A neuroendokrin és az immunrendszer kapcsolata

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Semmelweis Egyetem I. sz. Belgyógyászati Klinika

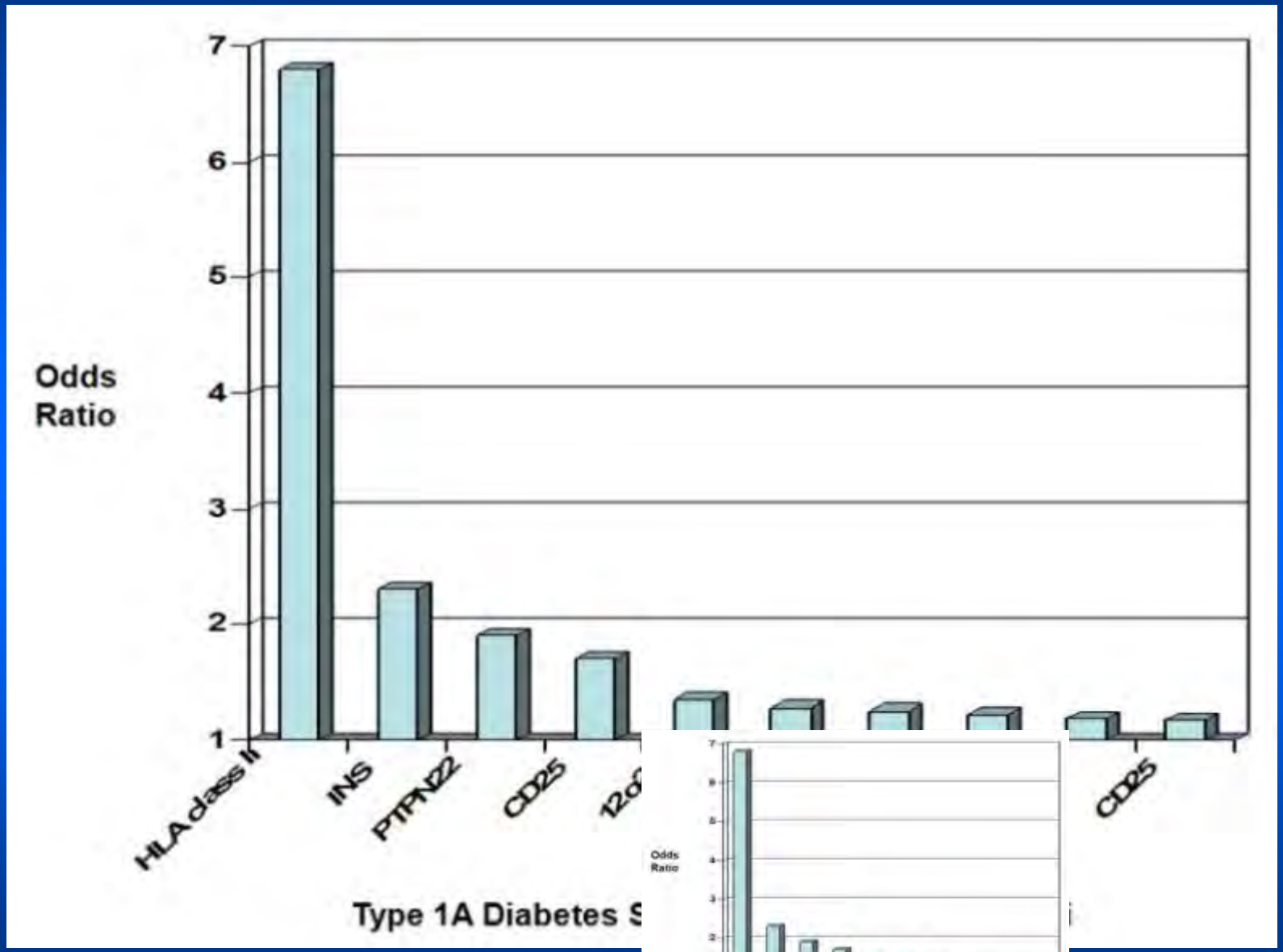
Diabetes mellitus

Diabetes mellitus

- Type 1A: immun-mediált
- Type 1B: nem immun-mediált
- USA: 1.5 millió 1A beteg (170.000 <20 éves)
- Genetikai szuszceptibilitás (HLA allélek)
- Monogénes, nem immunmediált diabetes:
  - permanent neonatal diabetes mellitus (PND)
  - transient neonatal diabetes (TND)
  - maturity-onset diabetes of the young (MODY)
- Monogénes formákat gyakran jobb szulfanilureával kezelni
- ATP-szenzitív K-csatorna, HNF-1 alfa, glukokináz mutációk – nem kell kezelés
- APS-1 és IPEX szindrómák

Harjutsalo V, et al, Lancet. 2008 May 24;371(9626):1777–82.
Erlich H et al, Diabetes. 2008. 5;57:1084–92.

Diabetes mellitus



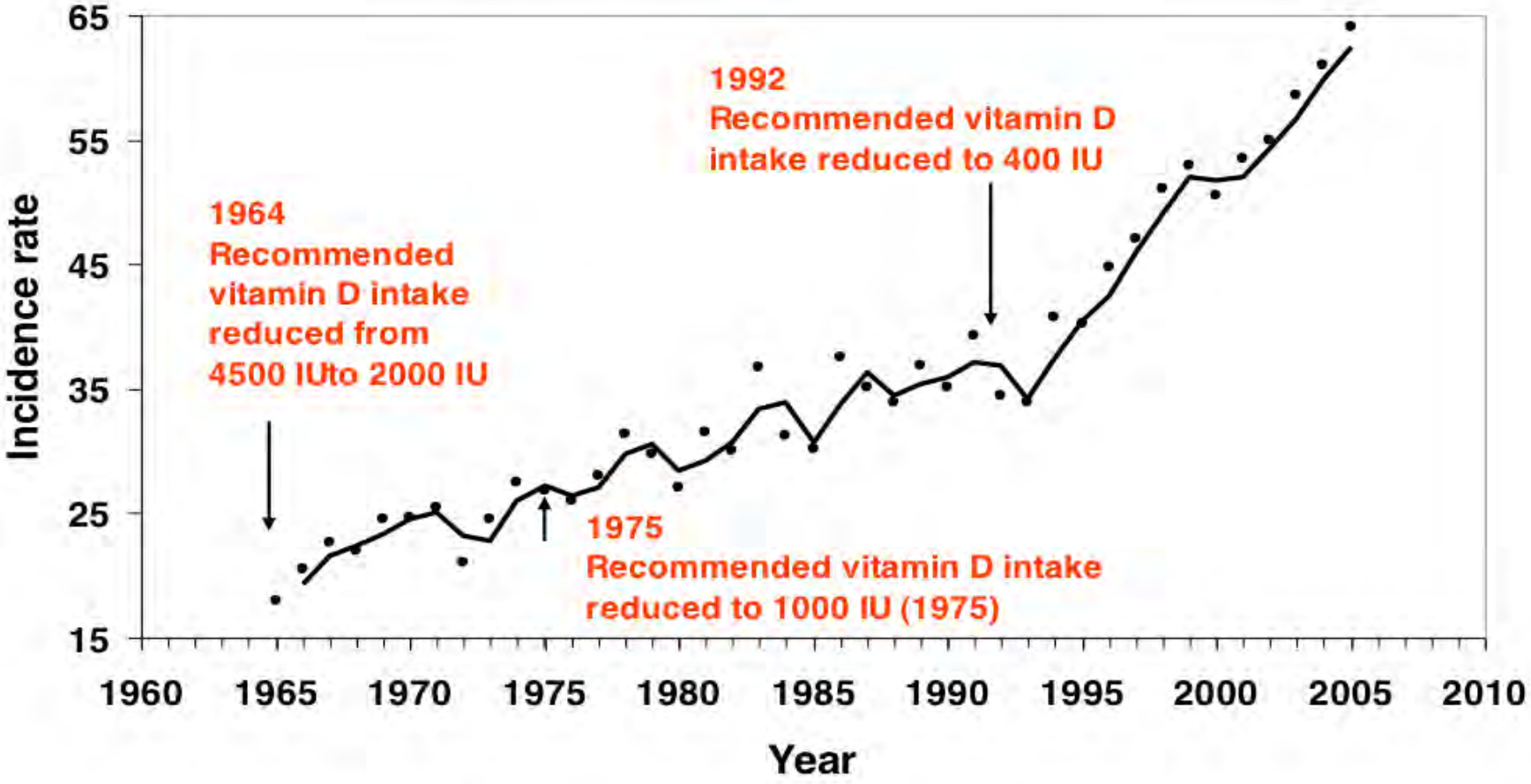
Harjutsalo V, et al, Lancet. 2008 May 24;371(9626):1777–82.
Erlich H et al, Diabetes. 2008. 5;57:1084–92.

Diabetes mellitus

- Környezeti tényezők:
  - tehéntej? Autoimmunity Study of the Young: neg. (?)
  - viszont a csökkent omega-3 bevitel és a korai cereáliák poz.
  - D vitamin

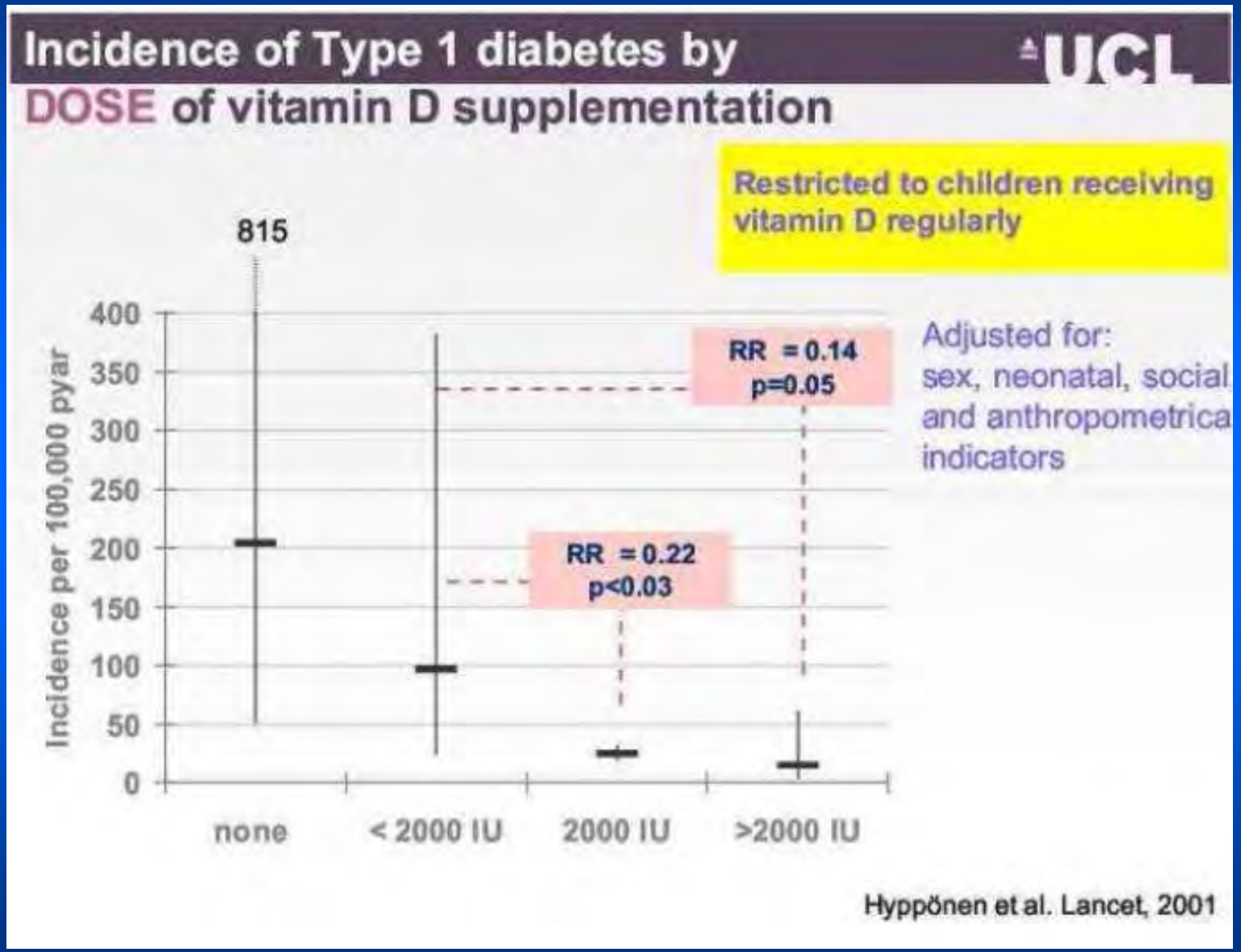
Michels AW, Eisenbarth GS, J Allergy Clin Immunol. 2010 February ; 125(2 Suppl 2): S226–S237.
Norris JM et al, JAMA 2007. 26(298):1420-1428.

Annual age-adjusted incidence rates of type 1 diabetes, children ≤ 14 years old, per 100,000 population, and dates of changes in recommended daily intake of vitamin D in infants, Finland, 1965-2005



Mohr SB et al, Am J Prev Med 2010;39(2)189 –190.

1-es típusú diabetes mellitus és a D vitamin



Type I Diabetes in Children and Vitamin D

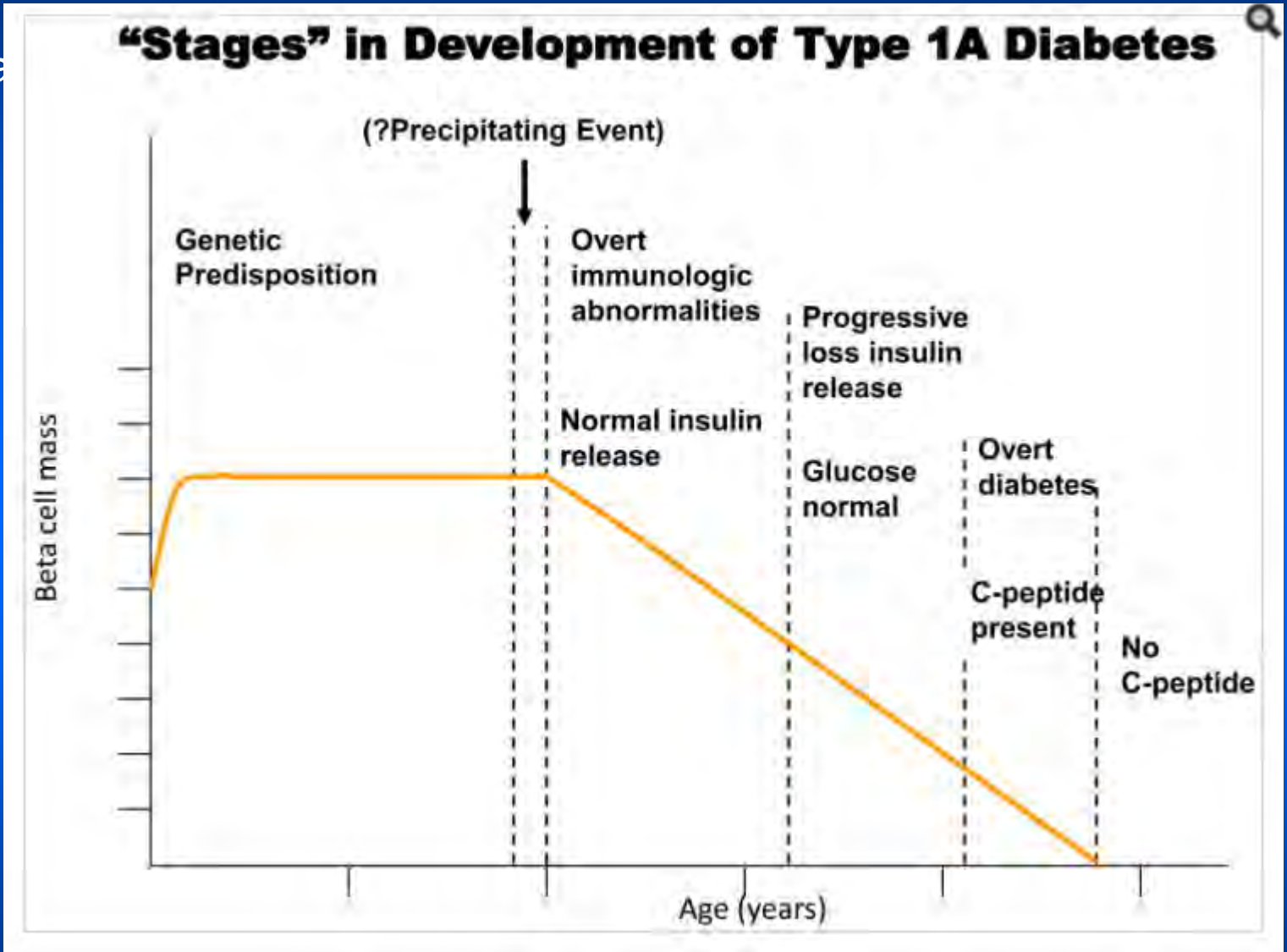
AUTHOR	YEAR	DESIGN	FINDINGS
EURODIAB Study Group	1999	Case control study	• 7 centers in Europe studied 820 T1DM patients aged birth to 14 and 2335 controls • Found Vitamin D supplementation in infancy was associated with a decreased risk of developing T1DM. Combined odds ratio of children was 0.67
Pozzilli, P. et al.	2005	Surveillance study	• 88 consecutive newly diagnosed T1DM and in 57 healthy age and sex matched subjects • Mean levels of both 25OHD3 and 1,25OH2D3 were significantly lower in patients compared to controls (p<0.01 and p<0.03, respectively)
Janner, M. et al.	2010	Prospective cross sectional study	• 129 diabetic youth • The vitamin D levels of diabetics showed marked seasonal fluctuations, but no relationship to diabetic control.
Alemzadeh, R. et al.	2008	Retrospective Case-cohort	• 127 children and adolescents (ages 6.0-17.9 years) who met the criteria for obesity (BMI >95th percentile) • Although mean serum glucose levels and HbA1c were similar among groups, serum insulin levels were slightly highers in the *hypovitaminosis D* group than in the vitamin D-sufficient group, but did not reach statisitical significance
Borkar, V.V. et al.	2010	Cross sectional case control study	• 50 children aged 6-12 years within one week of diagnosis of T1DM and in 50 healthy children • Mean levels of Vitamin D were significantly lower in patients compared to their controls [20.02 ± 10.63 ng/ml vs. 26.16 ± 12.28 ng/ml, p = 0.009]
Bener, A. et al.	2009	Matched case-control study	• Studied 170 diabetics and 170 controls of male and female Qatari children (less than 16 years old) • Vitamin D deficiency was considerably higher in T1DM children (90.6%) compared to controls (85.3%) • There was a significant difference found in the mean value of Vitamin D between T1DM and non-diabetic children (p=0.009). • Vitamin D supplementation with breast milk was very poor in diabetic children (47.7%). • Family history of Vit. D deficiency was higher in diabetics compared to non-diabetics (p<0.012).
Baumgartl, H.J. et al.	1991		• 49 recently diagnosed diabetics were compared with 42 healthy controls • A marked decrease of 1,25OH2D3 was found at the onset of diagnosis compared to normal controls (p <0.01). • Grouping of patients according to season demonstrated that the decrease of 1,25OH2D3 was present primarily during the summer months and likely due to a loss of seasonal rhythm of this hormone observed in healthy controls (p<0.001)
Littorin, B. et al.	2006	Cross sectional study	• Plasma 25OHD3 levels were measured in 459 patients at the time of diagnosis and in 138 of those patients 8 years later • At diagnosis, plasma 25OHD3 were signficantly lower in patients with T1DM than in controls (p<0.0001). • 8 years later, plasma 25OHD3 had decreased in patients (p=0.04). • Plasma levels of 25OHD3 were significantly lower in diabetic males than females at diagnosis and followup

AUTHOR	YEAR	DESIGN	FINDINGS
Simmons, J. et al.	2011	Cross sectional study	• 57 adolescents with T1DM who had HbA1c > 9% (unfavorable control) and <9% (favorable control). • Study revealed no difference between HbA1c groups in Vitamin D status • The prevalence of vitamin D deficiency was similar to that of the general population.
Mutlu, A. et al.	2011	Cross sectional study	• Evaluated 120 children and adolescents (aged 3-20) levels of 25OHD, Parathyroid hormone, and Alkaline phosphatase, as well as A1c and daily insulin requirements • Controls were more likely to be Vitamin D deficient, compared to only 21.7% T1DM patients. • There were no correlations between insulin requirements and 25OHD level.
Zipitis, C.S. and A.K. Akobeng	2008	Meta-analysis	• Total number of participants was 1429 cases and 5026 controls Data from the case control studies showed risk of T1DM was significantly reduced in infants who were supplemented with Vitamin D compared to those who were not (pooled odds ratio 0.71, 95% CI 0.60 to 0.84)
Hypponen, E. et al.	2001	Birth cohort study	• 10,821 children were included in the analysis and followed up at one year Vitamin D supplementation was associated with a decreased frequency of T1DM. • Regular vs no supplementation 0.12 (95% CI 0.03-0.51) and irregular vs no supplementation 0.16 (95% CI 0.04-0.74) • Children who regularly took the supplementation had a RR of 0.22 (0.05-0.89) compared to those that received less than the recommended amount.
Brekke, H.K. and J. Ludvigsson	2007	Birth cohort study	• 18,070 infants were included at birth, and 11,081 and 8805 at 1 and 2.5 years, respectively • Use of vitamin D associated supplements during pregnancy was associated with a reduced diabetes related autoimmunity at 1 yr (adjusted odds ratio 0.707, p=0.026), but not at 2.5 years
Greer, R.M. et al.	2007	Retrospective	• Children and adolescents with diabetes were more than 3x as likely to have vitamin D deficiency as those in the control group
Svoren, B.M. et al.	2009	Cross sectional study	• 25OHD3 was measured in 126 youth with T1DM • The majority of youth with T1DM had inadequate levels: insufficiency (61%) or deficiency (15%), with only 24% being sufficient. • Participants with Vitamin D deficiency were significantly older (p<0.001) and had a longer diabetes disease duration (p<0.01) and had lower HbA1c (p=0.05)
Frazer, T.E. et al.	1981		• 45 white insulin dependent age 7-18yr diabetics • Circulating 24,25OH2D3 was significantly elevated and 1,25OH2D3 was significantly decreased. • The increase in 24,25OH2D3 was seen in diabetics with the most severe bone loss and maximally increased during the first 5 years of disease
Kaur, H. et al.	2011	Cross sectional study	• Vitamin D levels were measured in 517 patients age 8-20 • Retinopathy was more prevalent in patients with vitamin D deficiency (18 vs. 9%, p=0.02) • In logistic regression, retinopathy was associated with vitamin D deficiency (odds ratio 2.12 CI 1.03-4.33), diabetes duration (1.13, 1.05-1.23) and HbA1c (1.24, 1.02-1.50).

Litchfield AB et al, W V Med J. 2015 Jan-Feb;111(1):32-7.

Diabetes mellitus

Pa



Michels AW, Eisenbarth GS, J Allergy Clin Immunol. 2010 February ; 125(2 Suppl 2): S226–S237.

Diabetes mellitus

Diagnózis:

- Antitestek kimutatása

Non-antigen Specific Immunotherapy Trials for New Onset Type 1A Diabetes

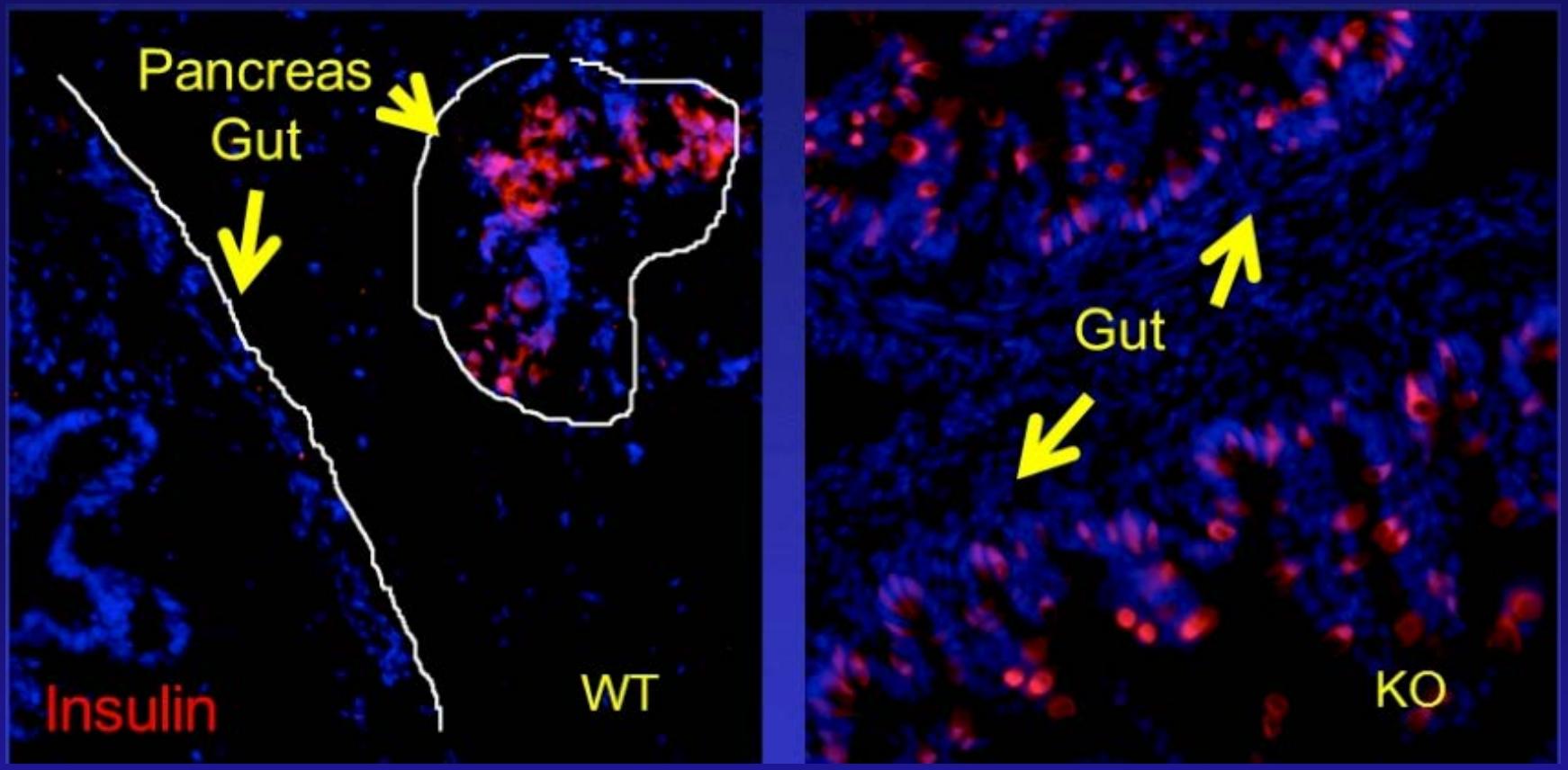
Agent	Stage of Development	Comments	References and Links

Selected Antigen Specific Immunotherapy Trials for Type 1A Diabetes

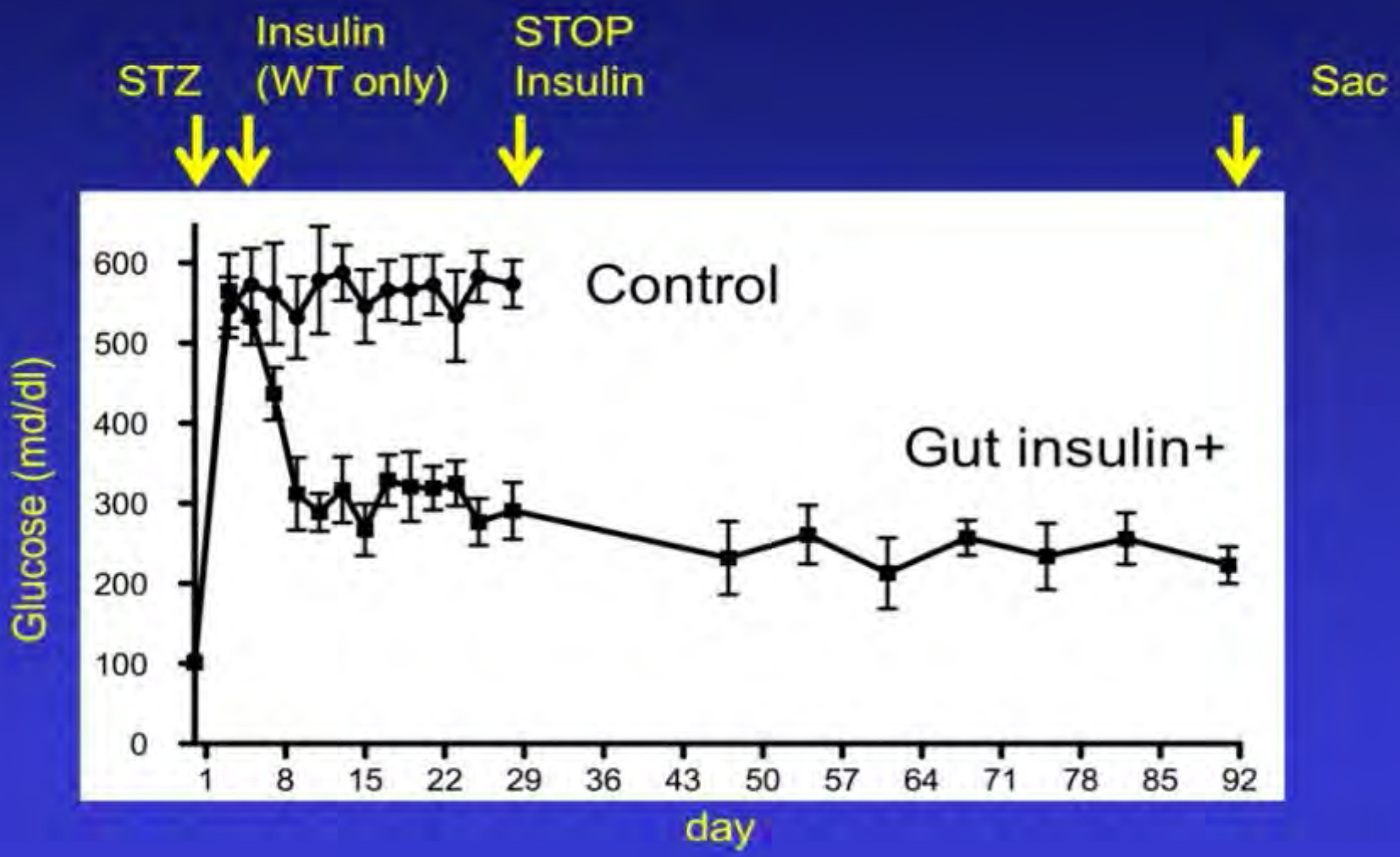
Agent	Stage of Development	Comments	References and Links
GAD65	Phase II/III	C-peptide preserved at 18 months	(90)
Insulin B Chain in Incomplete Freund's Adjuvant	Phase I	Ongoing	www.clinicaltrials.gov/ct2/show/NCT00057499
Proinsulin-based DNA vaccine (BHT-3021)	Phase I	C-peptide preserved at 12 months	www.bayhilltx.com
Oral Insulin	Prevention Trial	Subset with insulin autoantibodies having a potential response	www.clinicaltrials.gov/ct2/show/NCT00419562
CTLA-4 Ig (Abatacept)	Phase I	Ongoing	www.clinicaltrials.gov/ct2/show/NCT00505375
Mycophenolate and Daclizumab	Phase I	No effect	www.clinicaltrials.gov/ct2/show/NCT00100178

Michels AW, Eisenbarth GS, J Allergy Clin Immunol. 2010 February ; 125(2 Suppl 2): S226–S237.

Endokrin progenitor sejtekben FoxO “abláció”

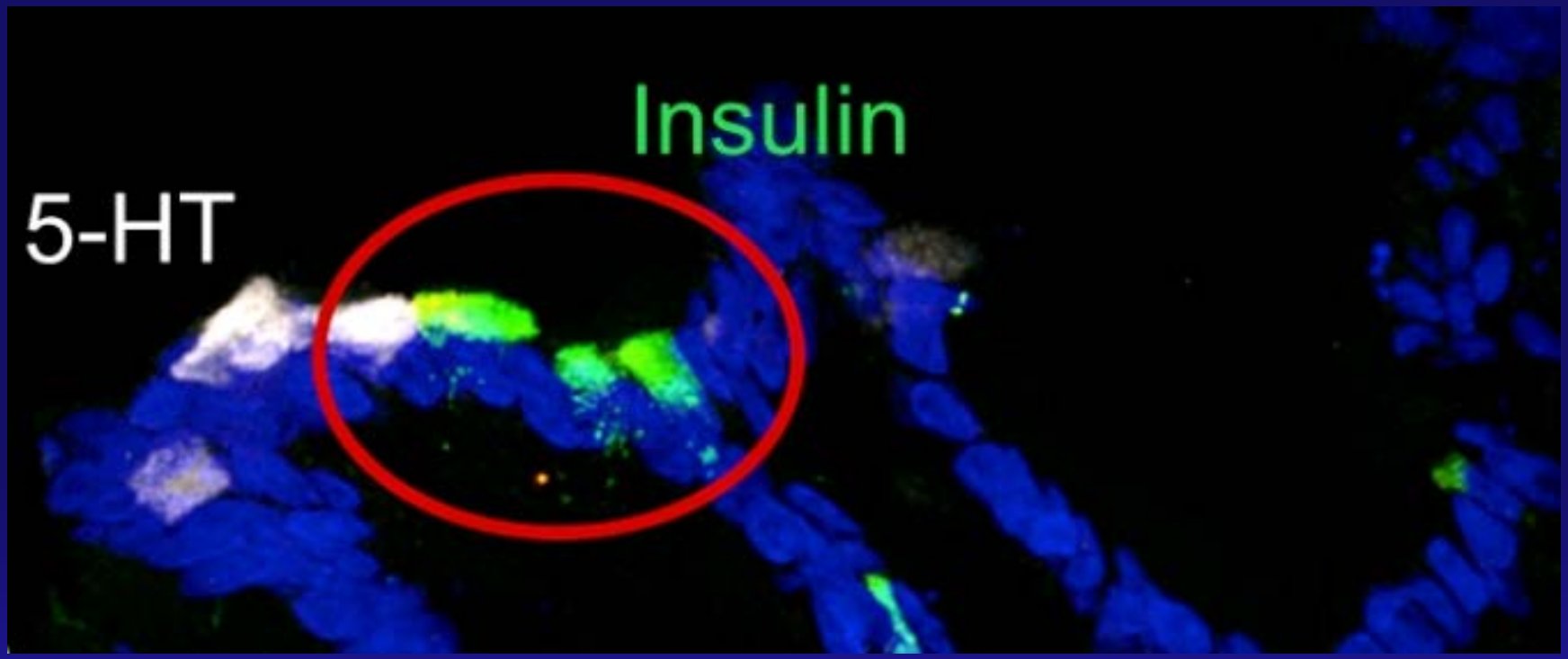


Közel fiziológiás inzulin termelés



Endokrin progenitor sejtekben FoxO “abláció”emberi sejteken

Endokrin progenitor sejtekben FoxO “abláció”emberi sejteken



Inzulin autoimmun szindróma

Inzulin autoimmun szindróma – Hirata betegség

- Inzulinnal reagáló autoantitestek
- Dg:
  - éhgyomri hypoglycaemiák exogén inzulinadagolás nélkül
  - magas szérum inzulin koncentráció
  - magas inzulinellenes antitest titer (monocl. és polycl.)
- Polyclonalis antitestek gyakran DRB1*0406 haplotípusban methimazol kezelés után

Uchigata Y et al, J Clin Endocrinol Metab. 1993;77:249–54.

Autoimmun pajzsmirigy betegségek

Autoimmun pajzsmirigy betegségek

- A populáció 5-10%-ában fordulnak elő!
- Graves-Basedow betegség: TSHR ellenes stimuláló antitestek (TSI)
- HLA DR3 és DQA1*051 hordozza a legnagyobb rizikót
- Monozigóta ikreknél a konkordancia 20%
- Lymphocytás infiltráció a pajzsmirigyben
- Ophthalmopathia (orbitopathia) 20-50%-ban – külön entitás – IL4 és IL10 – dohányzás nagy kockázat!
- Dg: hyperthyreosis, diffúz pm, TSHR antitestek
- Kezelés: thyreostatikus gyógyszerek, radiojód, műtét

Marga M et al, Am J Med Genet. 2001 August 1;102(2):188–91.
Martin A et al, J Clin Endocrinol Metab. 1997 October;82(10):3361–6.
Starkey KJ et al, J Mol Endocrinol. 2003 June;30(3):369–80.

Autoimmun pajzsmirigy betegségek

- Hashimoto thyroiditis
- A lakosság 10%-át érinti!
- CTLA-4 és TG gén mutációk
- T sejt infiltráció
- aTPO antitestek
- Dg: hypothyreosis, jellegzetes citológia, aTPO antitest

Ban Y et al, Proc Natl Acad Sci U S A. 2003 December 9;100(25):15119–24.
Ban Y et al, Genes Immun. 2003 December;4(8):586–93.

Autoimmun pajzsmirigy betegségek

- Postpartum thyroiditis
- Szülést követő 1 éven belül a nők 10-14%-ában
- Tünetszegény
- Kb. 4% lesz tartósan hypothyreosisos

De Groot L et al, J Clin Endocrinol Metab. 2012 Aug;97(8):2543-65.

D vitamin hiány autoimmun pajzsmirigy betegségekben

Graves' disease (GD), Hashimoto's thyroiditis (HT), and postpartum thyroiditis (PPT).

Minden 5 nmol/L serum 25(OH)D növekedés 1.55-, 1.62- és 1.51-szeres csökkenést okozott a GD, HT és PPT kockázatban.

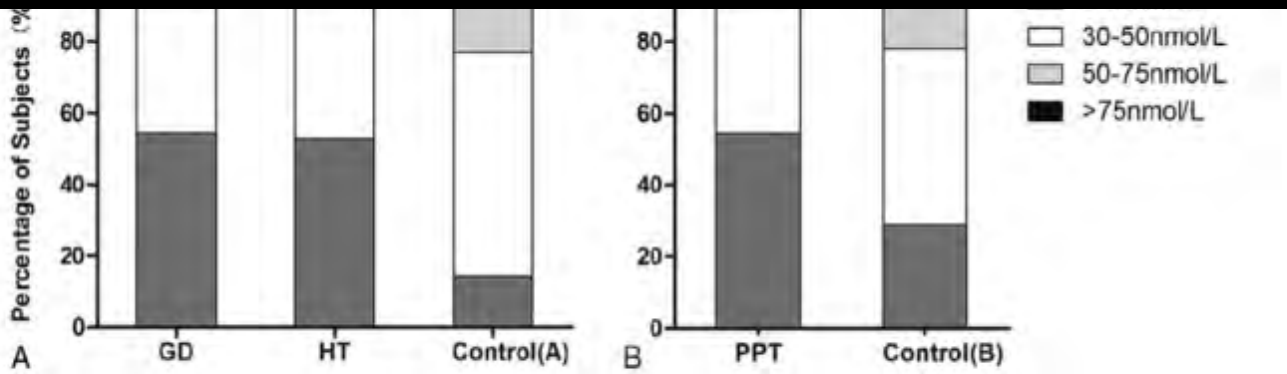
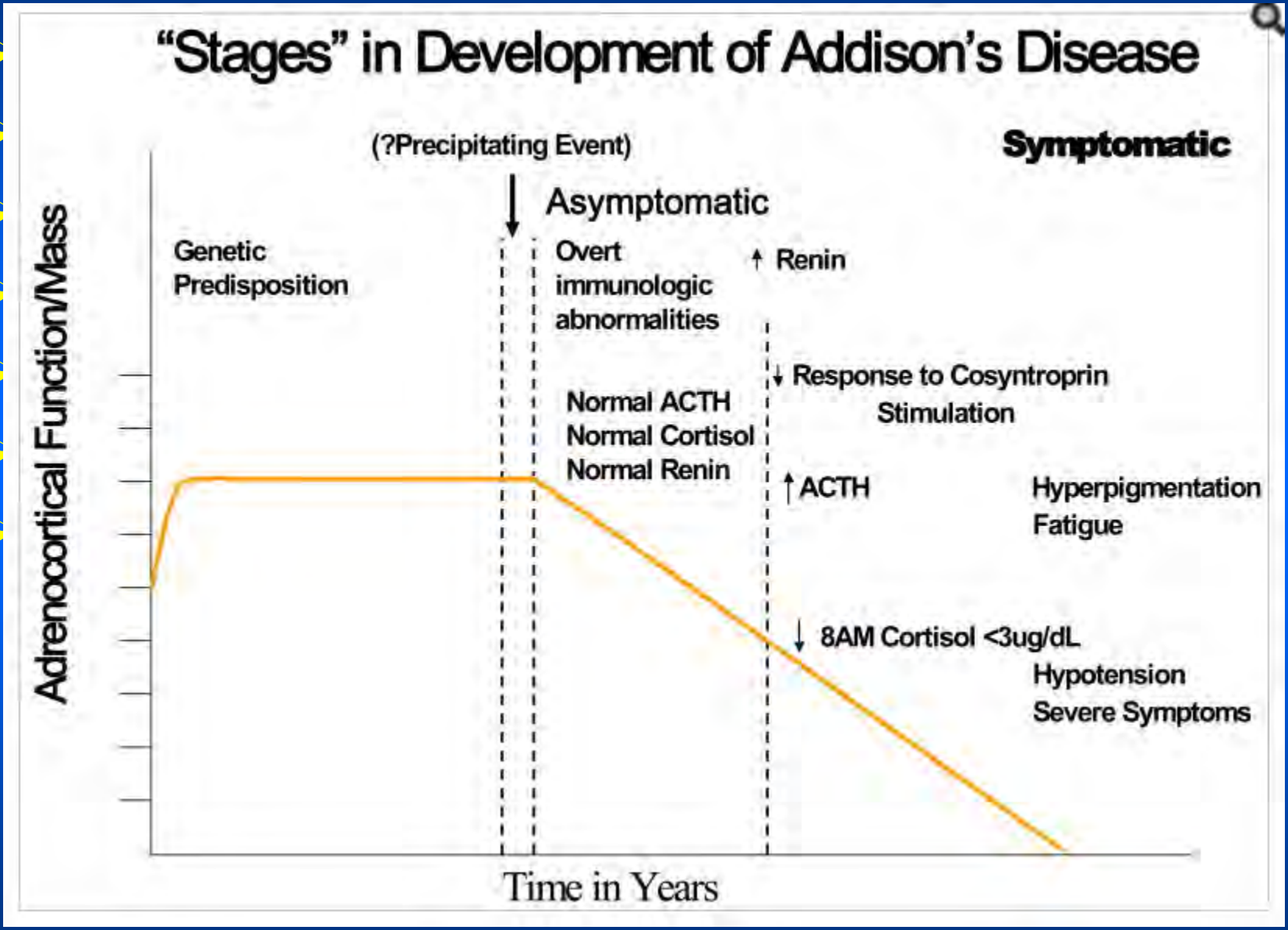


FIGURE 2. Prevalence of vitamin D deficiency in AITD patients and controls. (A) Cross-sectional case-control study, prevalence of vitamin D deficiency in GD patients, HT patients, and controls. *GD group compared with control group, $P = 0.009$. #HT group compared with control group, $P = 0.004$. (B) Nested case-control study, prevalence of vitamin D deficiency in PPT patients and controls. $PPT group compared with control group, $P < 0.05$. AITD = autoimmune thyroid disease, GD = Graves' disease, HT = Hashimoto's thyroiditis.

Ma J et al, Medicine (Baltimore). 2015 Sep;94(39):e1639. doi: 10.1097/MD.0000000000001639.

Hypadrenia – Addison betegség

Hypadrenia – Addison betegség



Eisenbarth GS, Gottlieb PA. Autoimmune polyendocrine syndromes. N Engl J Med. 2004 May 13;350(20):2068–79.

Hypadrenia – Addison betegség

- Dg:
  - csökkent cortisol szint
  - emelkedett ACTH
  - cortisol nem emelkedik ACTH stimulációs tesztben
  - 21-hidroxiláz antitestek
- Th: hormon szubsztitúció
- Javasolt a 21-hidroxiláz antitest szűrés:
  - type 1A diabetes
  - idiopathiás hypoparathyreosis
  - polyendocrin autoimmuniás
- Ha antitest jelen van, évenkénti ACTH stimulációs teszt
- Addison betegek 40-50%-ában fejlődik ki más autoimmun betegség

Eisenbarth GS, Gottlieb PA. Autoimmune polyendocrine syndromes. N Engl J Med. 2004 May 13;350(20):2068–79.

Idiopathiás hypoparathyreosis

Idiopathiás hypoparathyreosis

- PTH hiánya
- Gyakran része az APS-1-nek gyermekekben
- Felnőttekben lehet sporadikus
- Gyakran társul Hashimoto thyroiditishez, illetve egyéb autoimmun betegségekhez
- NACHT leucine-rich-repeat protein 5 (NALP5) antitestek
- Calcium-sensing receptor (CaSR) antitestek

Alimohammadi M et al, N Engl J Med. 2008 March 6;358(10):1018–28.
Kifor O et al, J Clin Endocrinol Metab. 2003 January;88(1):60–72.
Clarke BI et al, J Clin Endocrinol Metab 2016. (in press)

Idiopathiás hypoparathyreosis

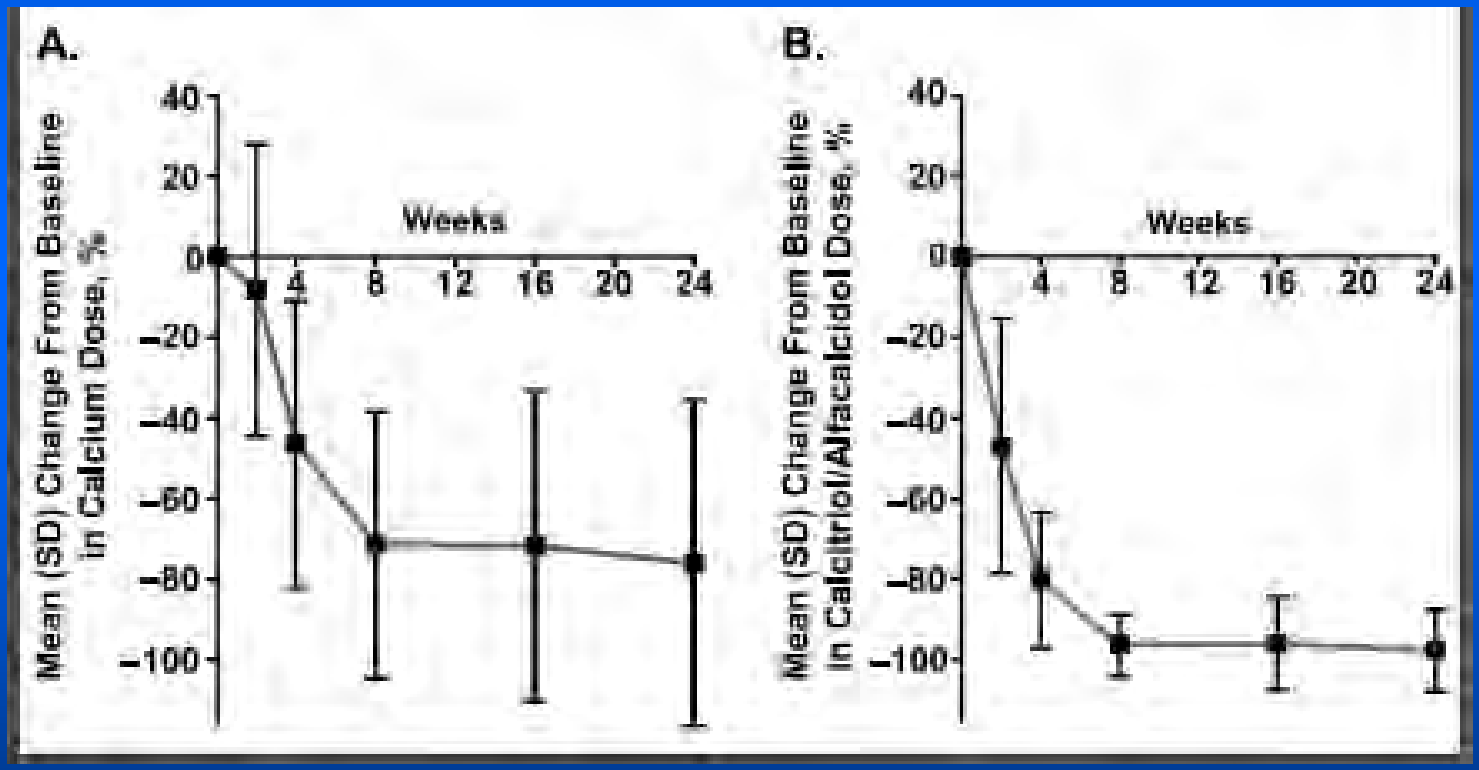
TABLE 3. Genetic Disorders Associated with Hypoparathyroidism

Disease	Inheritance	Gene / Protein	Chromosomal location
Syndromic forms			
Hypoparathyroidism associated with polyglandular autoimmune syndrome (APECED)	Autosomal recessive	AIRE-1	21q22.3
DiGeorge type 1	Autosomal dominant	TBX1	22q11.2/10p
DiGeorge type 2	Autosomal dominant	NEBL	10p13-p12
CHARGE	Autosomal Dominant	CHD7, SEMA3E	8q12.1-q12.2, 7q21.11
HDR Syndrome	Autosomal dominant	GATA3	10p14
Kenney Caffey type 1, Sanjad-Sakati	Autosomal dominant/recessive	TBCE	1q42.3
Kenney-Caffey type 2	Autosomal recessive	FAM111A	11q12.1
Barakat	Autosomal recessive †	Unknown	?
Dubowitz	Autosomal recessive†	Unknown	?
Bartter type 5	Autosomal dominant	CaSR	3q21.1
Lymphedema	Autosomal recessive	Unknown	?
Nephropathy, nerve deafness	Autosomal dominant †	Unknown	?
Nerve deafness without renal dysplasia	Autosomal dominant	Unknown	?
Hypoparathyroidism associated with KSS, MELAS and MTPDS	Maternal	Mitochondrial genome	
Non-syndromic forms			
Isolated hypoparathyroidism	Autosomal dominant	PTH, GCMB	11p15*, 6p24.2
	Autosomal recessive	PTH, GCMB	11p15*, 6p24.2
	X linked recessive	SOX3¶	Xq26-27
ADH1	Autosomal dominant	CaSR	3q21.1
ADH2	Autosomal dominant	Gα11	19p13

Alimohammadi M et al, N Engl J Med. 2008 March 6;358(10):1018–28.
Kifor O et al, J Clin Endocrinol Metab. 2003 January;88(1):60–72.
Clarke BI et al, J Clin Endocrinol Metab 2016. 101(6):2284-2299.

Idiopathiás hypoparathyreosis

- Kezelés:
  - D vitamin és aktív analógjai
  - Magnézium!
  - 1-84-PTH



Lakatos P et al, Endocr Pract. 2015 Dec 18. [Epub ahead of print]

Korai ovarium elégtelenség

(korai menopauza)

(premature ovarian failure)

POF

Korai ovarium elégtelenség

(premature ovarian failure – POF)

- Dg:
  - amenorrhea
  - emelkedett gonadotropin szintek
  - hypoestrogenaemia
- Idiopathiás POF adrenalis autoimmunitással
  - Addisonos betegek 10%-ában POF
  - autoantitestek a 21-hidroxiláz és a 17-hidroxiláz ellen
  - keresztreakció a theca interna/granulosa sejtekkel a follikulusban
  - autoantitestek jelenléte korrelál az oophoritis-szel
  - MHC class II expresszált a granulosa sejteken a POF betegekben
  - ez potencírozza a helyi T sejtek immunválaszát
- Idiopathiás POF kizárólagos ovarium ellenes autoimmunitással
  - a betegek 90%-a, 14%-uk pajzsm. autoimmunitással
  - rezisztens ovarium szindróma (exogén gonadotropin indukcióra)

Bakalov VK et al, Fertil Steril. 2005 October;84(4):958–65.
Hill JA et al, Am J Obstet Gynecol. 1990 February;162(2):534–40.

Korai ovarium elégtelenség

(premature ovarian failure – POF)

- Kezelés:
  - ösztrogénhiány kezelése
  - IVF donor petesejttel
  - autoimmunitás hullámzása miatt elképzelhető a spontán terhesség
  - obszerválandóak egyéb autoimmun betegségek irányában

Bakalov VK et al, Fertil Steril. 2005 October;84(4):958–65.
Hill JA et al, Am J Obstet Gynecol. 1990 February;162(2):534–40.

Lymphocytas hypophysitis

Lymphocytas hypophysitis

- Ritka betegség, kb. 500 eset az irodalomban
- Nőkben gyakoribb
- Főként terhesség alatt, illetve a postpartum időszakban
- Más autoimmun betegségekkel is társulhat
- ipilimumab, egy CTLA-4-et blokkoló monoklonális antitest is okozhatja
- Tünetek:
  - fáradtság, fejfájás, látótérkiesés
  - dg hypophysis biopsziával
- Kezelés:
  - nagydózisú glükokortikoiddal
  - szükség esetén hormonpótlás

Caturegli P et al, Autoimmun Rev. 2008 September;7(8):631–7.
Lansfield JA et al, J Immunother.2005 November;28(6):593–8.
Kristof RA et al, J Neurol Neurosurg Psychiatry.1999 September;67(3):398–402.

Autoimmun polyendocrin szindrómák

Autoimmun polyendocrin szindrómák (APS)

- APS-1
- APS-2
- IPEX
- POEMS
- Nem szervspecifikus autoimmunitás (pl. lupus erythematosus) anti-inzulin receptor antitestekkel
- thymus tumor endocrinopathiával
- Graves-Basedow betegség inzulin autoimmun szindrómával

Anderson MS, et al, Science. 2002 November 15;298(5597):1395–401.
Kumar PG et al, Endocrinol Metab Clin North Am. 2002 June;31(2):321–38.
Ramsey C, et al, Hum Mol Genet. 2002 February 15;11(4):397–409.

Autoimmun polyendocrin szindrómák (APS)

- APS-1

  - Whitakker sy
  - APECED (Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy)
  - ritka, főként gyermekeken
  - **hypoparathyreosis, Addison**, **candidiasis,** type 1A diabetes, vitiligo, alopecia, hepatitis, anemia perniciosa, hypothyreosis, asplenia
    - mutáció az AutoImmune REgulator (AIRE) génben
    - autosomalis recesszív
    - transzkripciós faktor, amely a saját antigén toleranciához kell
    - autoreaktív T sejtek

Anderson MS, et al, Science. 2002 November 15;298(5597):1395–401.
Kumar PG et al, Endocrinol Metab Clin North Am. 2002 June;31(2):321–38.
Ramsey C, et al, Hum Mol Genet. 2002 February 15;11(4):397–409.

Autoimmun polyendocrin szindrómák (APS)

APS-1	APS-2
• Onset Infancy • Siblings AIRE Gene Mutated • Not HLA Associated • Immunodeficiency Asplenism Mucocutaneous Candidiasis • 18% Type 1A Diabetes • 100% Anti-interferon Antibodies	• Older Onset • Multiple Generations • DR3/4 Associated • No Defined Immunodeficiency • 20% Type 1A Diabetes

* Available from the teaching slides at www.barbaradaviscenter.org.

Eisenbarth GS, et al, Ann Intern Med. 1979;91(4):528–33.
Michels AW et al, J Intern Med. 2009 May;265(5):530–40.
Yu L et al, J Clin Endocrinol Metab. 1999;84(1):328–35.

Autoimmun polyendocrin szindrómák (APS)

- IPEX (immune dysfunction, polyendocrinopathy, enteropathy, X-linked)
  - mutációk a forkhead box protein 3 (FOXP3) génben
  - diszfunkcionális regulatorikus T sejtek
  - az élet első hónapjaiban
  - dermatitis, növekedési retardáció, endocrinopathiák, infekciók
  - DM1T
  - sepsis, fatális kimenet
- Kezelés: nagydózisú glükokortikoid, tacrolimus, cyclosporine, methotrexate, sirolimus, infliximab, rituximab

Bacchetta R et al, J Clin Invest. 2006 June;116(6):1713–22.
Brunkow ME at al, Nature Genet. 2001;27(1):68–73.
Khattri R et al, Nat Immunol. 2003 April;4(4):337–42.

Autoimmun polyendocrin szindrómák (APS)

- POEMS - Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, Skin manifestations (hyperpigmentation and hypertrichosis)
- Plasmacytoma és osteoscleroticus lesiok
- Kezelés: Autolog csontvelő transzplantáció

Creange A et al, Nat Clin Pract Neurol. 2008 December;4(12):686–91.

Iatrogen endocrine autoimmun betegségek

Iatrogen endocrine autoimmun betegségek

- Interferon alfa – anti HCV kezelés: a kezeltek 5-10 %-ában Hashimoto thyyroiditis, Graves-Basedow betegség, DM1T
- IL-2 - metastatikus melanoma, vesesejtes carcinoma, HIV: 16%-ában a kezelteknek Hashimoto thyroiditis
- Ipilimumab – metastatikus vesesejtes carcinoma, melanoma: a kezeltek 56%-ában endocrinopathiák, hypophysitis, hypothyreosis, nem endokrin autoimmun betegségek
- Campath-1H – alemtuzumab – sclerosis multiplex: a kezeltek 30%-ában Hashimoto thyroidtitis, Graves-Basedow betegség, thrombopenia akár 48 hónappal a kezelés után is!
- Highly Active Antiretroviral Therapy (HAART) – HIV: ritkán Graves-Basedow betegség 16-19 hónappal a kezelés megkezdése után

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ÖSSZEFOGLALÁS

- Az autoimmun endocrin betegségek ismerete célszerű, mivel számos szakterületet érintenek.
- Érdemes ismerni a kombinációkat a gyorsabb diagnózishoz jutás érdekében.
- Ha autoimmun endocrin betegséget észlelünk, működjünk együtt endokrinológussal.

Köszönöm a figyelmet!