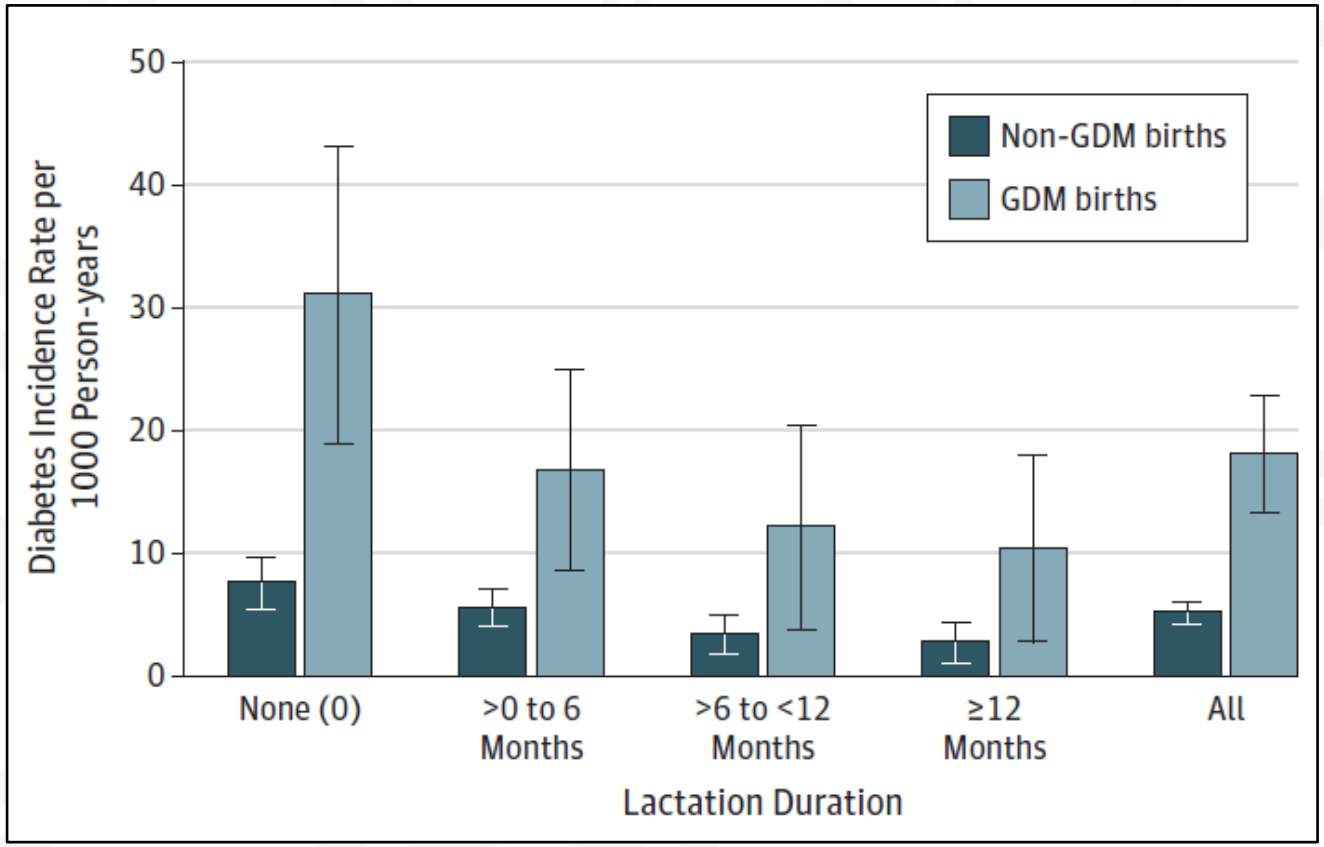
	Endocrine tissue (per cent)	β cells (per cent)
Non-pregnant women		
1	1·6	75
2	1·5	68
3	2·0	78
4	1·4	69
5	1·3	74
Mean ± SD	1·56 ± 0·27	72·8 ± 4·2
Pregnant women		
1	3·2	81
2	3·1	83
3	2·9	79
4	3·6	84
5	3·7	83
Mean ± SD	3·3 ± 0·3	82·0 ± 1·8
P	<0·001	<0·005

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



Butler et al. Diabetologia. 2010

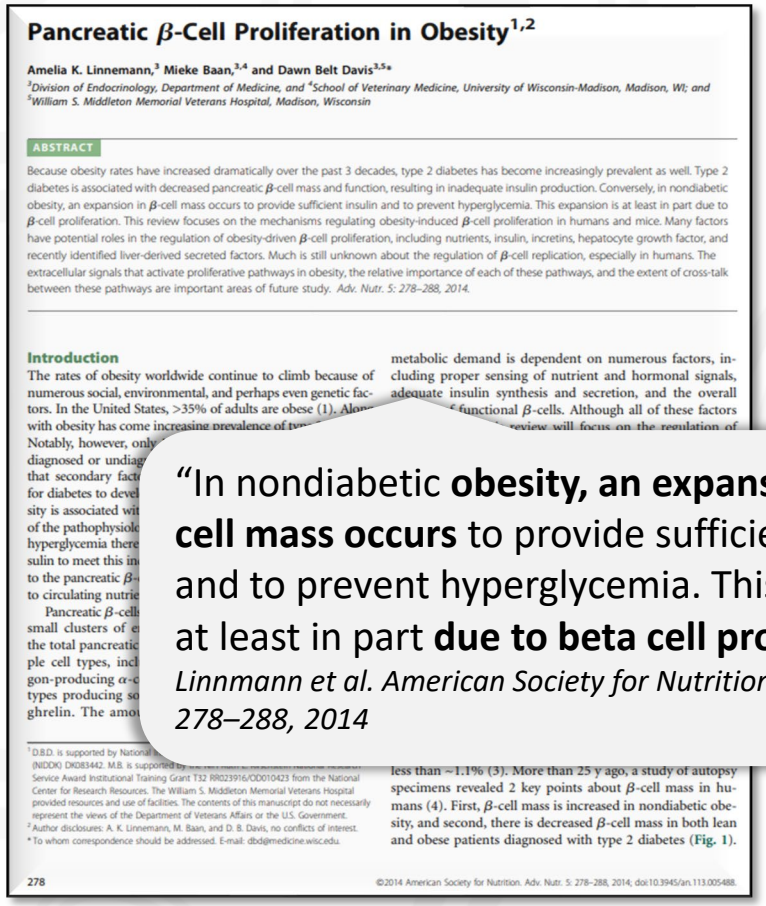
Lactation Duration Showed a Strong, Graded Inverse Association with Diabetes Incidence



Among young white and black women in this observational 30-year study*, increasing lactation duration was associated with a strong, graded 25% to 47% relative reduction in the incidence of diabetes even after accounting for prepregnancy biochemical measures, clinical and demographic risk factors, gestational diabetes, lifestyle behaviors, and weight gain.

*Gunderson et al. JAMA Intern Med. 2018;178(3):328-337

Beta Cells Proliferate in Obesity



Pancreatic β-Cell Proliferation in Obesity[1,2]

Amelia K. Linnemann,[3] Mieke Baan,[3,4] and Dawn Belt Davis[3,5]*
[3]Division of Endocrinology, Department of Medicine, and [4]School of Veterinary Medicine, University of Wisconsin-Madison, Madison, WI; and [5]William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin

ABSTRACT

Because obesity rates have increased dramatically over the past 3 decades, type 2 diabetes has become increasingly prevalent as well. Type 2 diabetes is associated with decreased pancreatic β-cell mass and function, resulting in inadequate insulin production. Conversely, in nondiabetic obesity, an expansion in β-cell mass occurs to provide sufficient insulin and to prevent hyperglycemia. This expansion is at least in part due to β-cell proliferation. This review focuses on the mechanisms regulating obesity-induced β-cell proliferation in humans and mice. Many factors have potential roles in the regulation of obesity-driven β-cell proliferation, including nutrients, insulin, incretins, hepatocyte growth factor, and recently identified liver-derived secreted factors. Much is still unknown about the regulation of β-cell replication, especially in humans. The extracellular signals that activate proliferative pathways in obesity, the relative importance of each of these pathways, and the extent of cross-talk between these pathways are important areas of future study. *Adv. Nutr. 5: 278–288, 2014.*

Introduction

The rates of obesity worldwide continue to climb because of numerous social, environmental, and perhaps even genetic factors. In the United States, >35% of adults are obese (1). Along with obesity has come increasing prevalence of ty... Notably, however, only... diagnosed or undiag... that secondary fact... for diabetes to devel... sity is associated wit... of the pathophysiol... hyperglycemia there... sulin to meet this in... to the pancreatic β-... to circulating nutrie...

Pancreatic β-cells... small clusters of e... the total pancreatic... ple cell types, incl... gon-producing α-c... types producing so... ghrelin. The amo...

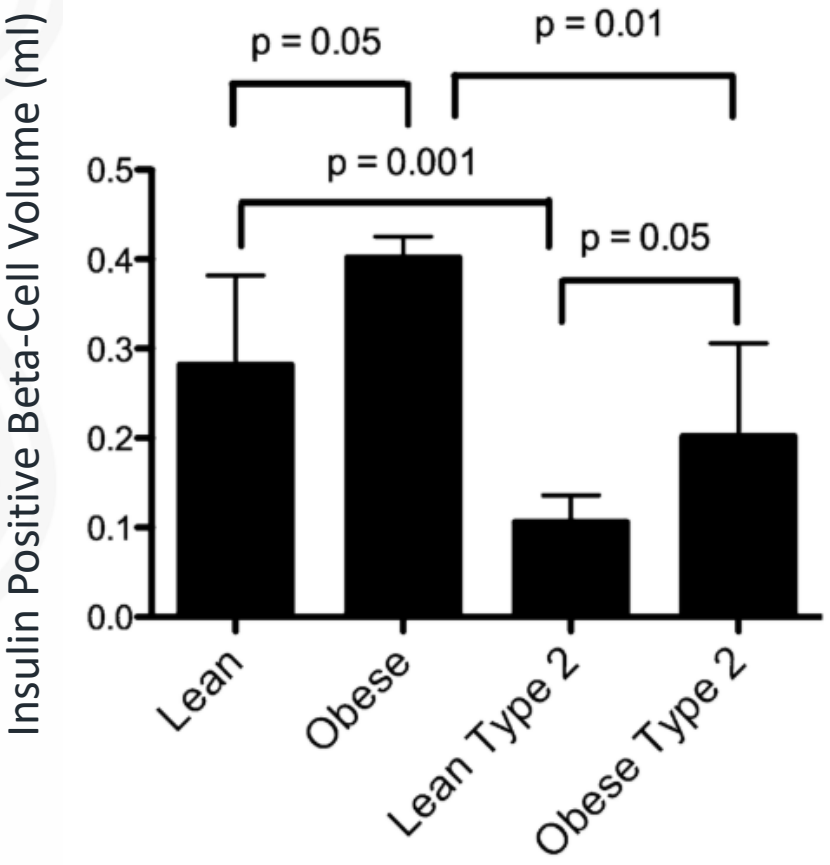
metabolic demand is dependent on numerous factors, including proper sensing of nutrient and hormonal signals, adequate insulin synthesis and secretion, and the overall ...f functional β-cells. Although all of these factors ...review will focus on the regulation of...

less than ~1.1% (3). More than 25 y ago, a study of autopsy specimens revealed 2 key points about β-cell mass in humans (4). First, β-cell mass is increased in nondiabetic obesity, and second, there is decreased β-cell mass in both lean and obese patients diagnosed with type 2 diabetes (Fig. 1).

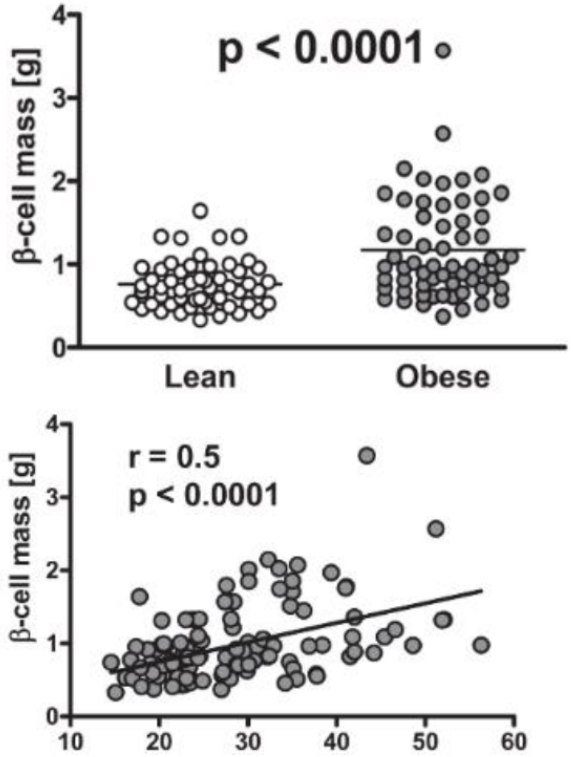
[1] D.B.D. is supported by National... (NIDDK) DK083442. M.B. is supported by ... Service Award Institutional Training Grant T32 RR023916/OD010423 from the National Center for Research Resources. The William S. Middleton Memorial Veterans Hospital provided resources and use of facilities. The contents of this manuscript do not necessarily represent the views of the Department of Veterans Affairs or the U.S. Government.
[2] Author disclosures: A. K. Linnemann, M. Baan, and D. B. Davis, no conflicts of interest.
* To whom correspondence should be addressed. E-mail: dbd@medicine.wisc.edu.

 Adv. Nutr. 5: 278–288, 2014; doi:10.3945/an.113.005488.

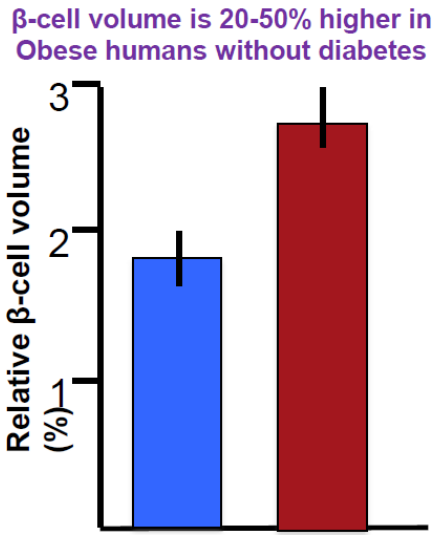
"In nondiabetic **obesity, an expansion in beta cell mass occurs** to provide sufficient insulin and to prevent hyperglycemia. This expansion is at least in part **due to beta cell proliferation**.
Linnmann et al. American Society for Nutrition. Adv. Nutr. 5: 278–288, 2014



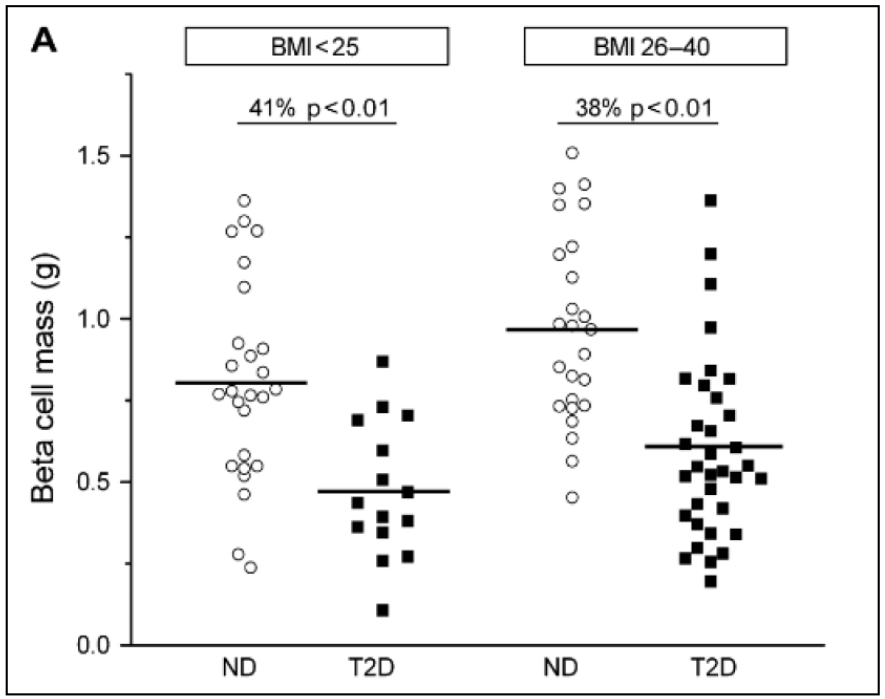
Beta Cell Mass and Volume Expands with Obesity



Saisho Y et al, Diabetes care, August 2012



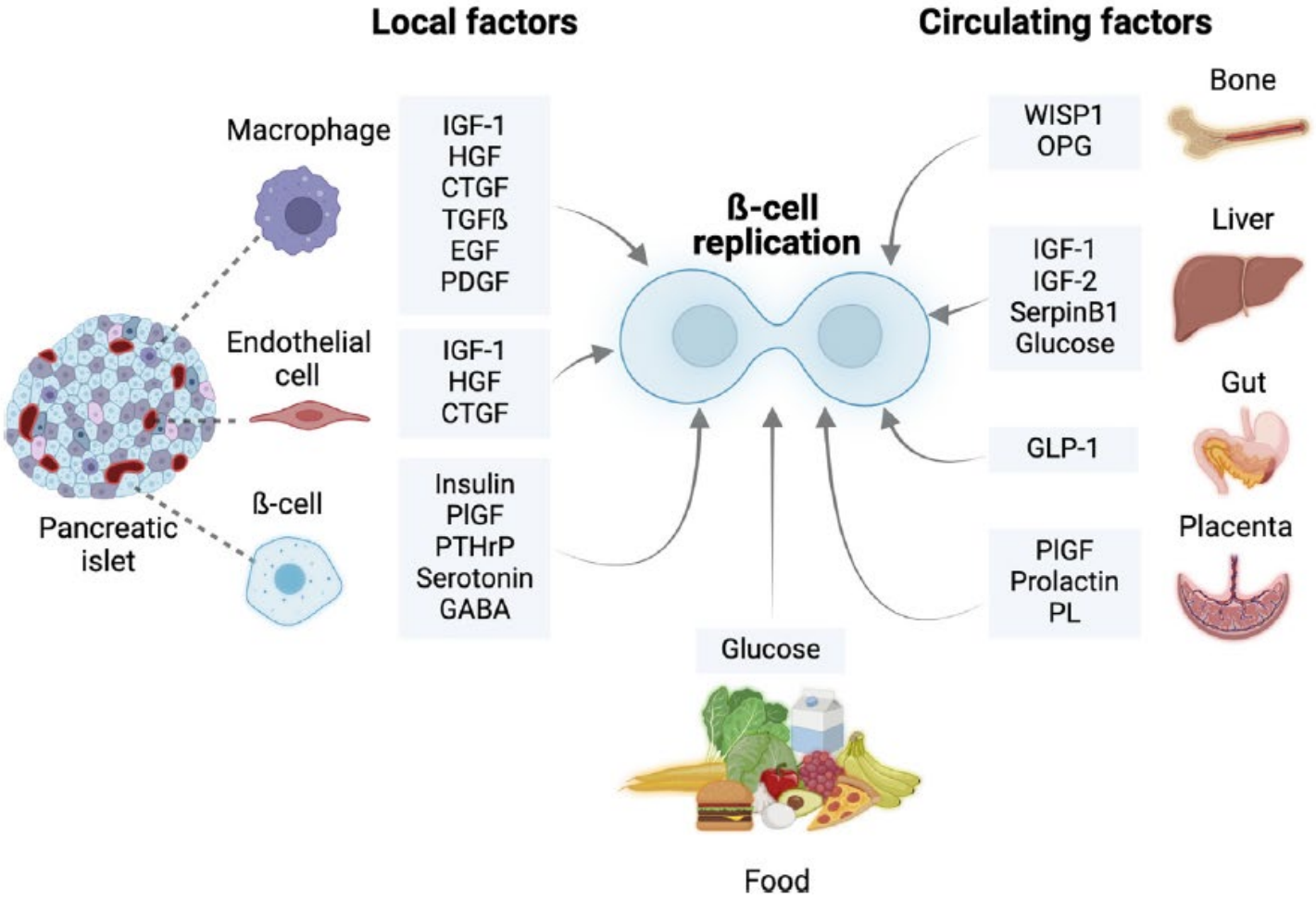
Adapted from Butler AE et al. *Diabetes*. 2003;52:102-10.



Rahier et al. Diabetes Obes Metab. 2008 4:32-42

Beta Cells Replicate

There are Local and Circulating Factors that support Beta Cell Replication



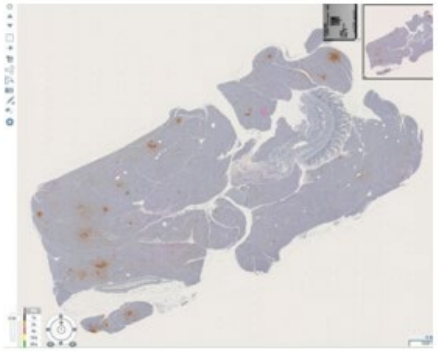
Dr. Kim, S.K. et al., Science. 2007 Nov 2. doi: 10.1126/science.1146812.; Linnmann et al. American Society for Nutrition. Adv. Nutr. 5: 278–288, 2014; F. A. Van Assche et al. British Jornal of Obstetrics and Gynaecology, 1978 November; Hughs et al. Endocrinology, March 2011, 152(3):847–855

Beta Cell Proliferation
- Validation from Preclinical Results of BMF-219

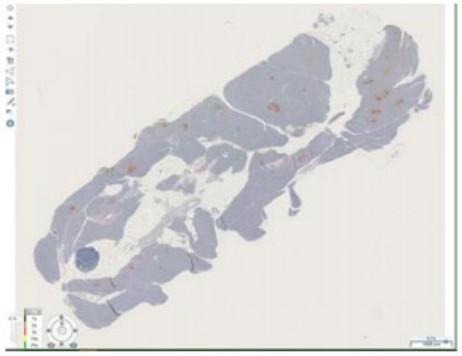
BMF-219 increases β-islets in pancreas sections of ZDF diabetic model

as presented during EASD 2022

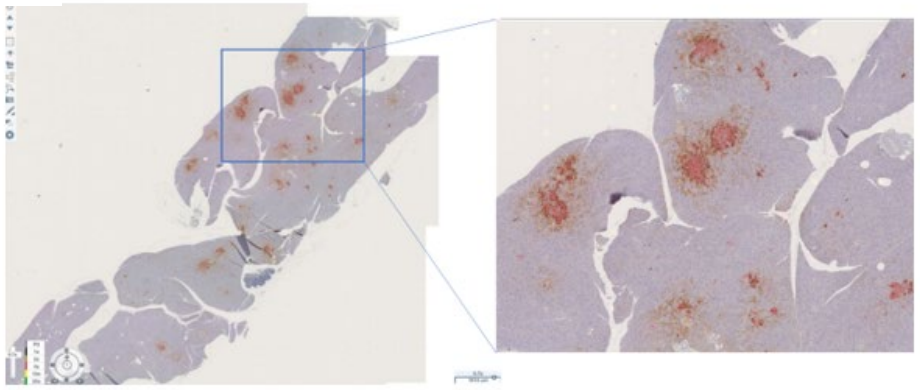
A. Vehicle; Day 31



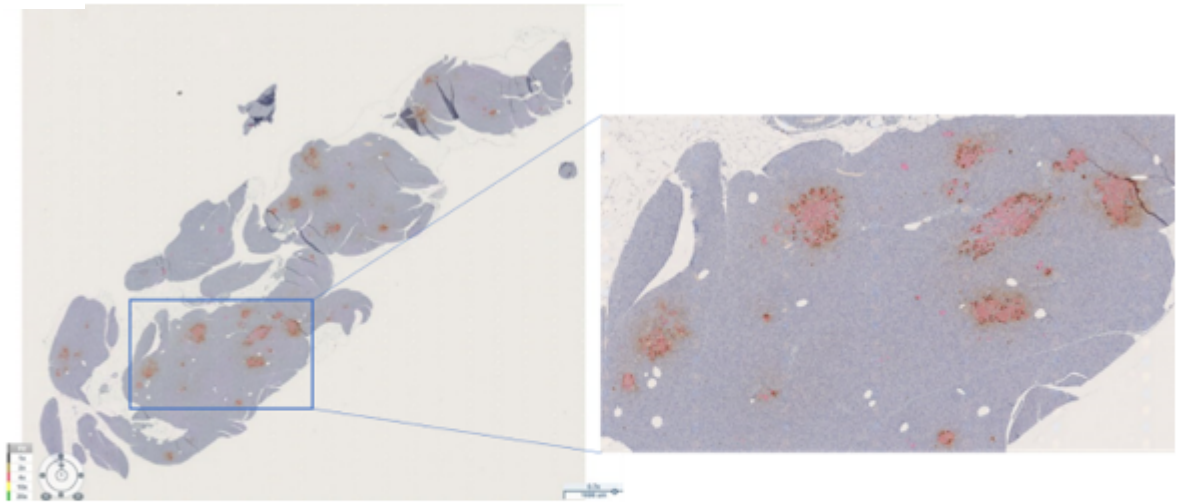
B. Pioglitazone; Day 17



C. BMF-219; Day 17



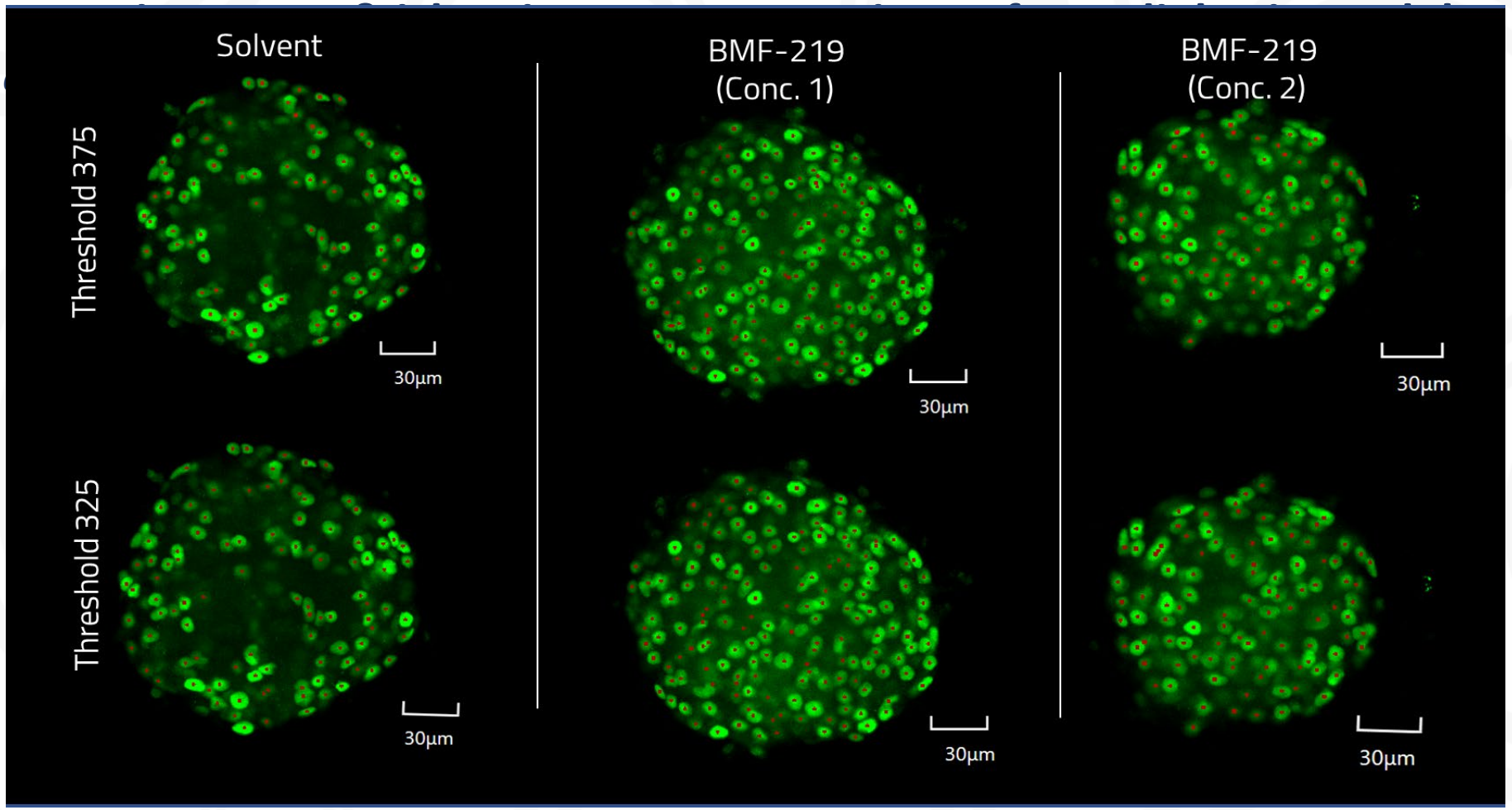
D. BMF-219; Day 31



A) Vehicle-treated animal, Day 31. Beta islets display low congregation and growth, while alpha cells dominate. **B)** Pioglitzaone-treated animal, Day 17. Beta islets display congregation and growth. **C)** BMF-219 treated animal, Day 17. In contrast to the pioglitazone-treated animal shown in Panel B, note that BMF-219 treatment results in high congregation and growth of the beta islets. **D)** BMF-219 treated animal, Day 31. Beta islets display high congregation and continue to increase and mature. Red is insulin-beta islets, brown is glucagon-alpha cells.

Human Donor Islets (Ex-Vivo) Statistically Significant Increase Beta Cells with BMF-219

as presented during EASD 2022



Beta Cell Proliferation
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