Περιπλέκει ή Βοηθάει ο Προσδιορισμός του C-Πεπτιδίου και των Αυτοαντισωμάτων στην Καθημερινή Πρακτική;

Ερυφίλη Χατζηαγγελάκη
Αναπλ. Καθηγήτρια Παθολογίας-Μεταβολικών Νοσημάτων
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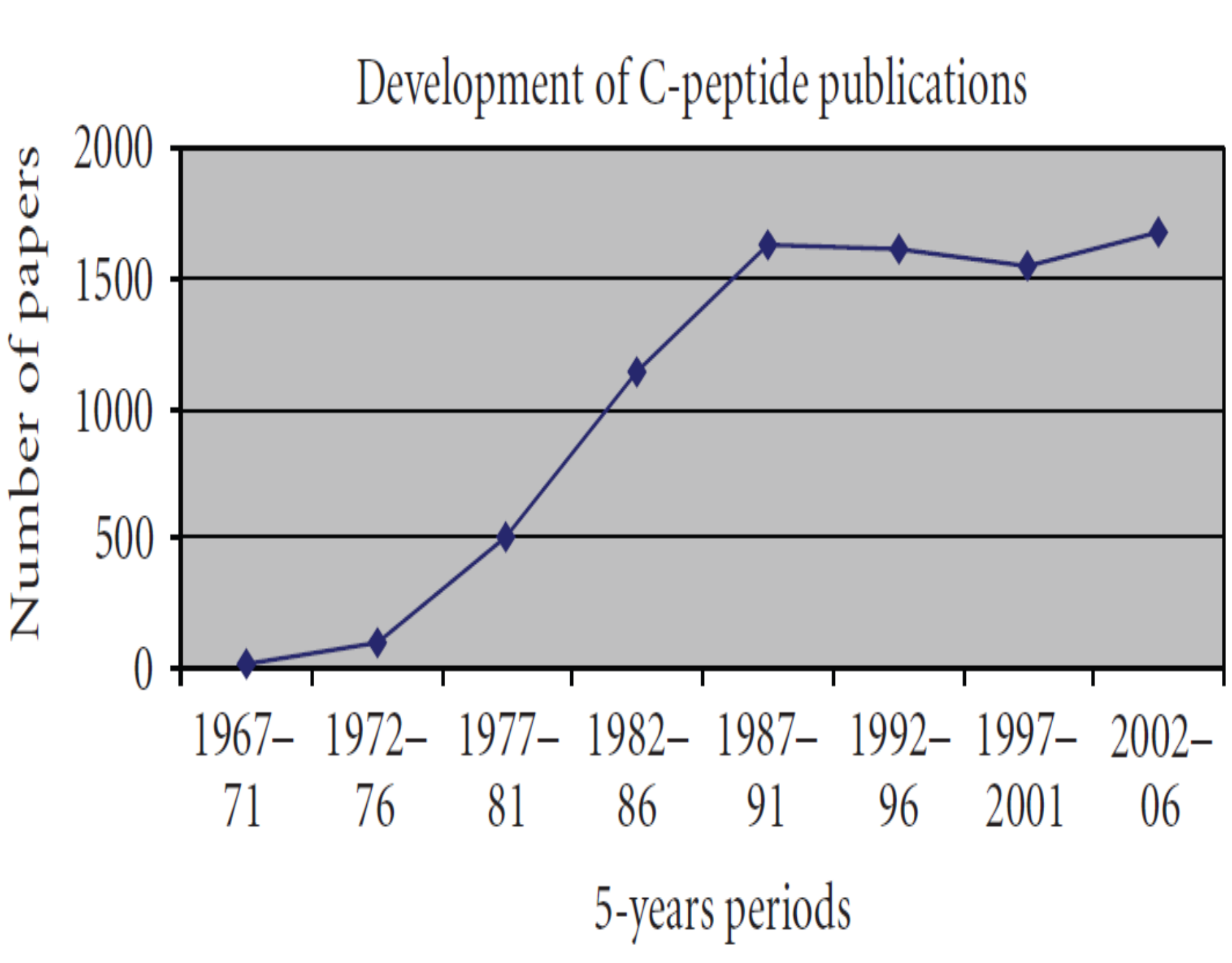
Πανεπιστημιακό Γ.Ν "Αττικόν"
Ιατρική Σχολή
Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών

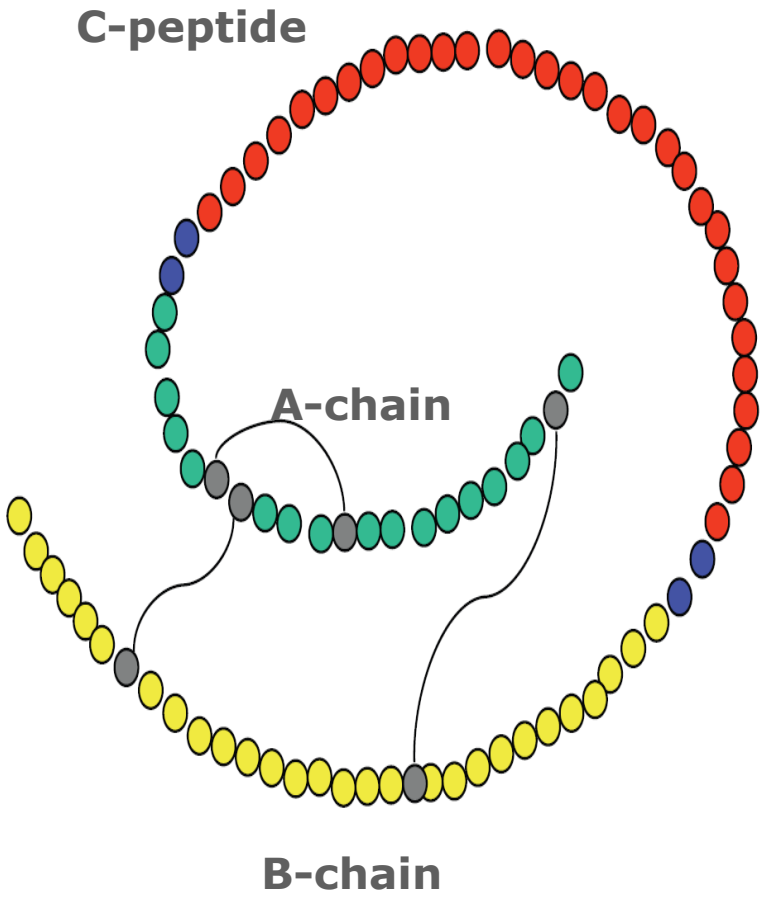

Development of C-peptide publications
Number of papers
2000
1500
1000
500
0
1967–71
1972–76
1977–81
1982–86
1987–91
1992–96
1997–2001
2002–06
5-years periods

Proinsulin - C-peptide
A Consensus Statement

- **Το C-πεπτίδιο παίζει ένα <u>σημαντικό ρόλο στη σύνθεση της ινσουλίνης</u>, χρησιμεύοντας ως συνδετικός κρίκος μεταξύ των Α-και Β-αλύσεων της ινσουλίνης, διευκολύνοντας έτσι τον σχηματισμό των δισουλφιδικών γεφυρών του μορίου ινσουλίνης**

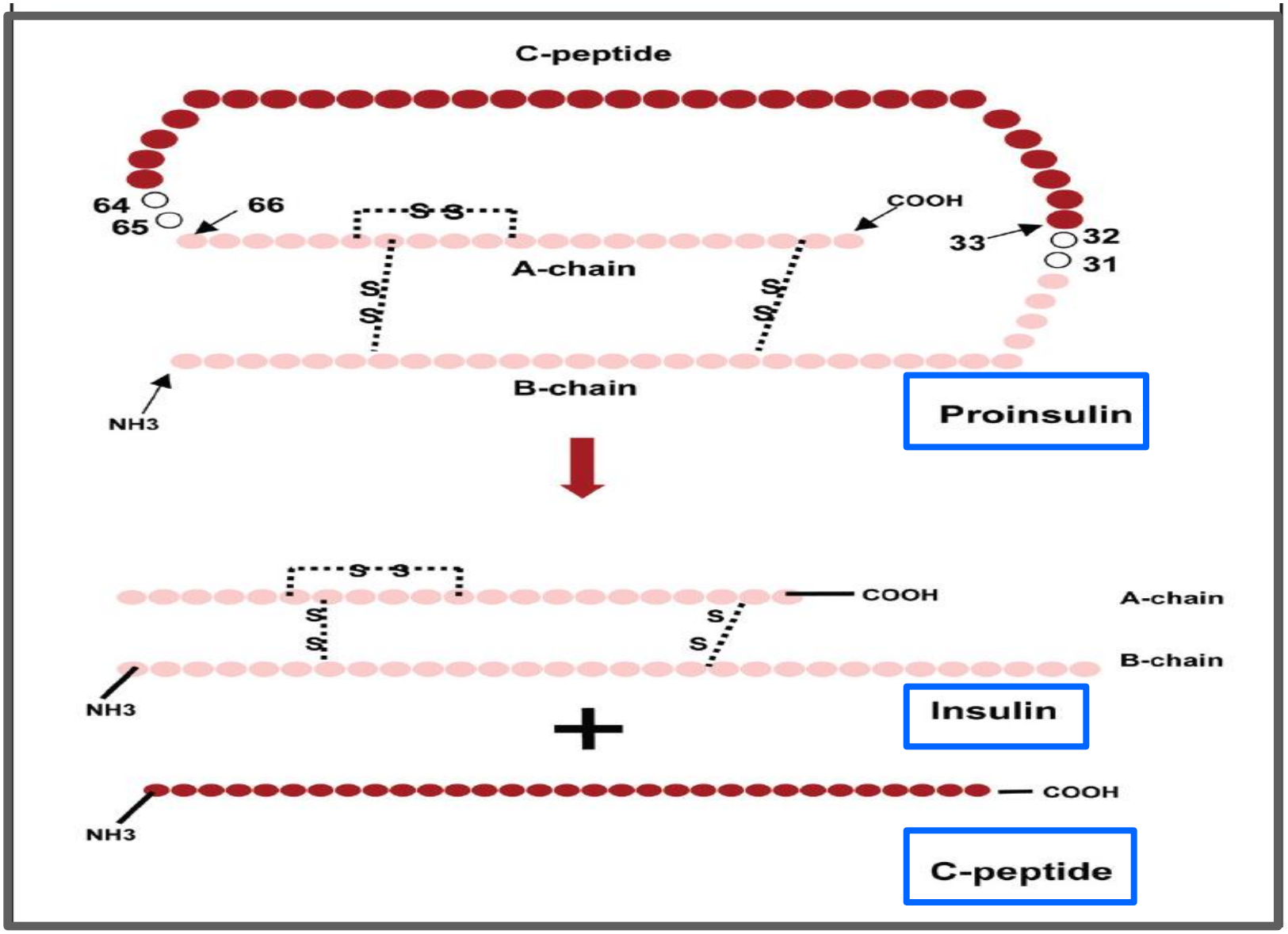
- **Το C-πεπτίδιο διασπάται από το μόριο της προϊνσουλίνης κατά τη διάκεια της βιοσύνθεσης της ινσουλίνης**

- **Αποθηκεύεται στα β-κύτταρα και τελικά απελευθερώνεται στην πυλαία και τη συστηματική κυκλοφορία σε ισομοριακές με την ινσουλίνη ποσότητες**



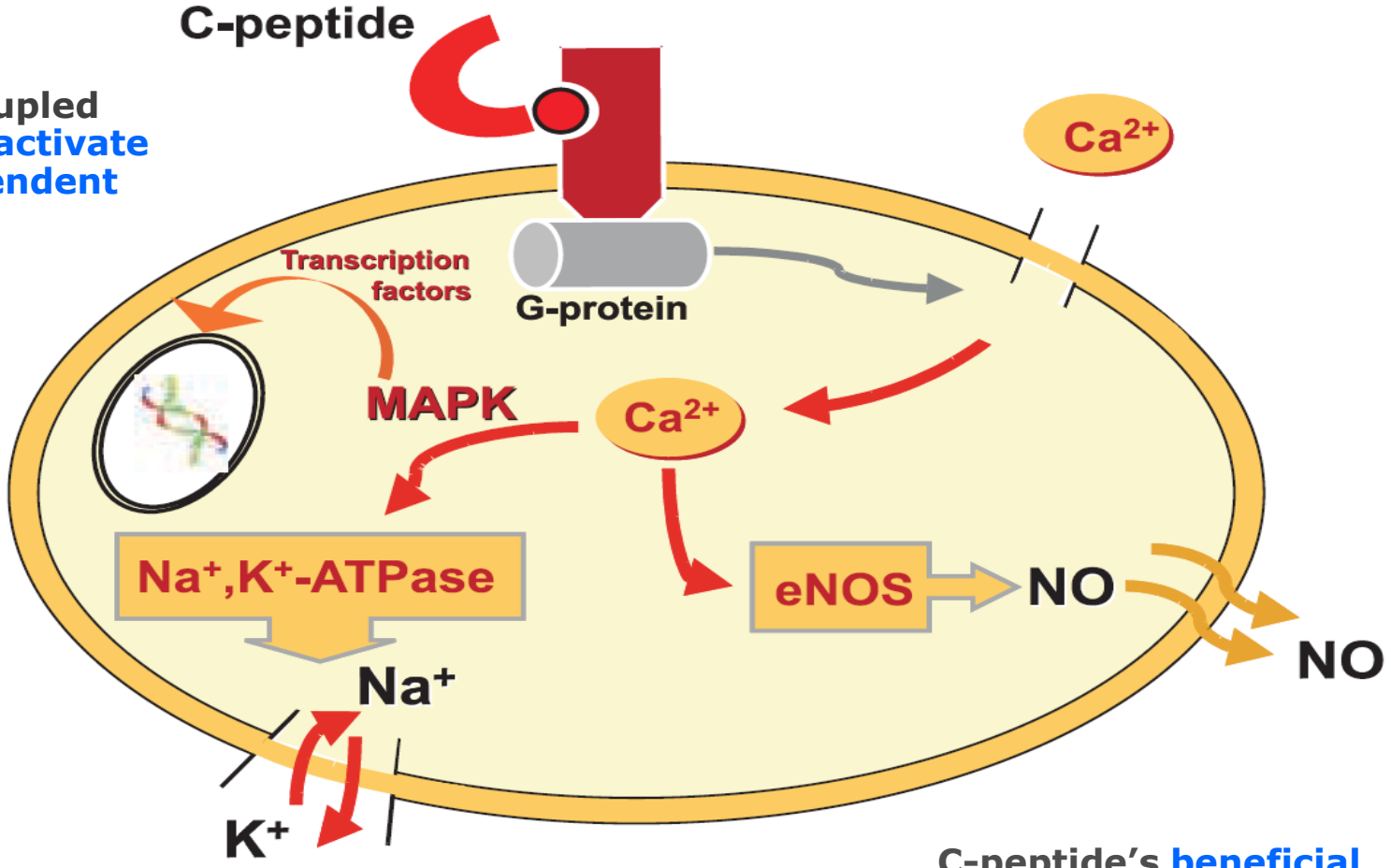
J. Wahren:, Clin Physiol Funct Imaging, 24, pp180–189, 2004

Processing of insulin and c-peptide from proinsulin



Schematic representation of C-peptide's molecular effects

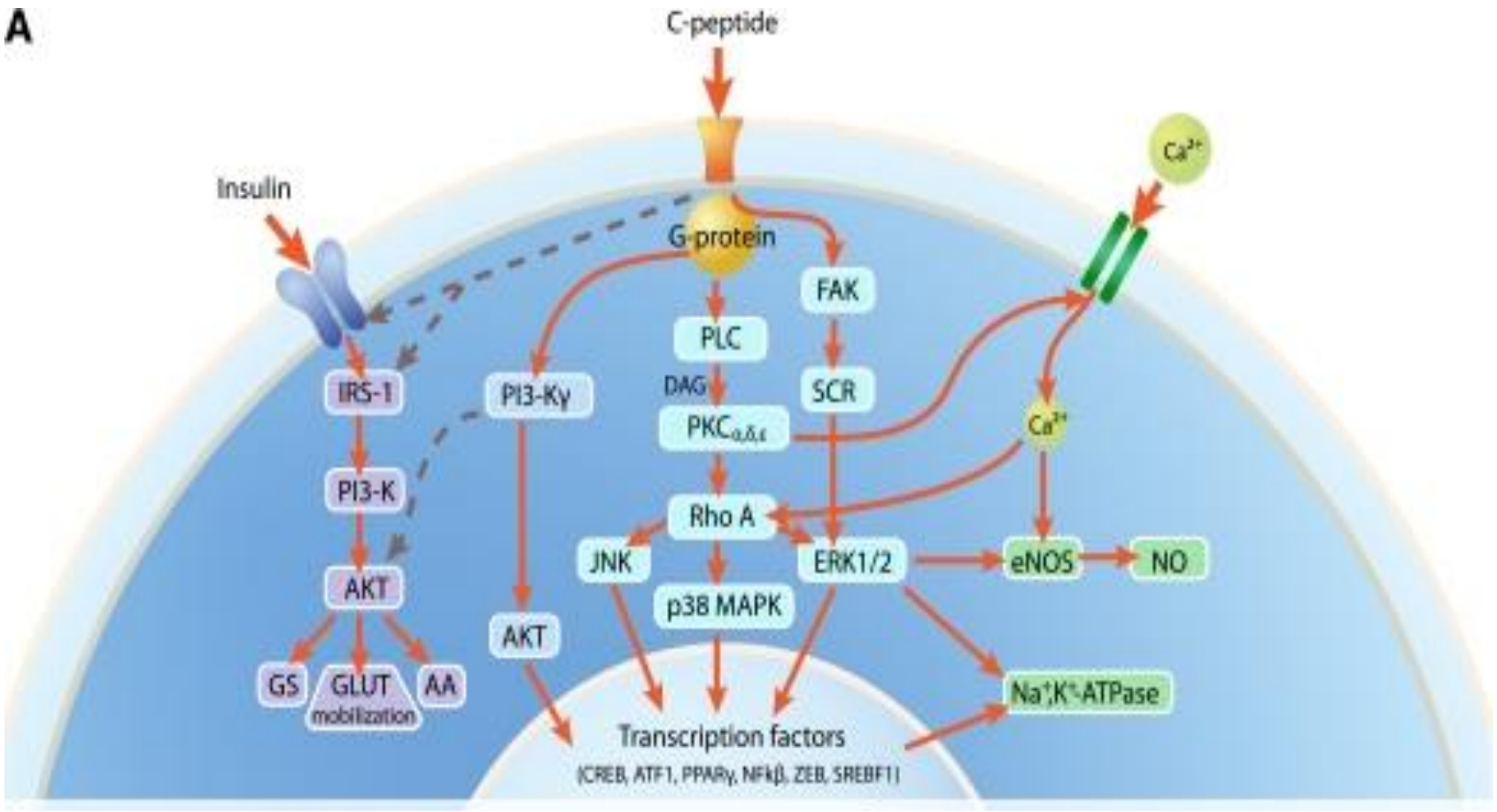
Acts through G-protein-coupled receptors to activate calcium-dependent signaling pathways



C-peptide activation of calcium signaling is thought to increase the activity of Na+-K+-ATPase, which has been found to be reduced in patients with the advanced microvascular complications of diabetes mellitus

C-peptide's beneficial affects on the microvascular complications of diabetes mellitus are thought to be mediated through endothelial nitric oxide synthase

General overview of intracellular signaling by C-peptide



J.Wahren et.al., Diabetes. 2012 Apr; 61(4): 761–772

Rationale for C-peptide measurement

Since C-peptide and insulin are released in equimolar amounts from the β-cells of the pancreas, the measurement of C-peptide has been used as a marker of β-cell function and an index of insulin secretion

C-Peptide: What it is, What it Does, Why You Test For It, What it Means (1)

- **Η Ινσουλίνη και το C-Πεπτιδίο εισέρχονται στην πυλαία κυκλοφορία και δρούν μέσω του ήπατος, όπου τουλάχιστον το 50% της ινσουλίνης προσδένεται σε υποδοχείς ενεργοποιώντας έτσι τη διέγερση της ηπατικής πρόσληψης γλυκόζης, την καταστολή της γλυκογονόλυσης, της γλυκονεογένεσης και της κετογένεσης και στη συνέχεια αποδομείται**

- **Τα περισσότερα από τα μόρια της ινσουλίνης που περνούν μέσα από το ήπαρ στην κυκλοφορία, συνδέονται σε περιφερειακούς υποδοχείς της ινσουλίνης και προωθούν την πρόσληψη γλυκόζης, ενώ τα υπόλοιπα μόρια αποβάλλονται από τα νεφρά**

C-Peptide: What it is, What it Does, Why You Test For It, What it Means (2)

- Σε αντίθεση με την ινσουλίνη, **το C-πεπτίδιο** δεν υπόκειται ούτε σε ηπατική ούτε σε περιφερική αποδόμηση, αλλά **απομακρύνεται κυρίως από τους νεφρούς**

- Ως αποτέλεσμα, το **C-πεπτίδιο έχει μεγαλύτερο χρόνο ημίσειας ζωής** από την ινσουλίνη **(30-35 min vs 5-10 min)**

C-peptide as a measure of insulin secretion

- **C-peptide gives a measure of the patient's current status *- does the patient produce endogenous insulin now? -***

  and has greater utility further from diagnosis, when rapid decline is less likely

- **Autoantibodies are of prognostic value**

  - will they continue to produce endogenous insulin in the future?-

  and have greatest utility at diagnosis

- ***This illustrates an important difference between the use of C-peptide and islet autoantibody testing***

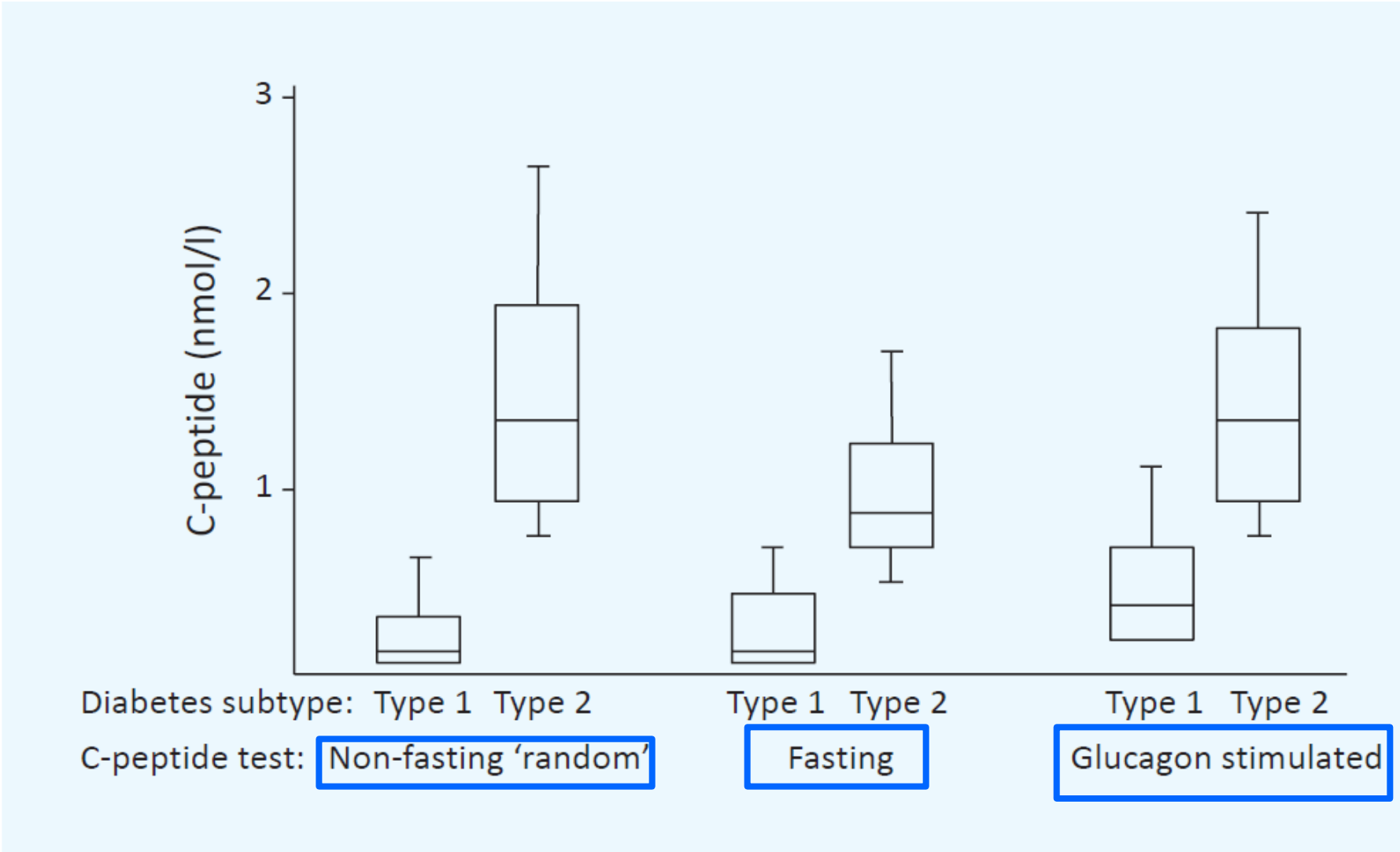
Measurement of C-peptide in blood

- **When assessing insulin production, C-peptide can be measured in a fasting or non-fasting ('random') sample or in a formal stimulation test (e.g. after intravenous glucagon or a standardized mixed-meal test)**

- **C-peptide – Fasting: 0.51-2.72 ng/mL**
  (or 0.17-0.90 nmol/L)

- **While formal stimulation tests are most accurate and reproducible for research purposes, a fasting or non-fasting ('random') sample is usually suitable in clinical practice**

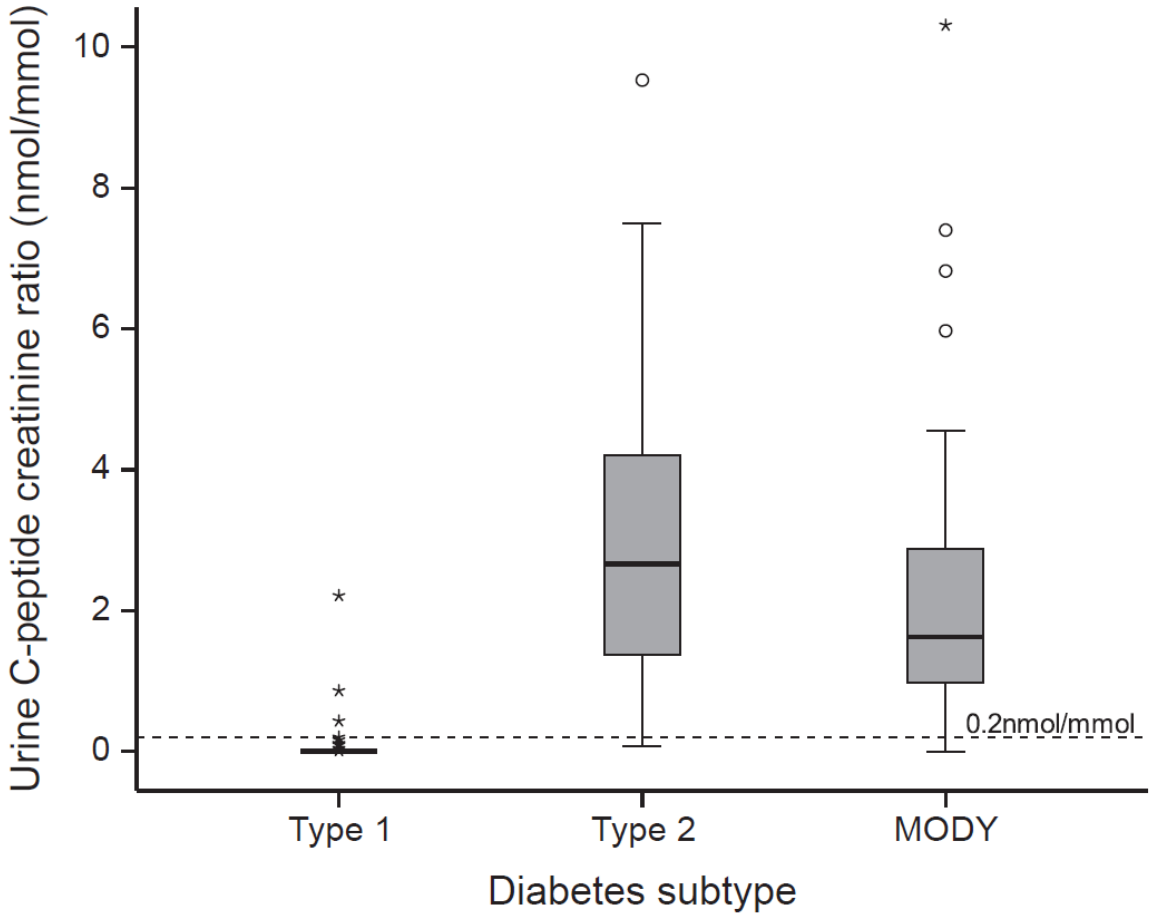
Boxplot of random non-fasting, fasting and glucagon-stimulated C-peptide in well-defined (on clinical features) Type 1 and Type 2 diabetes



Measurement of C-peptide in urine

- **Urine C-peptide** measurement is a potentially attractive non-invasive **measure of β-cell function**
- **C-peptide is excreted in the urine** through glomerular filtration and uptake from peritubular capillaries
- **The concentration in urine is typically 10–20 times higher than in plasma** and the absence of proteases found in blood mean that C-peptide is more

Urine C-Peptide:Creatinine ratio to discriminate Type 1 diabetes of over 5 years' duration from Type 2 diabetes and HNF1A/4A MODY



Adapted with permission from Besser *et al*

Η Κλινική Χρησιμότητα της Μέτρησης του C-Πεπτιδίου σε Ασθενείς με Σακχαρώδη Διαβήτη

- **Η εκτίμηση της έκκρισης ινσουλίνης είναι δυνητικά χρήσιμη στην κλινική πρακτική**

- **Το C-πεπτίδιο παράγεται σε ίσες ποσότητες με την ινσουλίνη, επομένως *Μπορεί να χρησιμοποιηθεί:***

1. Για την εκτίμηση της ενδογενούς έκκρισης ινσουλίνης, συμπεριλαμβανομένων και των ασθενών οι οποίοι λαμβάνουν ινσουλίνη

2. Για τις διαφορές στο γλυκαιμικό έλεγχο και τη θεραπευτική αντιμετώπιση μεταξύ του τύπου 1 και τύπου 2 διαβήτη

3. Αλλαγές στη θεραπεία του διαβήτη τύπου 2 και πρωτίστως όταν αφορά προοδευτική απώλεια της ικανότητας έκκρισης ινσουλίνης

A.G. Jones and A.T. Hattersley: Diabet Med.30 (7): 803–817, Jul.2013

Κλινική χρησιμότητα της μέτρησης του C-πεπτιδίου
Διαφοροποίηση του τύπου 1 και τύπου 2 διαβήτη (1)

- **Ένας σημαντικός κλινικός ρόλος του C-πεπτιδίου είναι στη διαφοροποίηση μεταξύ τύπου 1 και τύπου 2 διαβήτη**

- **Η απόλυτη έδειας ινσουλίνης είναι κύριο χαρακτηριστικό του διαβήτη τύπου 1 και πιο σχετικός δείκτης από ότι τα κλινικά χαρακτηριστικά όπως η ηλικία και το BMI κατά τη διάγνωση, τα οποία επικαλύπτονται ολοένα μεταξύ τύπου 1 και τύπου 2 διαβήτη**

- **Η χρησιμότητα είναι μεγαλύτερη σε μακροχρόνιο διαβήτη, καθώς μπορεί να υπάρξει μια ουσιαστική επικάλυψη των επιπέδων του C-πεπτιδίου μεταξύ του τύπου 1 και τύπου 2 διαβήτη κατά τη στιγμή της διάγνωσης**

- **Όταν ο διαβήτης ταξινομείται καθαρά με βάση την παρουσία ή απουσία αυτοαντισωμάτων, το C-πεπτιδίο παραμένει ένας σχετικά καλός προγνωστικός δείκτης από ότι ηλικία ή το BMI κατά τη διάγνωση**

Identifying patients with maturity-onset diabetes of the young (MODY)

- **Persistence of C-peptide is an important clinical feature of MODY**
- **In contrast to Type 1 diabetes, substantial insulin secretion persists in these forms of diabetes outside of the honeymoon period and the persistence of C-peptide in a patient thought to have Type 1 diabetes may be suggestive of MODY**
- **A random blood C-peptide of ≥ 0.2 nmol/l in those with diabetes diagnosed under 30 years of age and > 3 years' duration has been suggested as a criteria for consideration of MODY testing**

High Values of C-Peptide

- High levels of both C-peptide and blood glucose are found in people with type 2 diabetes or insulin resistance
- A high level of C-peptide with a low blood glucose level may mean that an insulin-producing tumor of the pancreas (insulinoma) is present or that the use of certain medicines such as sulfonylureas is causing the high level

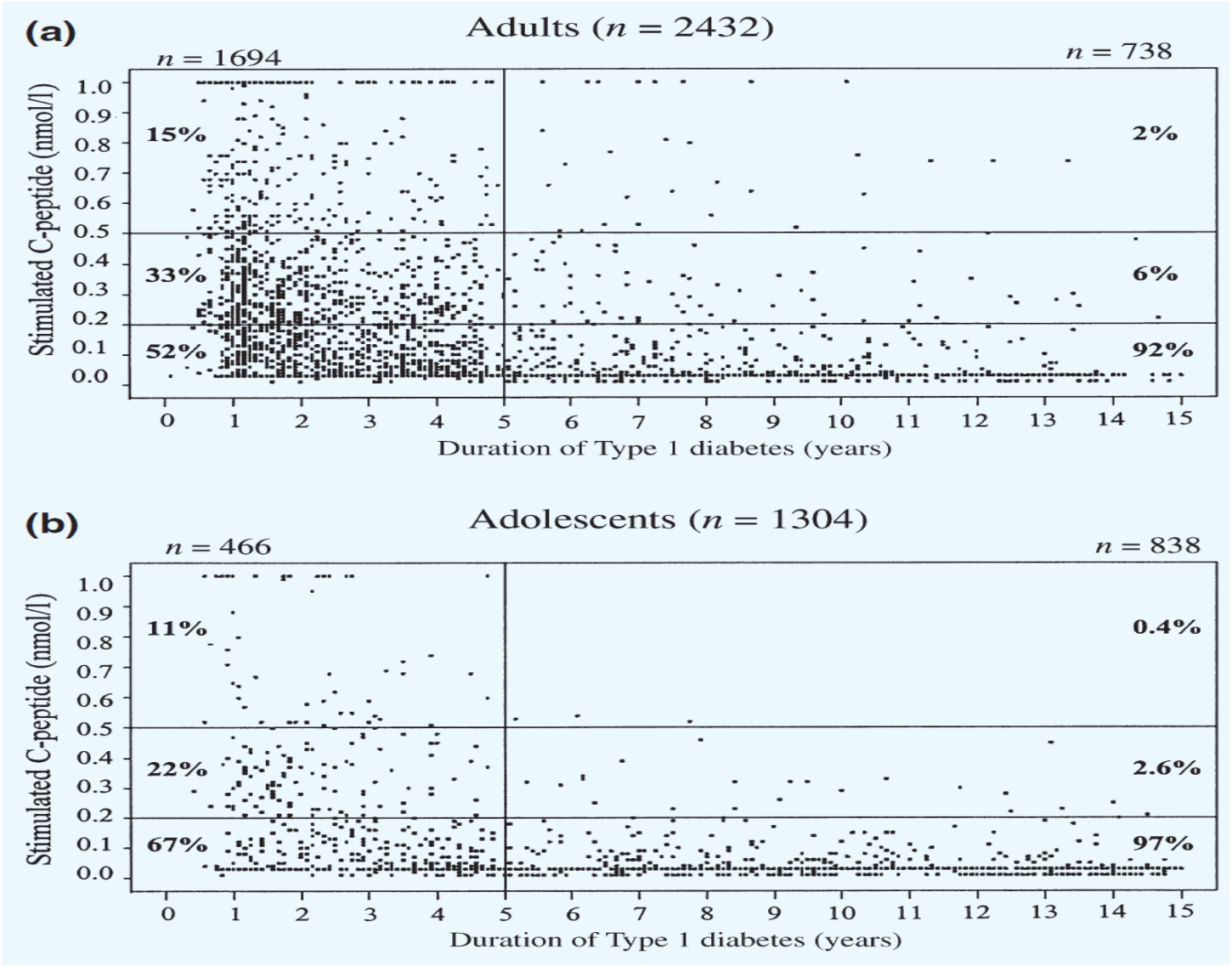
Low Values of C-Peptide

- A **low level of C-peptide** with a **high blood glucose** level is found in people with **type 1 diabetes**
- Persons with **LADA** typically have **low, although sometimes moderate levels of C-peptide** as the disease progresses and high blood glucose levels
- The most common **MODY** syndrome may also have **normal fasting C-peptide** results because the flaw in this case is in the secretion of insulin in response to rising glucose and fasting secretion is still near normal. Their **postprandial C-peptide** however is **below normal with elevated blood glucose**

2h-mixed-meal test C-peptide values in relation to diabetes duration *at entry screening for the DCCT*

adults > 18 ys

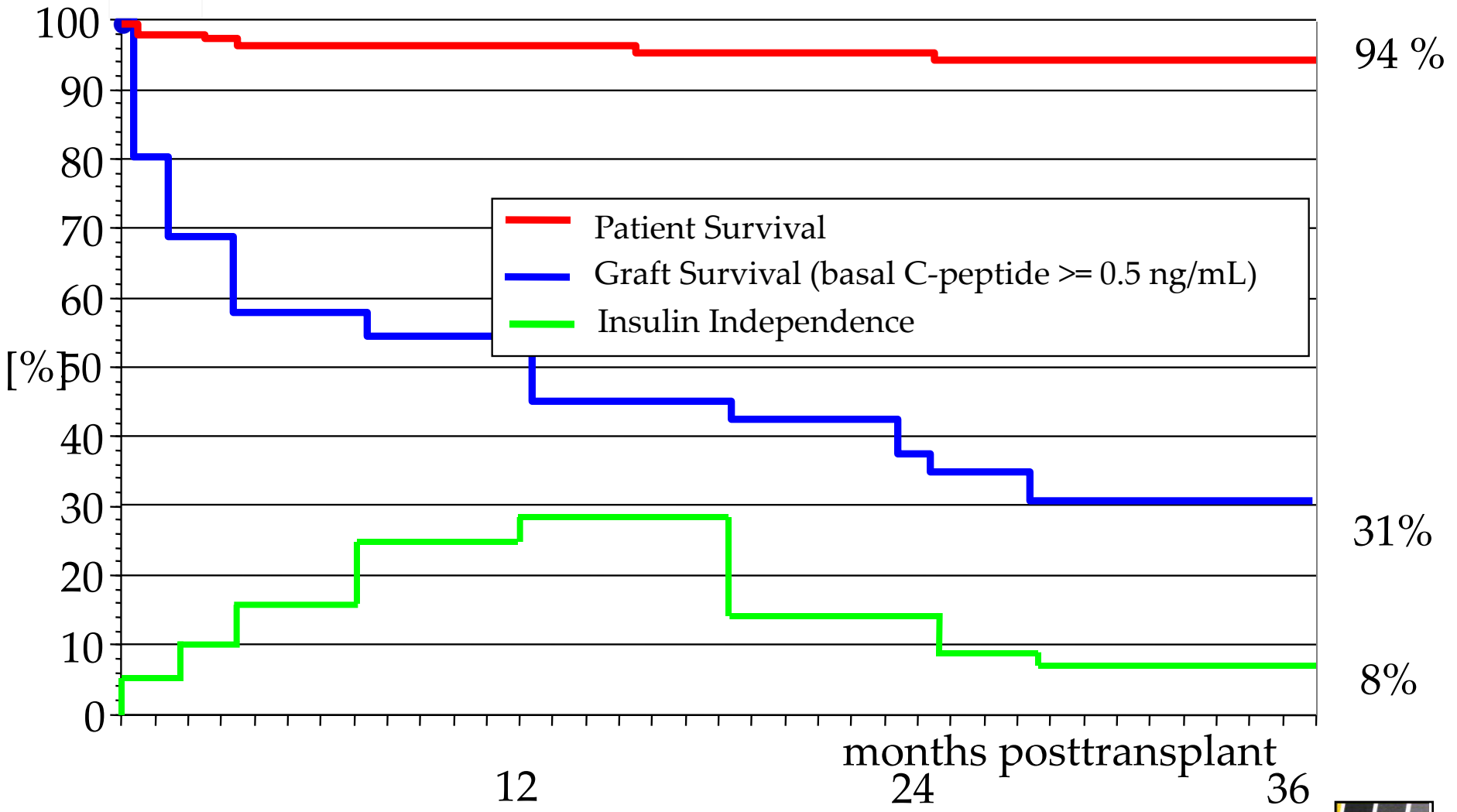
adults < 18 ys



C-Peptide and Transplant Failure

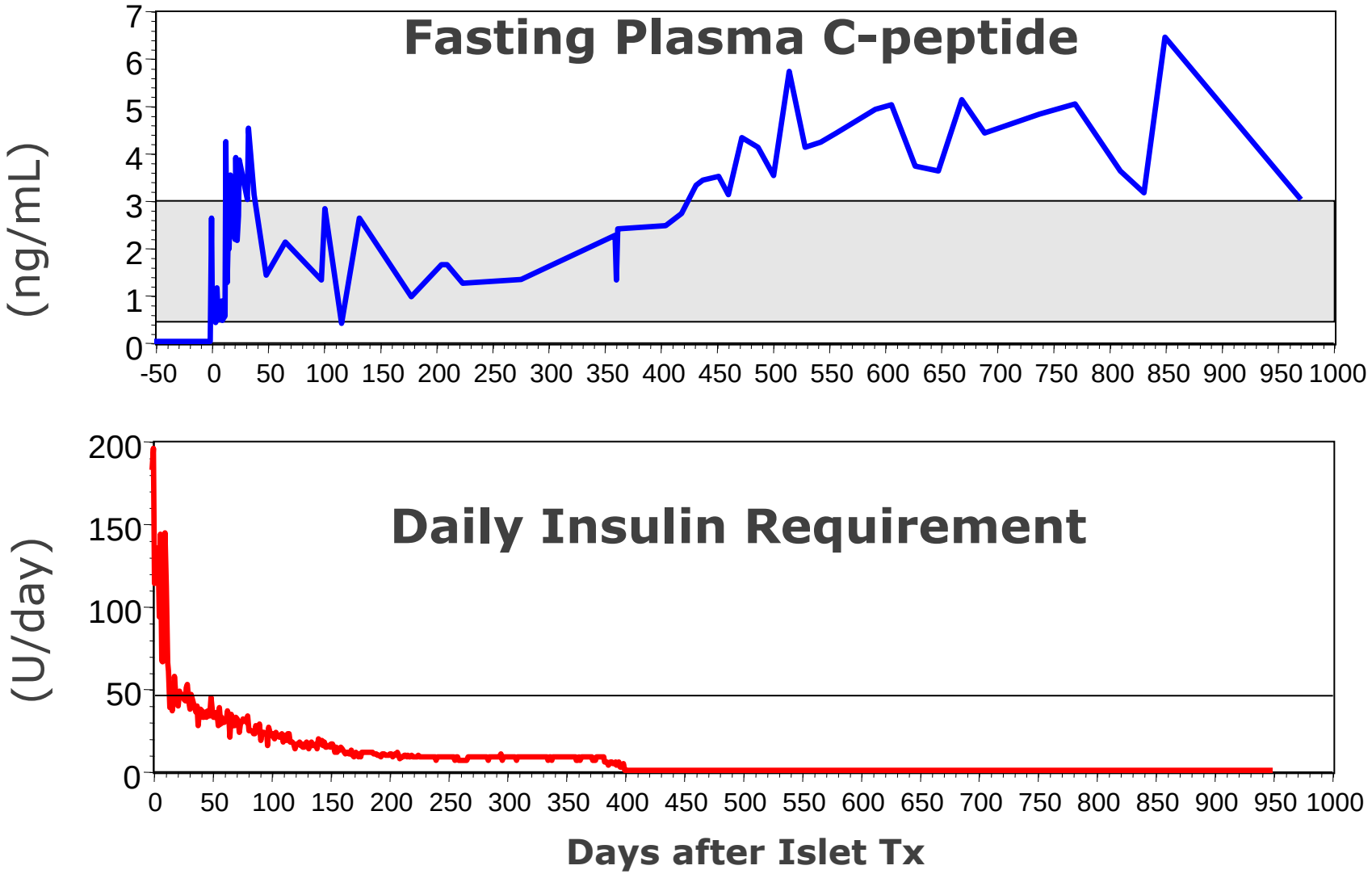
- C-peptide can be used to assist patient selection for islet cell transplantation
- After transplantation, monitoring graft function by monitoring β-cell function has been used to detect transplant failure
- Transplant failure is typically monitored with measurements of insulin, glucose, and C-peptide, and in some protocols, graft failure has been defined by a specific level of C-peptide

Cumulative Three-Year Patient and Graft Survival in C-Peptide Negative Type-1 Diabetic Recipients; 1991-2002; n=256*



* Only well documented cases

Islet-After-Kidney T1D-Recipient transplanted



Bretzel RG et al., Diabetes und Stoffwechsel 2, 378-390, 1993

Hypoglycemia

- In the evaluation of a nondiabetic patient with hypoglycemia, C-peptide can be a useful aid in narrowing the differential diagnosis
- C-peptide measurements in the evaluation of hypoglycemia are performed in the context of the 72-hour (prolonged) fast, the gold standard procedure
- Elevated C-peptide and insulin levels at the end of the fast point to an insulinoma or sulfonylurea ingestion as the cause for the hypoglycemia
- Low C-peptide levels and high insulin levels point to exogenous insulin administration

C-Peptide and Diabetes Complications

- **Studies have linked low levels of C-peptide to diabetes mellitus complications** and evidence suggests that maintaining higher levels of C-peptide is especially beneficial for type 1 diabetics

- C-peptide measurements have also been used to classify diabetes mellitus and as a marker of pancreatic β-cell function

Residual β-Cell Function 3–6 Years After Onset of Type 1 Diabetes Reduces Risk of Severe Hypoglycemia in Children and Adolescents

- **OBJECTIVE: To determine the prevalence of residual β-cell function** (RBF) in children after 3–6 yrs of type 1 diabetes **and to examine the association between RBF and incidence of severe hypoglycemia, glycemic control and insulin requirements**

- **CONCLUSIONS:** We demonstrated considerable phenotypic diversity in RBF among children after 3–6 yrs of type 1 diabetes. **Children with RBF are at lower risk for severe hypoglycemia, have better diabetes regulation and have lower insulin requirements compared with children without RBF.** There appears to be a lower limit for stimulated RBF of ~0.04 nmol/L that confers a beneficial effect on hypoglycemia and metabolic control

J.S. SØRENSEN et al., Diabetes Care 36:3454–3459, 2013

Impact of C-Peptide Preservation on Metabolic and Clinical Outcomes in the DCC - Trial

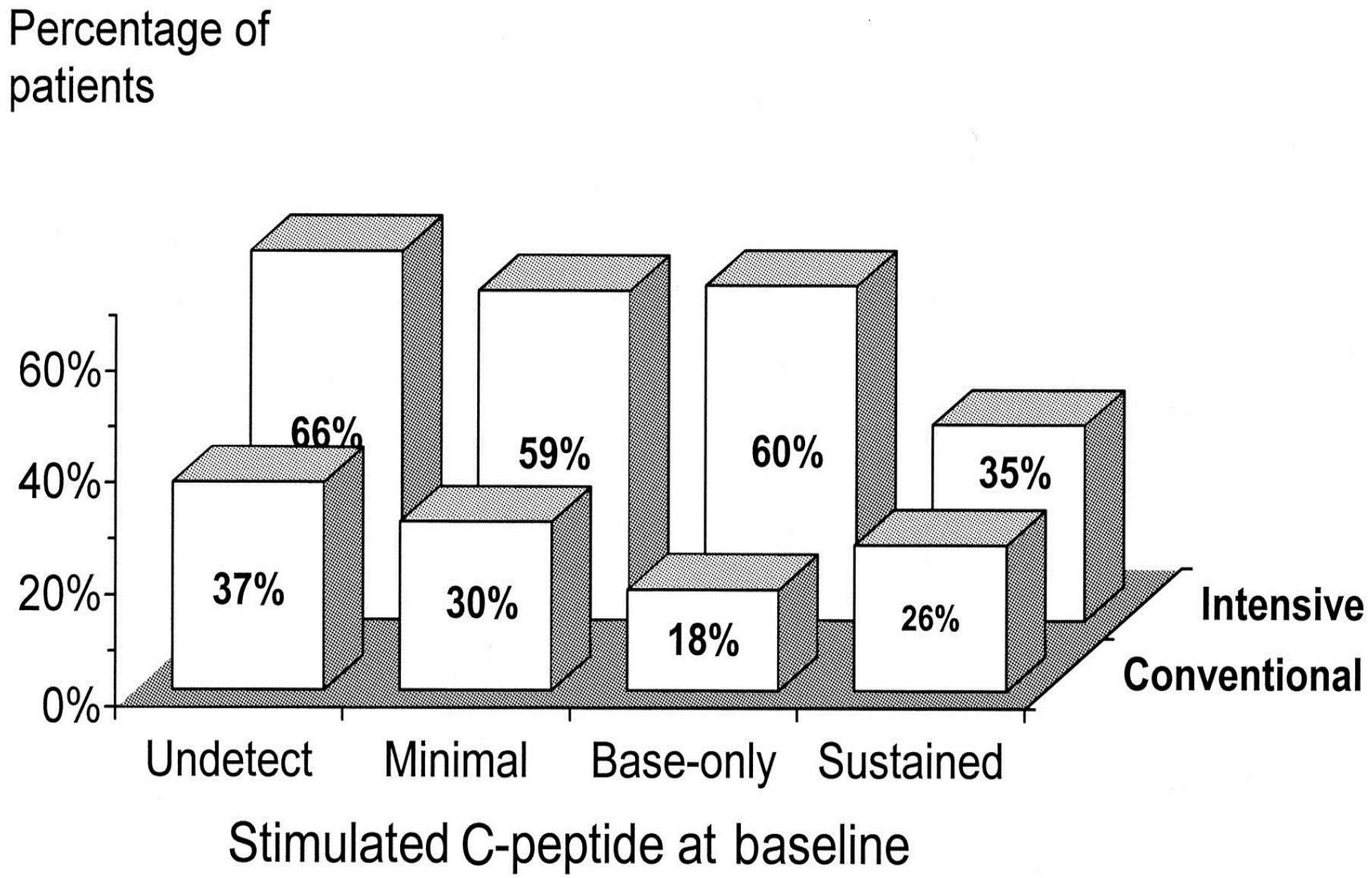
The DCC - Trial established that a stimulated C-peptide concentration ≥0.2 nmol/L at study entry among subjects **with up to a 5-year diabetes** duration **is associated with favorable metabolic and clinical outcomes** over the subsequent 7 yrs of follow-up

J.M. Lachin et. al. for the DCCT/EDIC Research Group*
Diabetes, Vol. 63, Feb., 2014

C-Peptide Used as Indicator of Glycemic Control and Declining β-Cell Function

- The DCCT found that there was **less retinopathy and nephropathy** with preserved β-cell function
- **GADA screen in combination with C-peptide measurements can be used to identify a subset of type 2 patients** whose disease is progressing and who may need to be treated more aggressively
- These data suggest that C-peptide levels might be able to identify type 2 diabetic patients that would be managed better with insulin

Percentages of subjects who experienced at least one episode of severe hypoglycemia over the first 6 years of the DCCT



Steffes M W et al. Dia Care;26:832-836, 2003

Impact of C-Peptide Preservation on Metabolic and Clinical Outcomes in the DCCT- Trial

Discussion

- **Preservation of β-cell function** as measured by C-peptide in patients with type 1 diabetes **is known to result in improved metabolic control and reduced microvascular complications**

- Across the range of values, **higher amounts of secreted C-peptide were associated with lower HbA1c, lower daily insulin dose, less severe hypoglycemia and less risk of retinopathy**

J.M. Lachin et. al. for the DCCT/EDIC Research Group*
Diabetes, Vol. 63, Feb., 2014

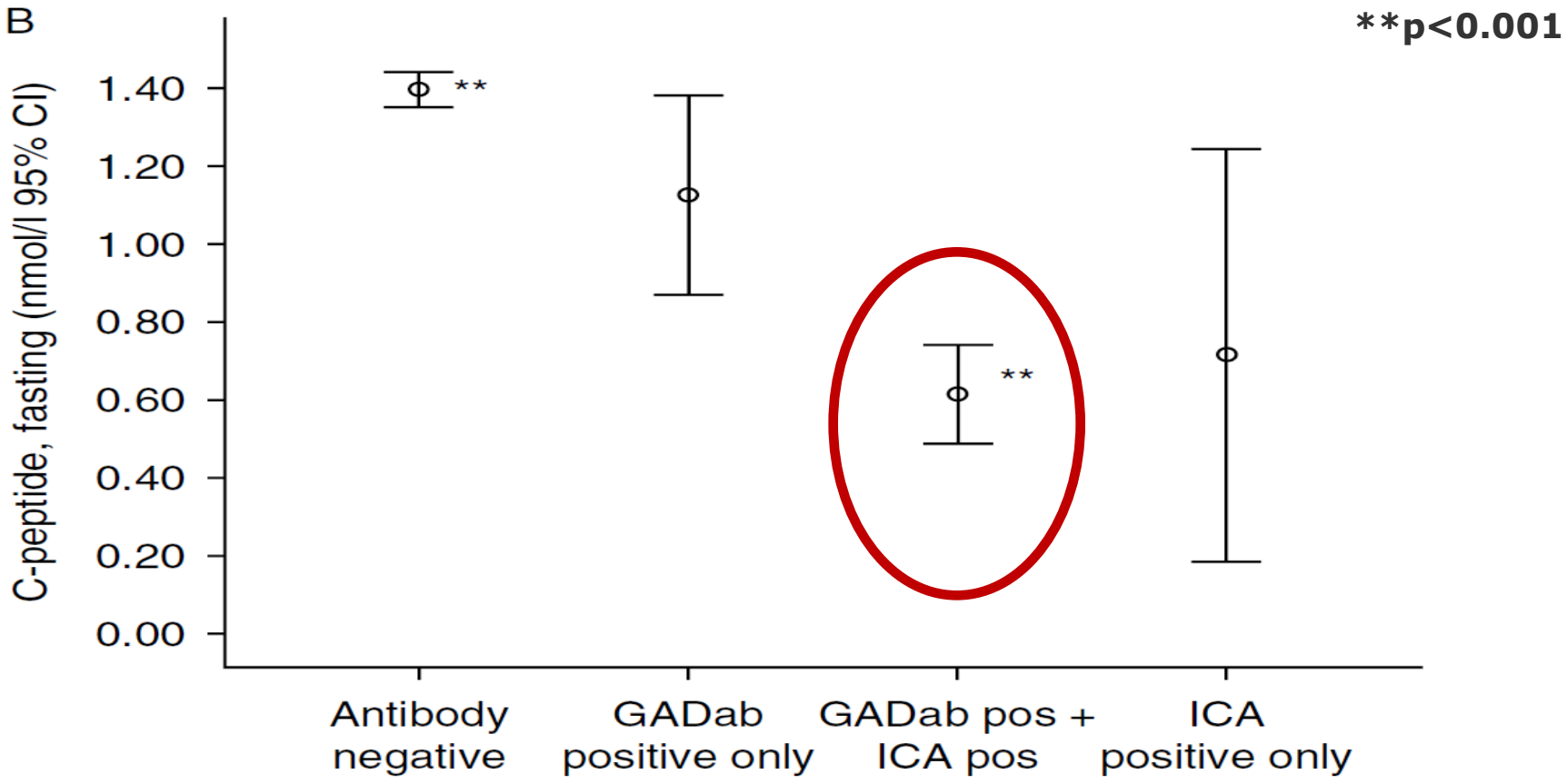
Levels of C-peptide, BMI and age and their usefulness in classification of diabetes in relation to autoimmunity, in adults with newly diagnosed diabetes in Kronoberg, Sweden

- **Aim: To check the ability of age, BMI and C-peptide to discriminate between autoantibody-positive (Ab+) and -negative (Ab−) diabetes.**

- **Classification:** Age and BMI are among the most frequently used tools for clinical classification but seldom tested in an evidence-based manner. **In our large** (1180 patients) **population-based cohort of newly diagnosed patients, we found that, while still not ideal, C-peptide was a better discriminator than both age and BMI for identifying those positive to at least one of GADA and/or ICA** and C-peptide AUC reached the same level in ROC analysis as several classification schemes for ketosis-prone diabetes

M.Thunander et.al., Eur J Endocrinol.166(6): 1021–1029, Jun 2012

Mean fasting C-peptide per antibody positivity in adults with newly diagnosed diabetes



M.Thunander, Eur J Endocrinol;166(6):1021-9, Jun 2012

Levels of C-peptide, body mass index and age, and their usefulness in classification of diabetes in relation to autoimmunity, in adults with newly diagnosed diabetes in Kronoberg, Sweden

Conclusions

- **At diagnosis of diabetes, C-peptide was superior to age and BMI in discriminating between autoimmune and non-autoimmune diabetes.** Most of the adults had normal or high levels of C-peptide at presentation of diabetes among the autoimmune patients

- **Analysis of C-peptide is less expensive than antibody analyses and better than both BMI and age at indicating autoimmune diabetes**

- **C-peptide can be a good complement in clinical practice in many settings**

M.Thunander et.al., Eur J Endocrinol.166(6): 1021–1029, Jun 2012

C-peptide levels can be predictive of autoantibodies

- Torn et al. have found that **C-peptide levels can predict the presence of autoantibodies**

They determined that:

- A random C-peptide value of **below** 0.91 ng/ml had a 94% positive predictive value for patients **with** autoantibodies
  and
- A value **above** 2.42 ng/ml had a 72% positive predictive value for patients **without** autoantibodies

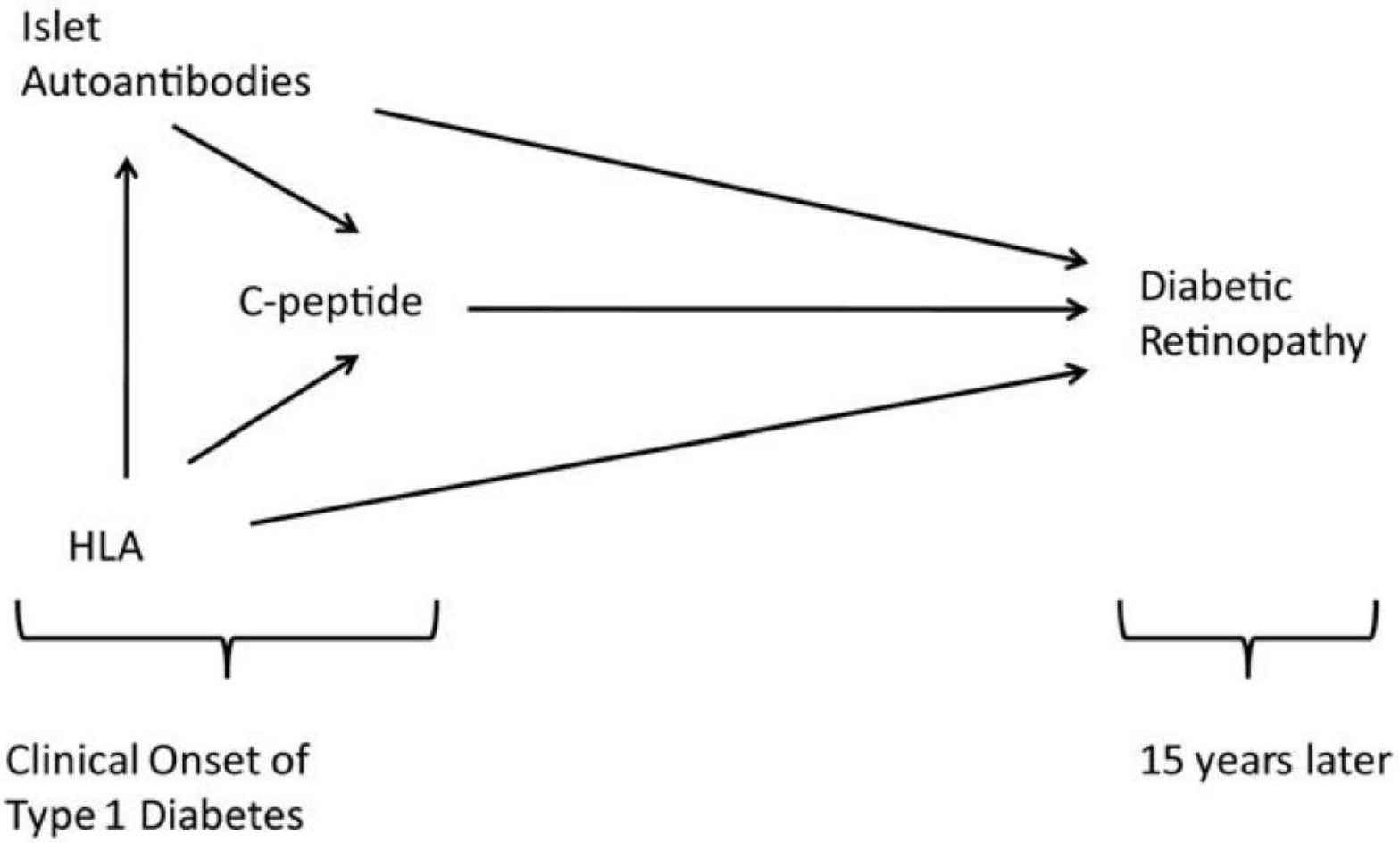
HLA Genes, Islet Autoantibodies and Residual C-Peptide at the Clinical Onset of Type 1 Diabetes Mellitus and the Risk of Retinopathy 15 Years Later

Aim: HLA genes, islet autoantibodies and residual C-peptide were studied to determine the independent association of each **exposure with diabetic retinopathy (DR), 15 years after the clinical onset of type 1 diabetes in 15–34 year old individuals**

In conclusion: Increased levels of GADA at the time of onset were associated with an increased risk of DR 15 years later

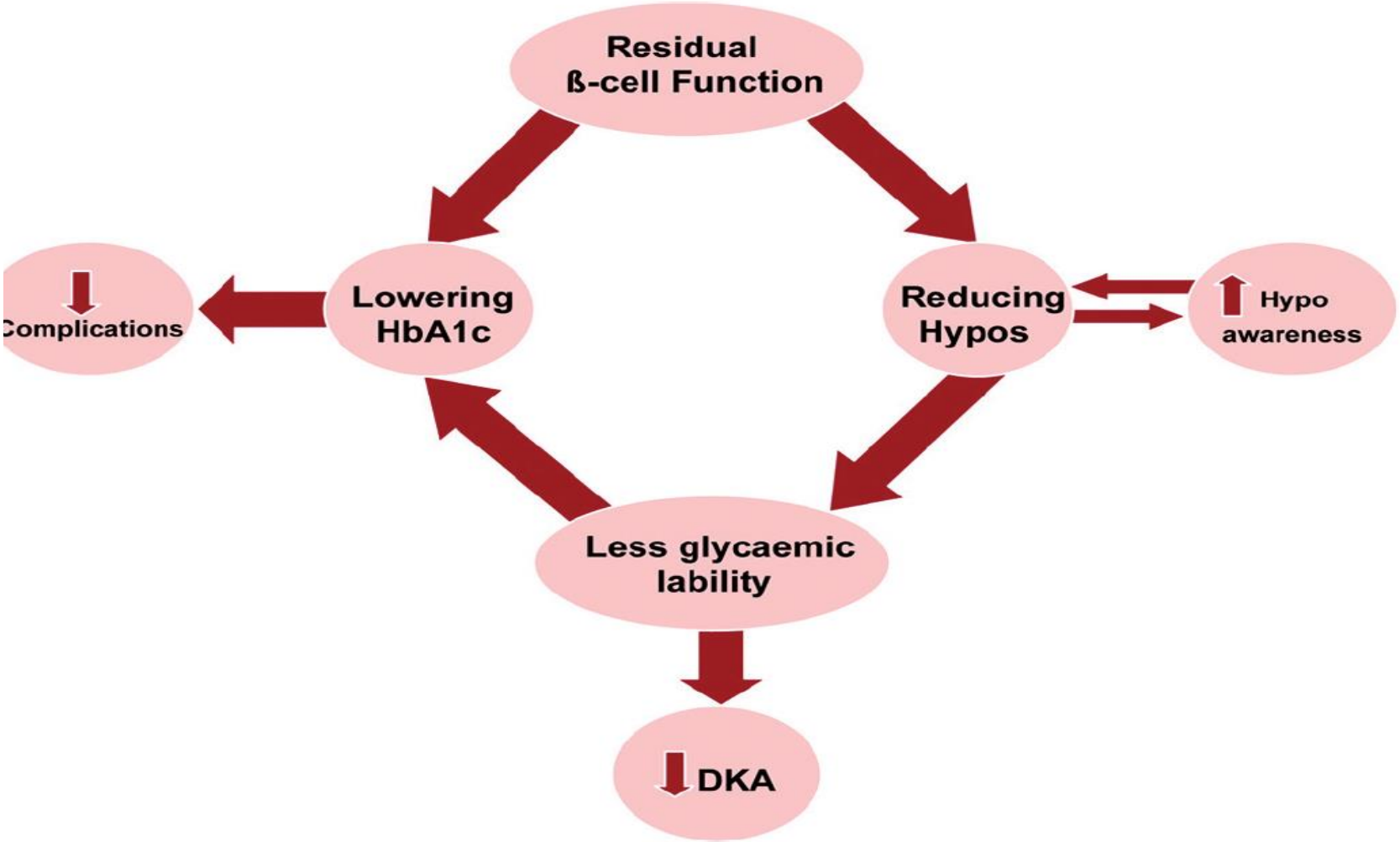
R. A. Jensenon et.al.,on behalf of the DISS: PLoS ONE, Vol. 6 (3), March 2011

HLA Genes, Islet Autoantibodies and Residual C-Peptide at the Clinical Onset of Type 1 Diabetes Mellitus and the Risk of Retinopathy 15 Years Later

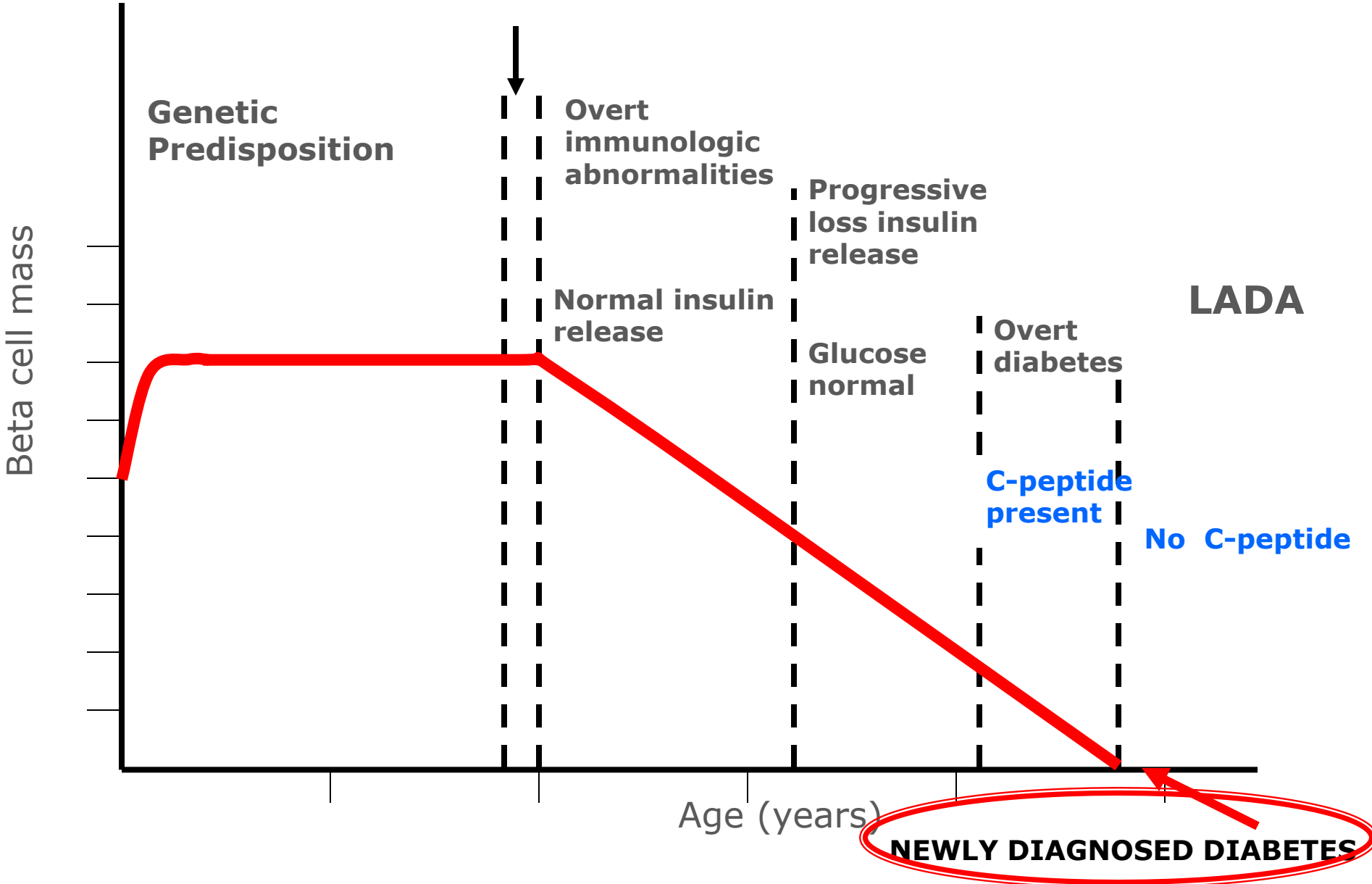


R. A. Jensenon et.al.,on behalf of the DISS: PLoS ONE, Vol. 6 (3), March 2011

Benefits of Preservation of Endogenous Insulin Secretion



"Stages" in Development of Type 1A Diabetes



ΑΥΤΟΑΝΤΙΣΩΜΑΤΑ

Αντι-ινσουλινικά αντισώματα (IAA)

- ✓ ΣΔ 1 16-69%
- ✓ Συγγενείς 1ου βαθμού 2-4%
- ✓ Γενικός πληθυσμός 1.5-3.9%

Αντι-νησιδιακά αντισώματα (ICA)

- ✓ ΣΔ 1 60-90%
- ✓ Συγγενείς 1ου βαθμού 1-9%
- ✓ Γενικός πληθυσμός 1.4-5.3%

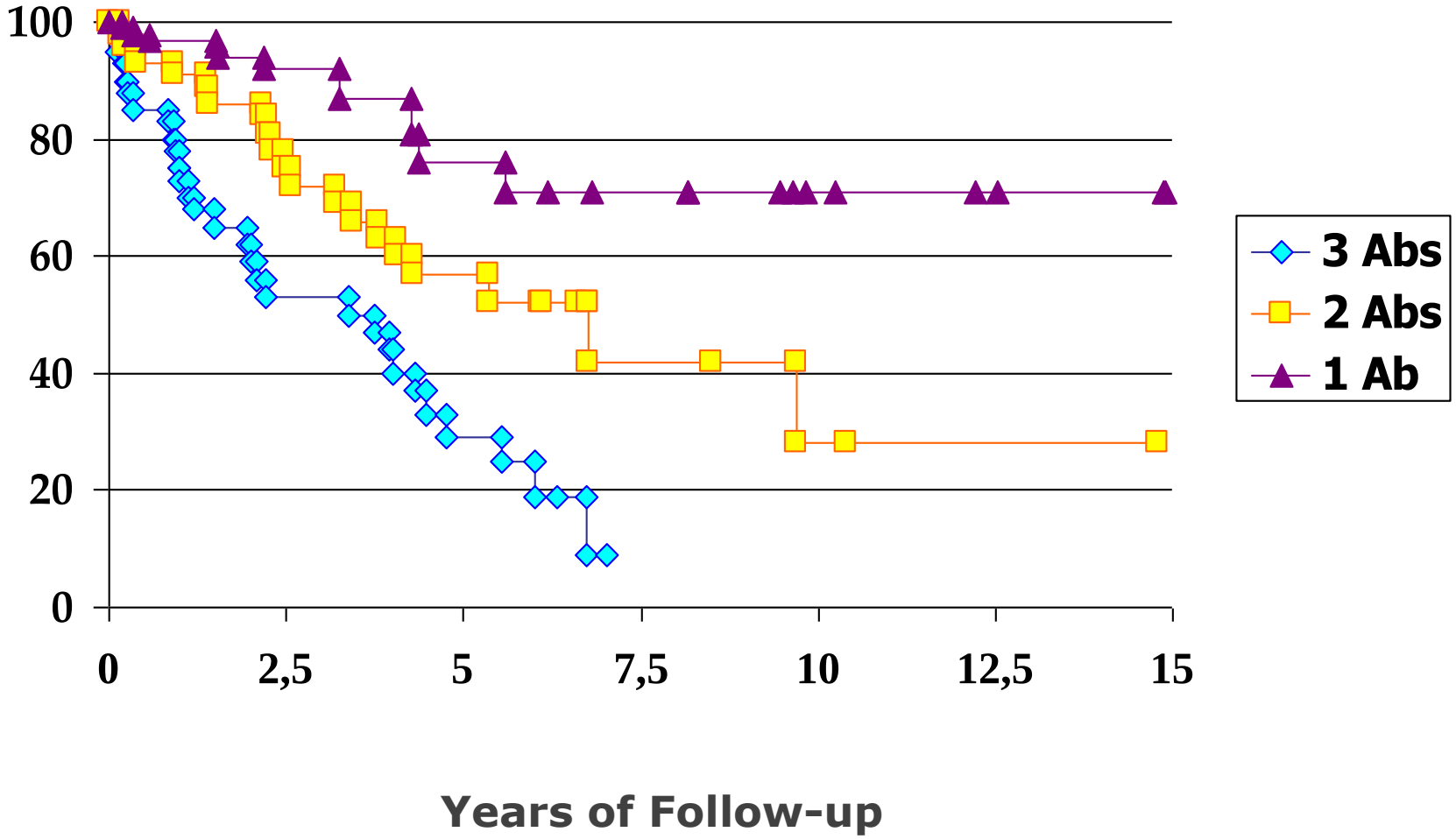
Αντισώματα έναντι της αποκαρβοξυλάσης του γλουταμινικού οξέος (GAD)

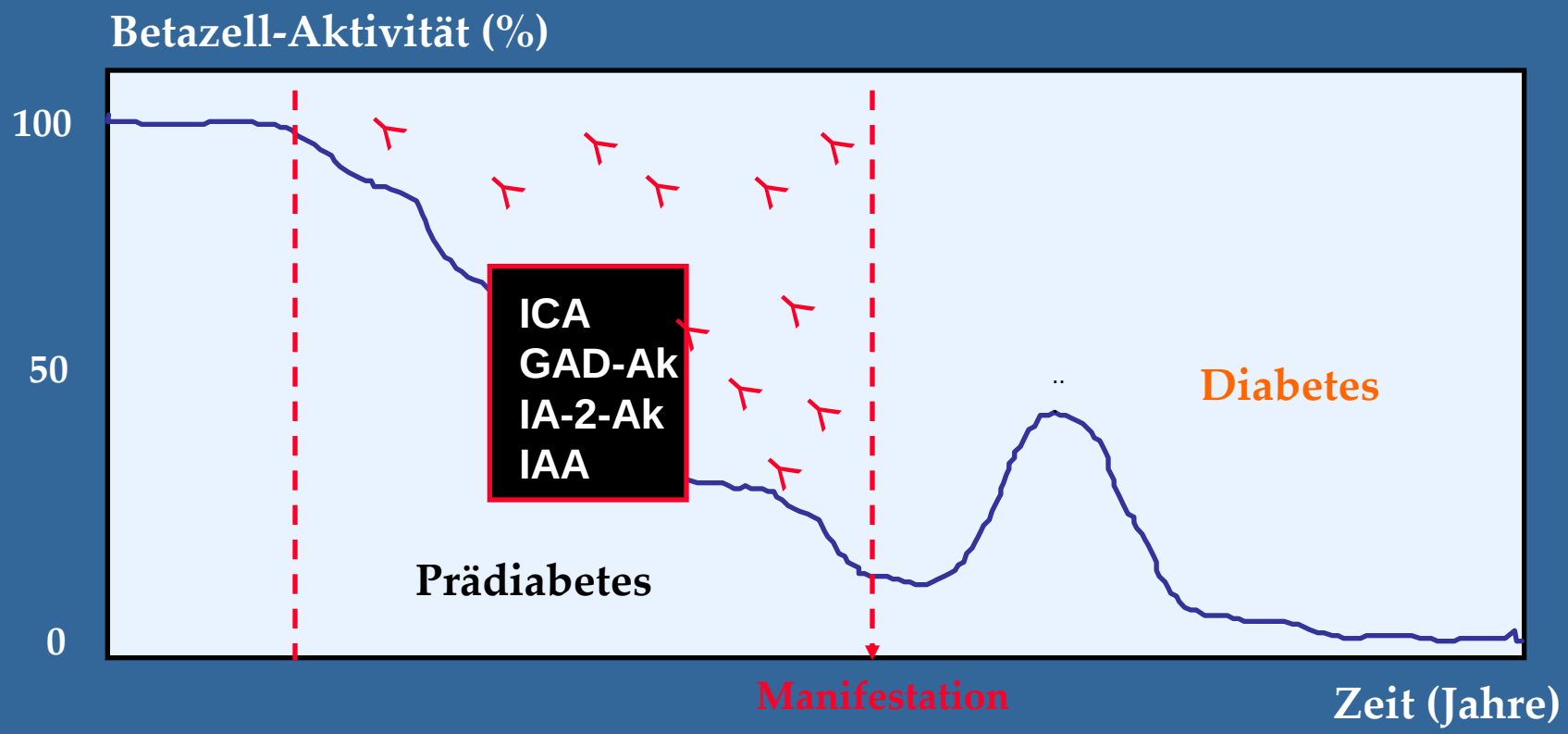
- ✓ ΣΔ 1 22-81%
- ✓ Συγγενείς 1ου βαθμού 5-13%
- ✓ Γενικός πληθυσμός 1.4-5.3%

Αντισώματα έναντι της φωσφατάσης της τυροσίνης (IA-2ic)

- ✓ ΣΔ 1 48-80%
- ✓ Συγγενείς 1ου βαθμού 2-5%
- ✓ Γενικός πληθυσμός 1.5-2.4%

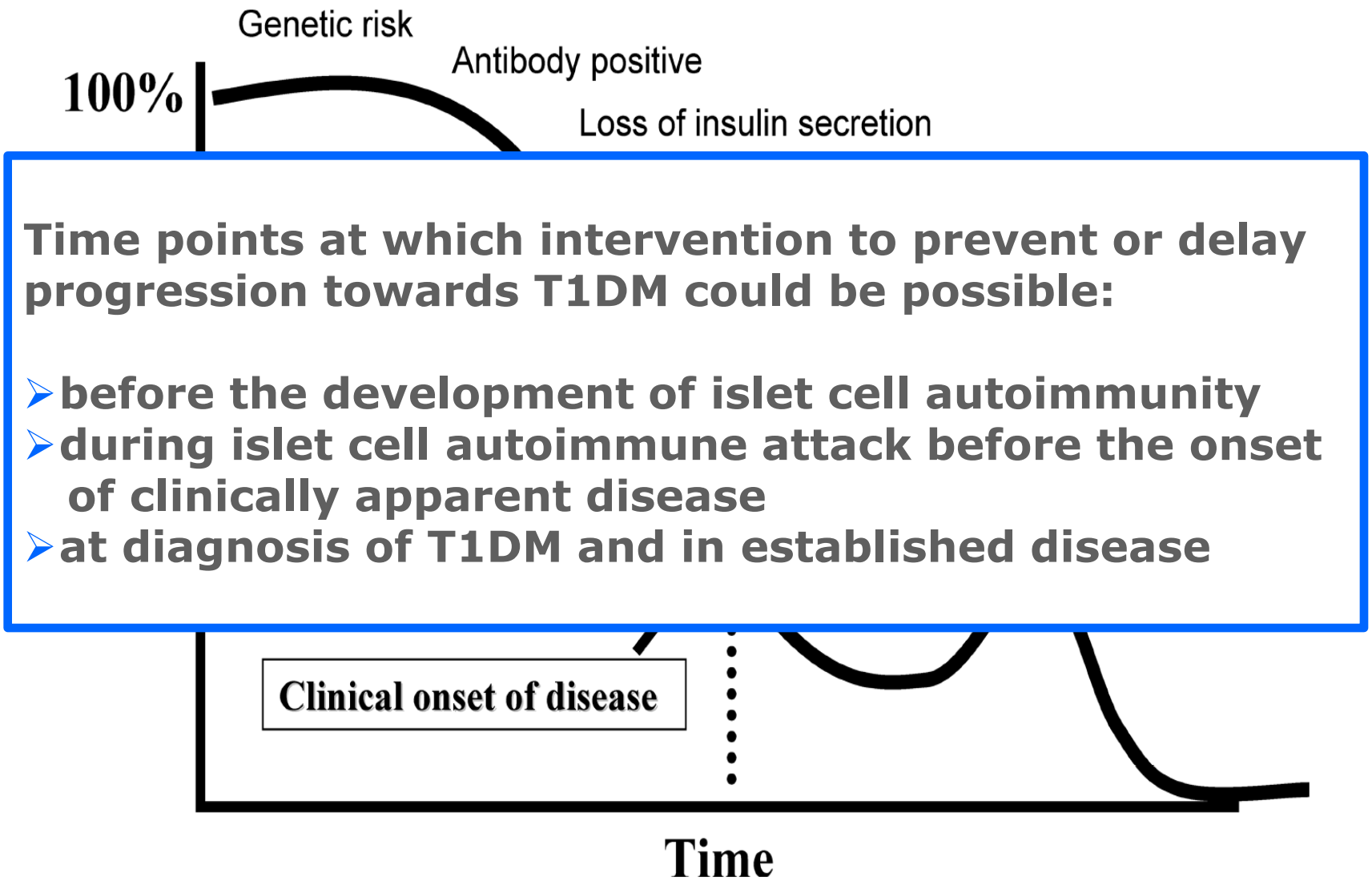
Progression to Diabetes vs Number of Autoantibodies (GAD, ICA512, Insulin)





Die 1. Serumprobe aller 882 Probanden wurde auf die vier derzeit aktuellen und im Stadium des Prädiabetes bereits nachweibaren Antikörpern untersucht.

Stages of Type 1 Diabetes Prevention



Time points at which intervention to prevent or delay progression towards T1DM could be possible:

- **before the development of islet cell autoimmunity**
- **during islet cell autoimmune attack before the onset of clinically apparent disease**
- **at diagnosis of T1DM and in established disease**

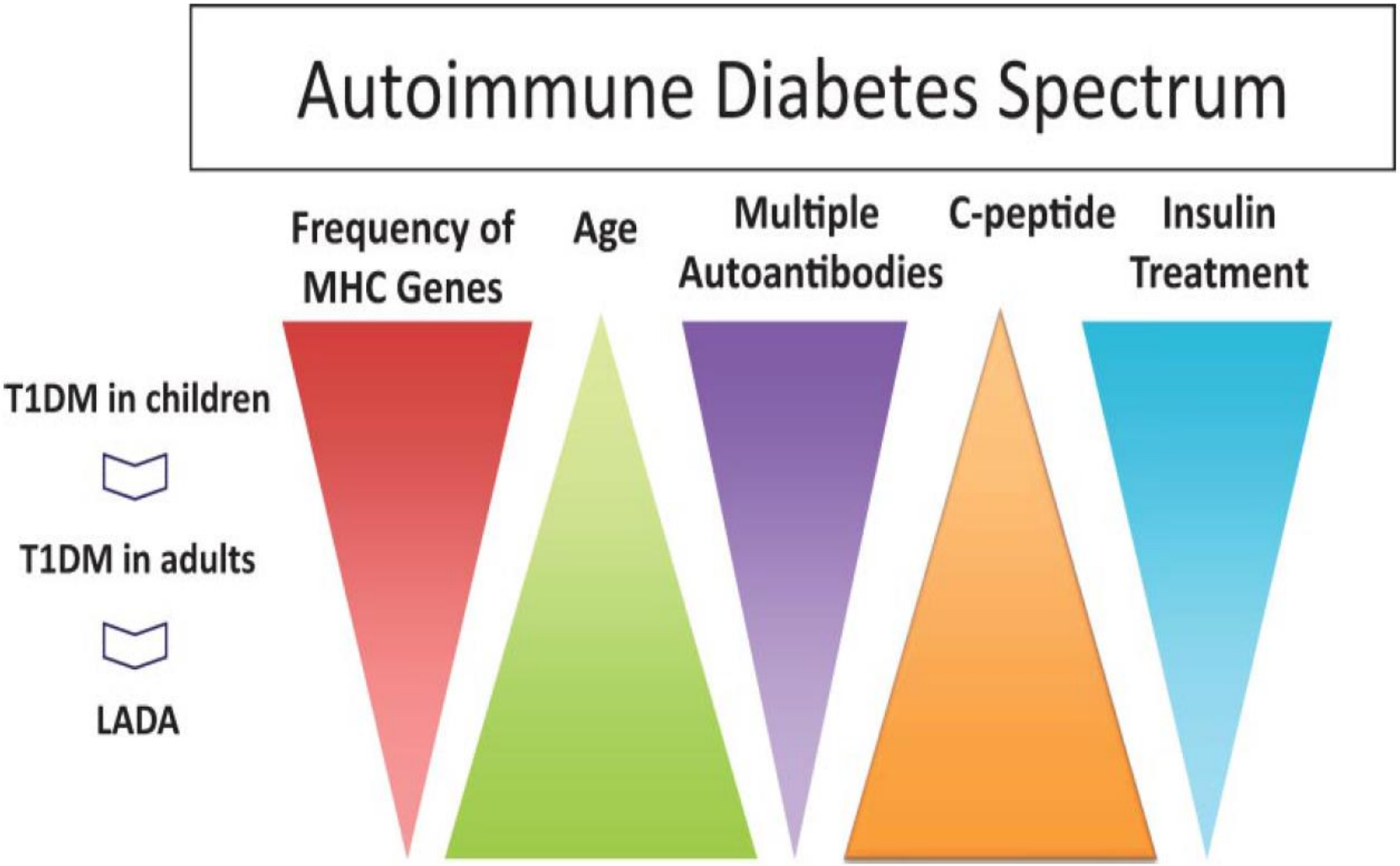
Intervention studies in man Completed large immunological intervention trials conducted in antibody-positive individuals

Agent/intervention	Antigen specific?	Proposed mechanism of action	Study population characteristics	Development of diabetes prevented/ delayed
Insulin (oral administration), DPT-1[40]	Yes	Down-regulation of the inflammatory immune response and induction of antigen-specific regulatory T cells	ICA- and IAA-positive relatives (age 3–45 years) of person with T1DM with 5-year projected risk for developing T1DM of 26–50%	No
Insulin (parenteral administration), DPT-1[39]	Yes	As for oral insulin + β-cell 'rest'	ICA- and IAA-positive relatives (age 3–45 years) of person with T1DM with 5-year projected risk for developing T1DM >50%	No
Insulin (nasal administration), DIPP study[42]	Yes	As for oral insulin	HLA susceptible infants, screened for development of two or more autoantibodies. Treatment commenced when tested antibody positive, aged 1–10 years	No
Nicotinamide (oral administration) European Nicotinamide Diabetes Intervention Trial (ENDIT)[44]	No	β-cell protection by prevention of NAD depletion	ICA-positive relatives of person with T1DM, age 3–40 years	No

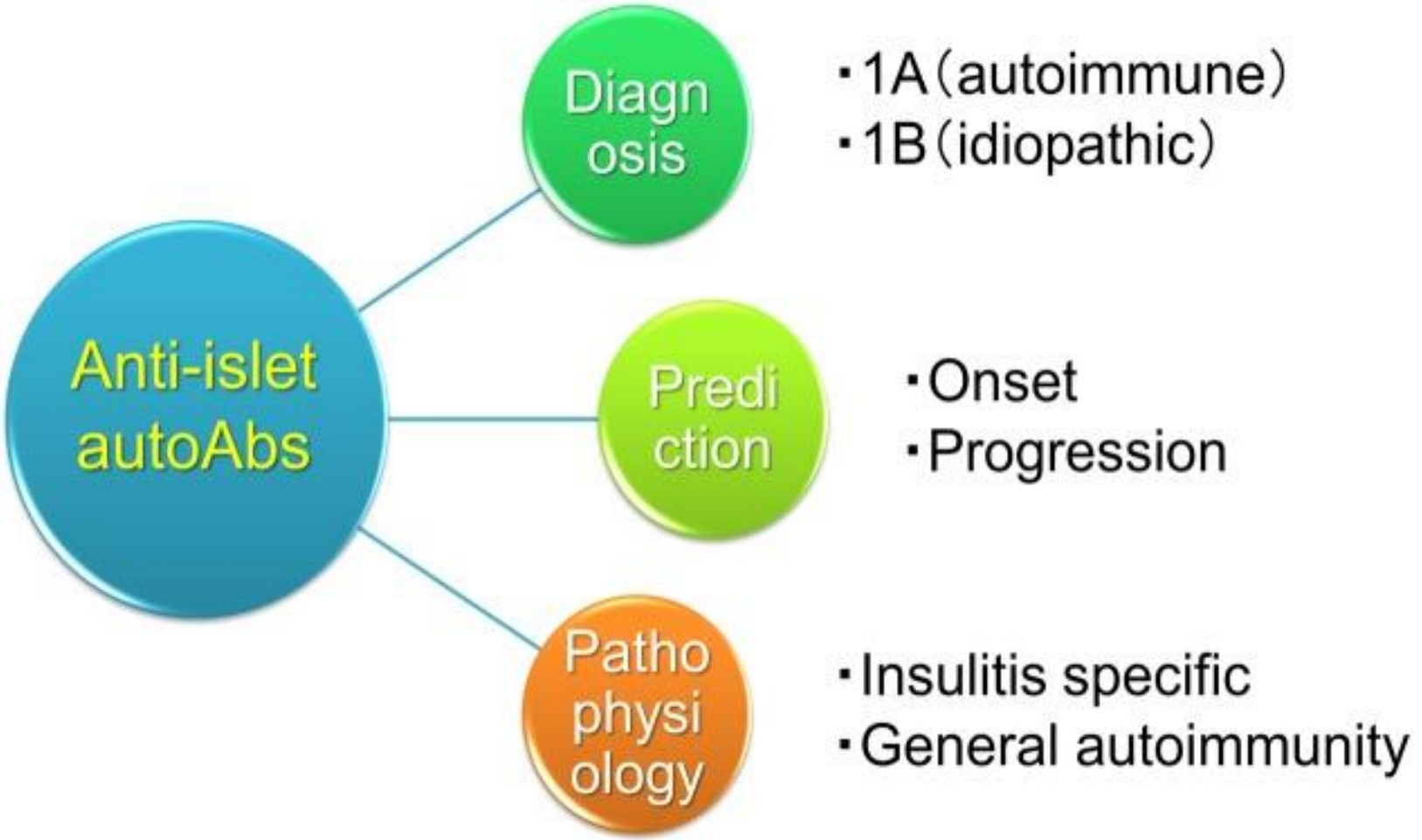
Predicting Adult-Onset Autoimmune Diabetes

Clarity From Complexity

R. David Leslie



Clinical utilities of anti-islet autoantibodies in patients with diabetes



Clin Pediatr Endocrinol. 2014 Oct; 23(4): 99–105

Clinical Applications of Diabetes Antibody Testing

Context:

- **Islet autoantibodies are characteristic of type 1 diabetes.**
- **They are detectable before clinical onset and define also the subgroup of patients with LADA diabetes**
- **Autoantibody assays are increasingly available to clinicians**

P.J. Bingley:J Clin Endocrinol Metab., 95: 25–33, 2010

Clinical Applications of Diabetes Antibody Testing

Evidence Synthesis:

- **Islet autoantibodies** appearearly in life and testing for multiple antibodies **identifies unaffected individuals at very high risk of type 1 diabetes with high sensitivity**

- This is **important for research**, **but currently no intervention prevents or delays diabetes** and evidence of benefit from awareness of risk is weak

- In **non-insulin-treated diabetes**, patients **with autoantibodies progress to insulin requirement more rapidly**, but evidence that testing benefits the individual patient is limited.

- **Antibody testing is useful in classifying diabetes of other types.**

P.J. Bingley:J Clin Endocrinol Metab., 95: 25–33, 2010

Clinical Applications of Diabetes Antibody Testing

Conclusions:

- Islet autoantibody testing allows prediction of type 1 diabetes and definition of the LADA diabetes
- **Although useful for research, until therapies modulating the disease process become available**, the benefit to individual patients is generally questionable
- **With a few exceptions, diabetes antibody testing does not yet have a role in routine clinical care**

P.J. Bingley: *J Clin Endocrinol Metab.*, 95: 25–33, 2010

Βοηθάει ο Προσδιορισμός του C-Πεπτιδίου και των Αυτοαντισωμάτων στην Καθημερινή Πρακτική;;;

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