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SC Endocrinologia e Malattie Metaboliche
Ospedale Maria Vittoria - Torino

PROGRAMMA DIDATTICO MODULO 4

DIABETE "SPECIALE"
Moderatore: Giorgio Borretta (Cuneo)

Terapia ipoglicemizzante nel:
- grande obeso
- nel paziente con IRC moderata-grave
- nel paziente oncologico
- nell'iposurrenalismo

Presentatori:
Alessandra Pissarelli (Sondrio)
Francesco Tassone (Cuneo)
Egle Ansaldi (Alessandria)
Alberto Blatto (Torino)

LIVSVIKTIG INFORMATION OM

KORTISOL BRIST

DENNA PATIENT BEHÖVER DAGLIG ERSÄTTNINGSBEHANDLING MED KORTISON.

Vid feber eller annan större påfrestning, t ex operation, infektion eller större olycksfall måste tillförseln av kortison ökas.

Vid feber över 38°C - ta dubbel dos kortison.

Vid kräkning/diarré då tabletterna ej kan behållas - uppsök sjukvård snarast för omedelbar tillförsel av Solu-Cortef (100 mg) iv/im samt koksalt i dropp.

Svenska Endokrinologföreningen

IMPORTANT

MEDICAL INFO.

THIS PATIENT NEEDS DAILY REPLACEMENT THERAPY WITH CORTISONE.

In case of serious illness, vomiting or diarrhoea, hydrocortisone 100 mg iv/im and iv saline infusion should be administered without delay.

Swedish Endocrine Society

Namn / Name

Personnummer / Date of birth

L'insufficienza surrenalica è una condizione clinica rara e potenzialmente letale, ma curabile.
Consegue alla incapacità delle ghiandole surrenali di produrre una quantità sufficiente di cortisolo.

Forma primitiva (m. di Addison): graduale distruzione della corteccia surrenalica, più frequentemente su base autoimmune, che si manifesta clinicamente quando almeno il 90% della ghiandola è stato distrutto. Segni clinici di deficit glicoattivo e mineraloattivo

Forma secondaria: consegue ad un deficit ipotalamo-ipofisario (tumore, chirurgia, RT) → deficit di produzione di ACTH; predominano i segni di deficit glicoattivo

PREVALENZA

Forma primitiva: 93-140 casi per milione

Forma secondaria: 150-280 casi per milione

The Approach to the Adult with Newly Diagnosed Adrenal Insufficiency

Wiebke Arlt

J Clin Endocrinol Metab, April 2009, 94(4):1059–1067

Consensus statement on the diagnosis, treatment and follow-up of patients with primary adrenal insufficiency

E. S. Husebye[1,2], B. Allolio[3], W. Arlt[4], K. Badenhoop[5], S. Bensing[6], C. Betterle[7], A. Falorni[8], E. H. Gan[9], A.-L. Hulting[6], A. Kasperlik-Zaluska[10], O. Kämpe[11], K. Løvas[1,2], G. Meyer[5] & S. H. Pearce[9]

J Intern Med 2014; **275**: 104–115.

Table 2 *Classification and causes of primary adrenal insufficiency*

Aetiology	Pathogenesis	Diagnosis
Autoimmune	T and B cell autoimmunity against adrenocortical cells	21OH-Ab
Infection	Mycobacteria Bacteria (e.g. meningococcus and Haemopholus influenzae) Fungus (e.g. *Pneumocystis carinii*) Virus (e.g. HIV, herpes simplex and cytomegalovirus)	Culture, Quantiferon test, PCR, adrenal CT
Bleeding	Antiphospholipid syndrome Anticoagulant therapy Disseminated intravascular coagulation	Evidence of bleeding on adrenal CT
Surgery	Tumour surgery, Cushing's syndrome, Radical nephrectomy	
Genetic	Congenital adrenal hyperplasia Adrenoleukodystrophy Hypogonadotrophic hypogonadism, Familiar glucocorticoid deficiency (ACTH resistance syndrome), Smith–Lemli–Opitz syndrome, mitochondrial forms (Kearns–Sayre syndrome)	Urine steroid profile, sequencing of steroidogenic genes (e.g. *CYP21B*) Measure VLCFA Sequencing of *NR0B1 (DAX1)*
Infiltrative	Amyloidosis, haemochromatosis, bilateral adrenal metastasis or lymphoma, xanthogranulomatosis	
Medication	Ketoconazole, etidomate, mitotane, metyrapone	

AUTOIMMUNITA'
E SINDROMI AUTOIMMUNI POLIGHIANDOLARI

A Study of Autoimmune Polyglandular Syndrome (APS) in Patients with Type1 Diabetes Mellitus (T1DM) Followed Up at a Teritiary Care Hospital

SHAHEEN BANU SHAIKH[1], ISMAIL M. HAJI[2], PARVEEN DODDAMANI[3], RAHMAN M.[4]

Journal of Clinical and Diagnostic Research. 2014 Feb, Vol-8(2):70-72

T1DM:

0.5% → Addison

15-30% → AITD (Hashimoto, Graves)

5-10% → gastrite autoimmune e/o anemia perniciosa

4-9% → morbo celiaco

2-10% → vitiligo

APS-2: picco 20/60 anni

AD, T1DM, AITD

ovarite, asplenismo, alopecia, vitiligo, cheratite, malassorbimento, epatite, enamel displasia

Sindrome di Schmidt APS 2:

picco 30 anni e prevalenza 1:200.000

AD, T1DM, AITD

Type 1 diabetes and polyglandular autoimmune syndrome: A review

Martin P Hansen, Nina Matheis, George J Kahaly

World J Diabetes 2015 February 15; 6(1): 67-79

Table 5 Polyglandular autoimmune syndromes[13,68,78,161-166]

	PAS Type I	PAS Type II-IV	IPEX
Onset	Childhood	Adulthood	Infancy
Incidence	< 1:100000/yr	1-2:100000/yr	Extremely rare
Male/Female ratio	3:04	1:03	Male >> Female
Genetics	Monogenetic (AIRE)	Polygenetic	X-linked (FOXP3)
Autoantibodies	Anti-interferon-α/ω antibodies 100%, additional Abs	Organ-specific Abs depending on the autoimmune components	ANA (42%) SSA (25%) TG Abs (25%)
Prevalence of T1D	2%-33%	40%-60%	80%
Additional autoimmune endocrine components	Hypoparathyroidism (80%-85%) Addison's disease (60%-70%) Hypogonadism (12%) Autoimmune thyroid disease (10%)	Autoimmune thyroid disease (70%-75%) Addison's disease (40%-50%) Hypoparathyroidism (0%-5%) Hypogonadism (0%-3%) Hypopituitarism (0%-2%)	Autoimmune thyroid disease (25%)
Concomitant non-endocrine diseases	Mucocutaneous candidiasis (70%-80%); autoimmune hepatitis; autoimmune gastritis; alopecia areata; vitiligo; keratoconjunctivitis	Autoimmune gastritis; pernicious anemia; neurodermitis; alopecia areata; myasthenia gravis; systemic lupus erythematosus; rheumatoid arthritis; autoimmune hepatitis	Malabsorption; autoimmune skin diseases; multiple sclerosis

Genetic Determinants of 21-Hydroxylase Autoantibodies Amongst Patients of the Type 1 Diabetes Genetics Consortium

Peter Baker, Pam Fain, Heinrich Kahles, Liping Yu, John Hutton, Janet Wenzlau, Marian Rewers, Klaus Badenhoop, and George Eisenbarth

J Clin Endocrinol Metab, August 2012, 97(8):E1573–E1578

Background: Autoantibodies to 21-hydroxylase (21OH-AA) precede the onset of autoimmune Addison's disease (AD) and are found in 1.5% of individuals with type 1 diabetes mellitus (T1DM). The greatest genetic risk for both disorders is found in the major histocompatibility complex (MHC), suggesting a common pathophysiology between AD and T1DM. Screening for 21OH-AA in newly diagnosed T1DM patients is a valuable prognostic tool, made stronger when MHC genotype is considered.

TERAPIA IPOSURRENALISMO (ADDISON)

premesse

- i glucocorticoidi sono secreti nel sistema circolatorio con un meccanismo pulsatile e circadiano
- il picco produttivo avviene al primo mattino, il nadir a mezzanotte
- una normale funzionalità surrenalica permette una produzione giornaliera di cortisolo tra 5 e 10 mg/m², equivalente ad una sostituzione orale di 15-25 mg/die di idrocortisone (HC)
- la scelta terapeutica solitamente è tra HC e CA (cortisone acetato)
- nessuno studio ha mostrato la superiorità di uno dei 2
- CA possiede un lieve ritardo di azione, legato alla sua attivazione CA → HC da parte della 11β idrossisteroidodeidrogenasi tipo 1 epatica

Terapia glucocorticoide cronica: 5 requisiti fondamentali

- Mimare il ritmo endogeno del cortisolo con nadir in serata e picco nelle prime ore del mattino
- Avere una bassa variabilità
- Essere flessibile permettendo di adeguare la dose sostitutiva alle esigenze cliniche
- Essere facile da monitorizzare
- Permettere di minimizzare i rischi da sovratrattamento

Consensus statement 2014

Table 3 *Glucocorticoid replacement in primary adrenal insufficiency*

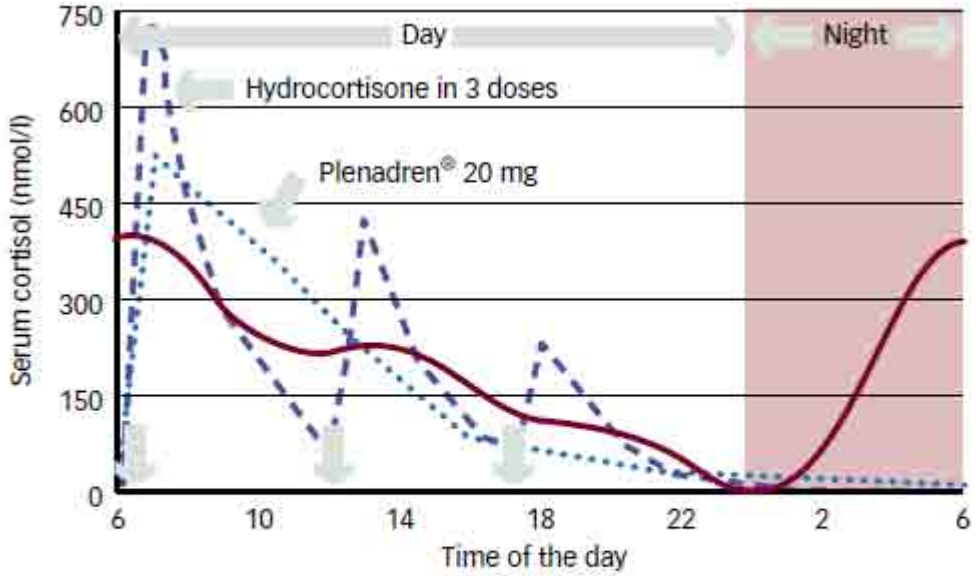
Glucocorticoid	Dose range (mg day^{-1})	Typical dose regimen (mg)	Long-shift regimen (mg)[a]
Hydrocortisone	15–25	Three doses (07:00, 12:00, 16:00 ± 1 h 15 + 5 + 5; 10 + 5 + 5; 10 + 5 + 2.5; 7.5 + 5 + 2.5	10 + 5 + 2.5 + 2.5..... + 2.5 **Durata di azione 8-12 ore**
		Two doses (07:00, 12:00 ± 1 h) 15 + 5; 10 + 10; 10 + 5	
Cortisone acetate	25–37.5	Three doses (07:00, 12:00, 16:00 ± 1 h 12.5 + 12.5 + 12.5; 12.5 + 12.5 + 6.25; 12.5 + 6.25 + 6.25	12.5 + 6.25 + 6.25 + 6.25 ..... + 6.25 **Durata di azione 8-12 ore**
		Two doses (07:00, 12:00 ± 1 h) 25 + 12	
Prednisolone[b]	4–5	One dose (07:00) 4 or 5 mg	Prednisolone
		Two doses (07:00, 14:00 ± 1 h) 3 + 2; 3 + 1	**Durata di azione 12-36 ore**

Metilprednisolone	**4**	**Durata di azione 12-36 ore**
Betametasone	**0.75**	**Durata di azione 36-72 ore**
Desametasone	**0.75**	**Durata di azione 36-72 ore**

Dual-release Hydrocortisone in Addison's Disease – A Review of the Literature

Roberta Giordano,[1] Federica Guaraldi,[2] Rita Berardelli,[2] Ioannis Karamouzis,[2] Valentina D'Angelo,[2] Clizia Zichi,[2] Silvia Grottoli,[2] Ezio Ghigo[2] and Emanuela Arvat[3]

European Endocrinology, 2014;10(1):75–8



Serum cortisol levels after administration of three daily doses of hydrocortisone (dashed line) or a single dual-release hydrocortisone preparation (Plenadren® 20 mg) (dotted line) compared with physiological average concentration (continuous line). Permission obtained from Falorni et al., 2013.[6]

Numerosi farmaci possono interferire con l'efficacia della terapia sostitutiva per interferenza con l'enzima CYP3A4:

- attivano l'enzima e **richiedono un aumento della dose**: anti-epilettici e barbiturici, anti-TBC, anti-fungini, etomidate e topiramato;
- inibiscono l'enzima e possono richiedere una riduzione della dose: liquirizia e succo di ananas.

Non esiste alcun dosaggio ormonale in grado di valutare l'adeguatezza del trattamento. Questa si basa principalmente sulla **valutazione clinica del benessere soggettivo** del paziente, parametro di difficile valutazione, della sua qualità di vita mediante specifici questionari, associata alla ricerca di **sintomi e segni di sovra-dosaggio** (incremento ponderale, insonnia, edemi declivi) **o sotto-dosaggio** (astenia, nausea, inappetenza, calo ponderale).

Commento

Altro criterio clinico utile per la valutazione dell'adeguatezza terapeutica è la glicemia a digiuno: ipoglicemia al mattino deve far pensare a sotto-dosaggio, mentre la comparsa di iperglicemia a sovra-dosaggio (evocato anche da dislipidemia e ipertensione).

Diabete e terapia dell' iposurrenalismo

Il problema della:

- **iperglicemia**
- **ipoglicemia**

Adrenal insufficiency: review of clinical outcomes with current glucocorticoid replacement therapy

Clinical Endocrinology (2015) 82, 2–11

Gudmundur Johannsson*, Alberto Falorni†, Stanko Skrtic‡§, Hans Lennernäs¶, Marcus Quinkler**, John P. Monson†† and Paul M.Stewart‡‡

This is thought to reflect a failure of treatment to replicate the natural circadian rhythm of cortisol release, together with a failure to identify and deliver individualized cortisol exposure and to manage patients adequately when increased doses are required. The resulting over- or under-treatment may result in Cushing-like symptoms or adrenal crisis, respectively.

Screening for associated conditions

Continuous surveillance for other autoimmune disorders is necessary. The presence of thyroid autoantibodies followed by the development of hypothyroidism is frequently seen, and thyrotoxicosis may also develop. Thus, regular monitoring of thyroid function every 12 months is important, including serum TSH, FT4 and TPO-Ab. It is important to detect subclinical thyroid disease as this can contribute to fatigue. The annual screening should also include plasma glucose levels, HbA1c and a complete blood count to screen for diabetes mellitus and anaemia, respectively.

Addison's disease presenting as reduced insulin requirement in insulin dependent diabetes

Lynne Armstrong, Patrick M Bell

BMJ VOLUME 312 22 JUNE 1996

An association between autoimmune Addison's disease and insulin dependent diabetes is well recognised. Other features of the polyendocrine autoimmune syndrome may be present.[1] The prevalence of insulin dependent diabetes in series of patients with Addison's disease ranges from 10% to 18%.[1-3] By contrast, the prevalence of Addison's disease in patients with insulin dependent diabetes is lower, perhaps less than 1.9%, and is therefore more likely to be overlooked.[6] Occasionally, both may present acutely with diabetic ketoacidosis provoking adrenal crisis.

ard textbooks of diabetes and endocrinology.[7] Addison's disease may present with spontaneous hypoglycaemia in the absence of diabetes mellitus.[8] The cause of the hypoglycaemia in both situations is presumably increased sensitivity to insulin when the cortisol concentration is low or absent.

Pediatr Diabetes. 2014 Sep;15(6):464-7. doi: 10.1111/pedi.12113. Epub 2014 Jan 13.

Newly diagnosed T1 diabetes presenting with hypoglycemia due to simultaneous co-existence of Addison disease.

Glynn N[1], Bashir M, Smith D, Thompson CJ

Abstract

Type 1 diabetes mellitus (TIDM) classically presents with symptomatic hyperglycemia and many patients develop diabetic ketoacidosis prior to their diagnosis. However, non-classical presentation or co-presentation with associated diseases may delay diagnosis or lead to challenges in acute, clinical management. An 18-yr-old girl presented to hospital with severe, symptomatic hypoglycemia. Clinical history and serum electrolyte concentrations suggested a diagnosis of adrenal insufficiency. She remained hypoglycemic until glucocorticoid replacement was commenced, at which point she developed persistent hyperglycemia requiring insulin therapy. Subsequent follow up confirmed the diagnosis of Addison's disease (AD), the treatment of which unmasked co-existing type 1 diabetes. Autoimmune diseases often cluster together in affected patients and first-degree relatives. Approximately 1 in 200 patients with T1DM develop AD. However, months or more commonly years usually elapse between the presentation of different autoimmune conditions. The co-diagnosis T1DM and AD in the acute setting is rare. Moreover, the first presentation of T1DM with severe hypoglycemia is even more exceptional. This case highlights the need for vigilance during the acute, emergency management of patients with autoimmune conditions and, in particular, to consider the possibility of concurrent antibody-mediated diseases which may need to be addressed during resuscitation.

Pediatr Diabetes. 2004 Dec;5(4):207-11.

Addison's disease presenting in four adolescents with type 1 diabetes.

Thomas JB[1], Petrovsky N, Ambler GR.

Author information

Abstract

Primary adrenocortical insufficiency (Addison's disease) is a potentially fatal condition that often develops insidiously and can be easily overlooked. Although rare in the general population, it is more common in patients with type 1 diabetes mellitus (T1DM). The combination of Addison's disease with T1DM and/or autoimmune thyroid disease is known as autoimmune polyendocrine syndrome type-2 (APS-2). T1DM commonly precedes the development of adrenocortical insufficiency in most patients with APS-2. We, in this study, present four cases of Addison's disease developing inadolescents with pre-existing T1DM. Risk factors for Addison's disease in this population include a history of other organ-specific autoimmunity, particularly thyroid, and a positive family history. In addition to the 'classic' Addisonian features, the development of unexplained recurrent hypoglycemia, reduction in total insulin requirement, improvement in glycemic control, or abnormal pigmentation should arouse suspicion of adrenocortical insufficiency. Adrenal antibodies have been proposed as a screening tool for Addison's disease in the T1DM population, but doubts remain about their specificity and sensitivity. The addition of specific HLA DRB1 subtyping has been proposed to improve predictive value.

Recurrent hypoglycaemia in type-1 diabetes mellitus may unravel the association with Addison's disease: a case report

BMC Research Notes 2014, **7**:634

Stefano Passanisi, Tiziana Timpanaro, Donatella Lo Presti and Manuela Caruso-Nicoletti*

Abstract

Background: Primary adrenocortical insufficiency or Addison's disease is caused by a progressive destruction of the adrenal cortex, resulting into a reduction of glucocorticoids, mineralocorticoids, and androgens. Autoimmune Addison's disease is the most common etiological form, accounting for about 80% of all cases.

Case presentation: We describe the case of a 16-year-old Caucasian boy affected by type-1 diabetes mellitus and autoimmune thyroiditis, who experienced recurrent hypoglycaemia as presenting symptom of Addison's disease.

Conclusions: Hypoglycaemia is not a common presenting feature of Addison's disease, both in patients with type-1 diabetes mellitus and in non-diabetic patients. However, hypoglycaemia may occur in association with primary and secondary glucocorticoid deficiency as a result of an enhanced insulin sensitivity. Hypoglycaemia is the most common acute complication of insulin therapy in patients with type-1 diabetes mellitus. Addison's disease has been described in approximately 0.5% of patients with type-1 diabetes mellitus, being more frequent in females and occurring in middle-aged patients. An association among type-1 diabetes mellitus, autoimmune thyroiditis, and Addison's disease is found in the "Schmidt's syndrome", a rare disorder that may occur in the paediatric age. Our case suggests that the presence of Addison's disease should be taken into consideration in patients with type-1 diabetes mellitus and frequent episodes of hypoglycaemia. We wish to highlight that there are no specific indications to screen for the association between Addison's disease and type-1 diabetes mellitus, although an early diagnosis of Addison's disease in diabetic patients would prevent the morbidity and potential mortality of this association.

Keywords: Type 1 diabetes mellitus, Addison's disease, Hypoglycaemia, Screening

Altered insulin requirement in patients with type 1 diabetes and primary adrenal insufficiency receiving standard glucocorticoid replacement therapy

European Journal of Endocrinology (2009) 160 919–924

Ulf Elbelt, Stefanie Hahner and Bruno Allolio

Clin Pediatr (Phila). 1965 Sep;4:543-7.
ADDISON'S DISEASE AND DIABETES MELLITUS IN AN ADOLESCENT.
BURKE G, EMANUEL B

…gli autori descrivono la difficoltà ad ottenere un adeguato controllo glicemico in un giovane paziente affetto da T1DM e concomitante iposurrenalismo, dovuta a spiccata variabilità glicemica ed aumentata sensibilità insulinica…

However, no information concerning problems of insulin therapy in patients with type 1 diabetes and concomitant adrenal insufficiency is available so far.

Confronto APS 2 e solo T1DM

APS 2 necessitano di una minore copertura di insulina basale → ipo!

APS 2 necessitano di una maggiore quantità di insulina per coprire i pasti, soprattutto il **pranzo** e la **cena**
(solo DM: maggiore richiesta di insulina per la **colazione**)

Queste differenze riflettono la diversa biodisponibilità dei gluco-corticoidi (nello studio la terapia sostitutiva era HC x 2 o x 3/die) e i grossi limiti della terapia stessa

Limiti che determinano anormali bassi livelli di cortisolo durante la notte e nel primo mattino, mentre invece i livelli di cortisolo endogeno hanno un nadir a mezzanotte per poi presentare un picco alle 7 nelle persone con surrenali intatte

La ridotta produzione di cortisolo aumenta la sensibilità insulinica, che esita in una aumentata utilizzazione periferica di glucosio, una alterata neoglucogenesi ed un ridotto output epatico di glucosio → maggiore rischio di ipo!

La sensibilità insulinica, inoltre, è relativamente alta al mattino (negli APS 2) → aumentato rischio di ipo!
e tende a ridursi dopo ingestione della terapia sostitutiva
(alcuni autori hanno dimostrato **IR** dopo ingestione di HC)

Poche le ipoglicemie severe in entrambi i gruppi, ma con decorso più sfavorevole in APS 2

Ruolo della **controregolazione:**
importanza massima dell' adrenalina e dimostrazione di una **inadeguata** CR nell' iposurrenalismo.

J Pediatr. 1998 May;132(5):882-4.
A novel presentation of Addison disease: hypoglycemia unawareness in an adolescent with insulin-dependent diabetes mellitus.
Phornphutkul C[1], Boney CM, Gruppuso PA.

Epinephrine synthesis in the adrenal medulla depends on high levels of local glucocorticoids stimulating the enzymatic activity of phenylethanolamine *N*-methyl-transferase. These local levels of glucocorticoids are not achieved by orally administered replacement therapy (26). The impaired epinephrine response may also explain the difficulties in glycaemic control during physical activity in our patients with APS-2 as it may facilitate activity related hypoglycaemia.

Problema principale: aumentato rischio di ipoglicemia, specie notturna

Utilizzo di terapie che riducano il rischio di ipoglicemia, specialmente notturna

Pazienti “insulino-trattati”:
insuline basali → glargine
detemir
DEGLUDEC

Pazienti non insulino dipendenti:
farmaci insulinosensibilizzanti
→ metformina
glitazoni
“incretine”

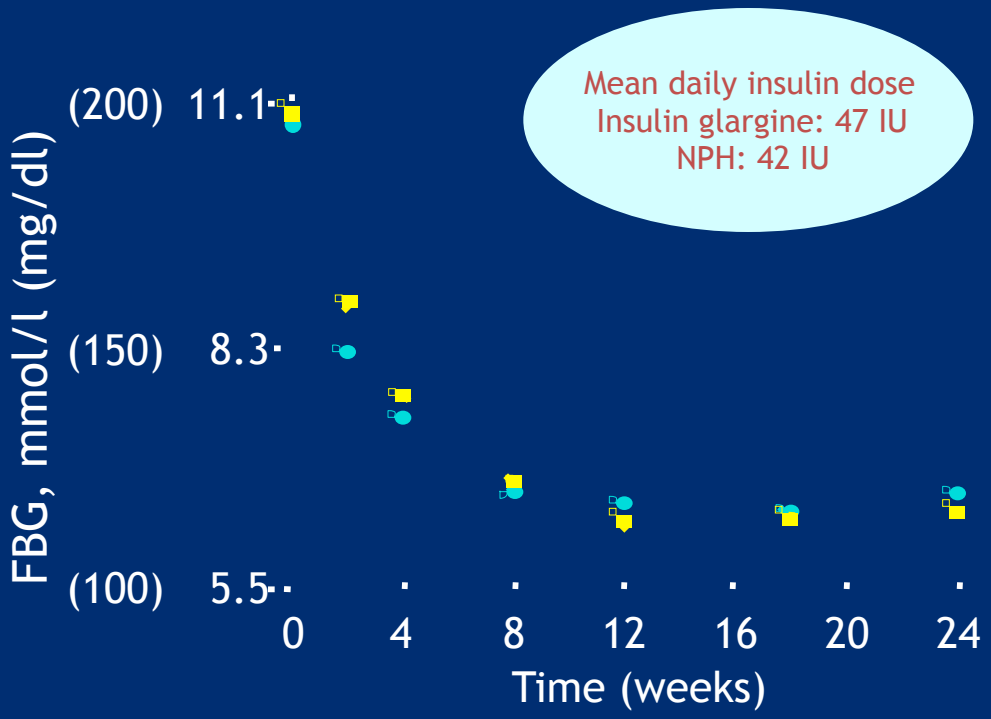
Assenza di studi clinici per ciascun farmaco menzionato

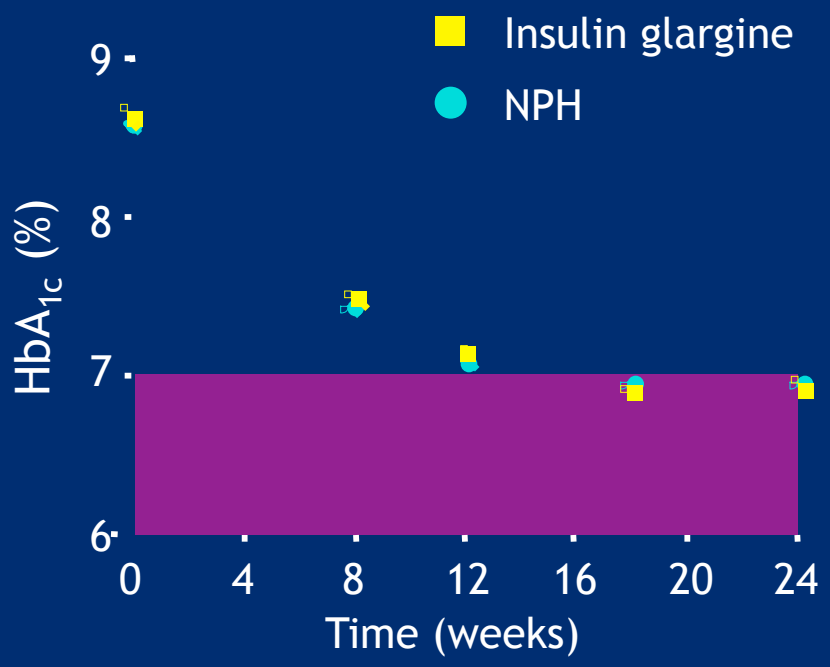
Treat-to-Target: proof-of-concept – titrated basal insulin reduced FBG and HbA_{1c} in both treatment groups

756 T2DM patients; average BMI 32kg/m^2; previously treated with 1–2 OHAs; poor metabolic control (HbA_{1c} >7.5%)

58% of individuals with T2DM on insulin glargine achieved $HbA_{1c} \leq 7\%$

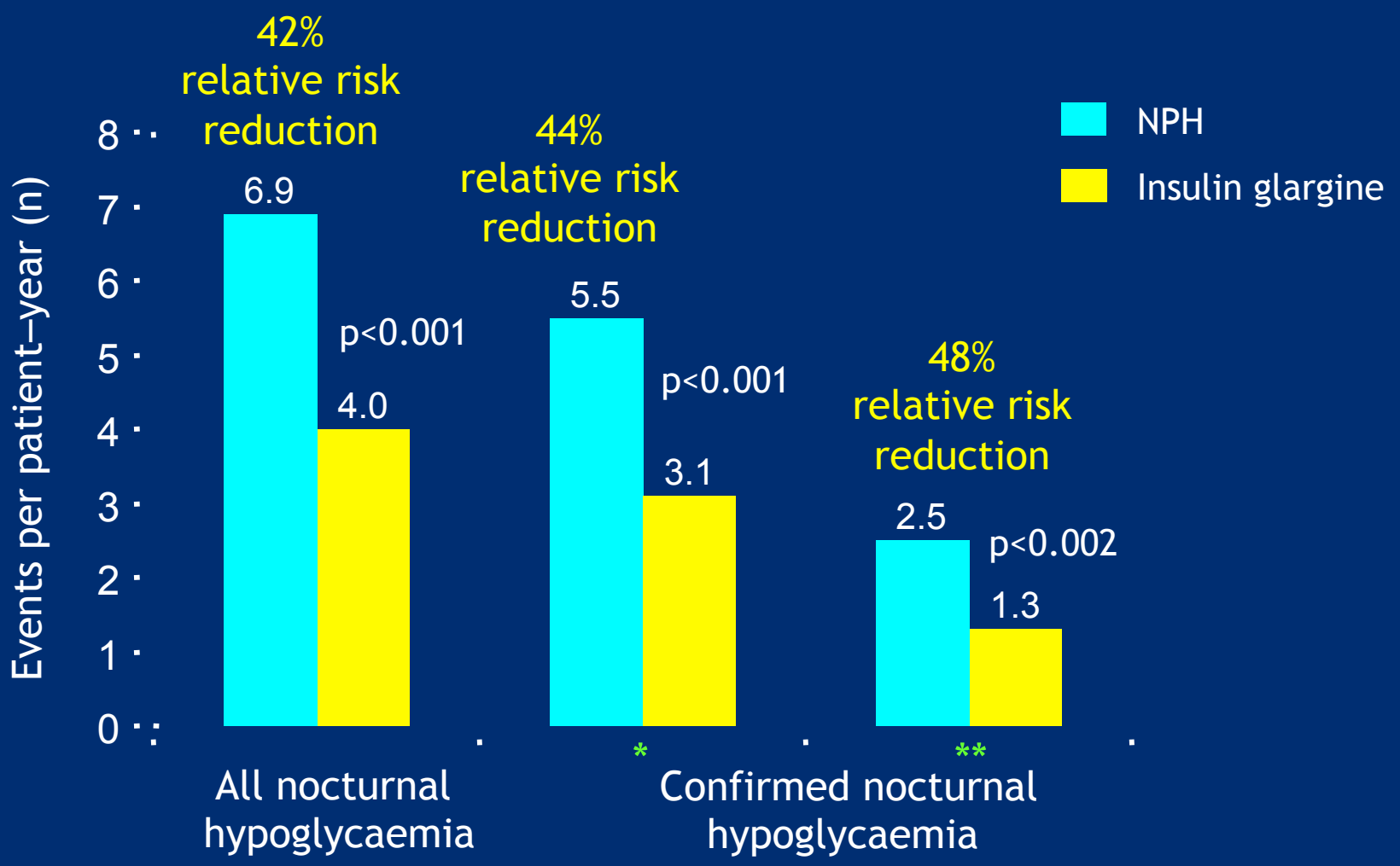
Mean daily insulin dose
Insulin glargine: 47 IU
NPH: 42 IU





Riddle M, et al. Diabetes Care 2003;26:3080–86.

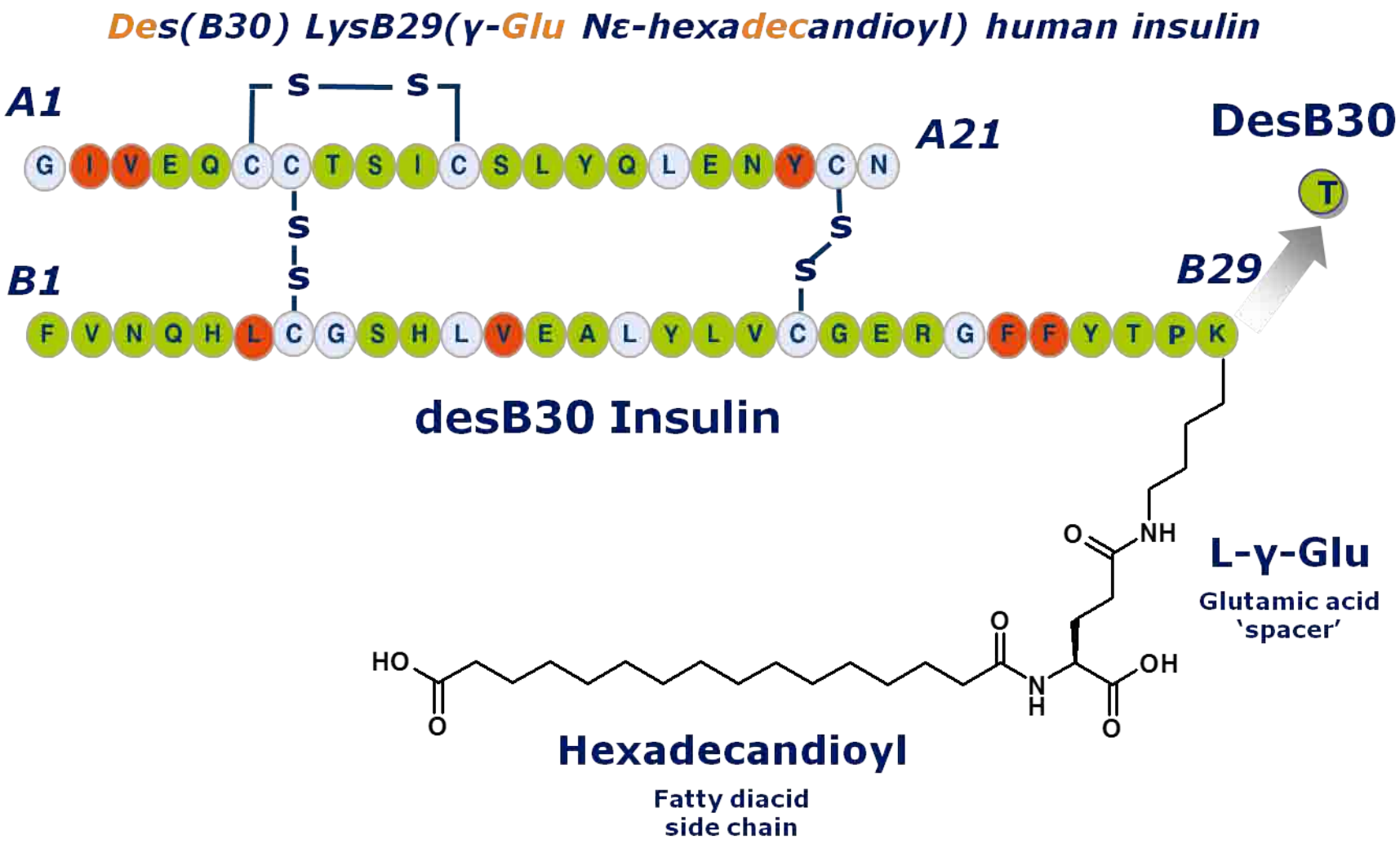
Reduced risk of nocturnal hypoglycaemia with insulin glargine



Confirmed hypoglycaemia: *≤4 mmol/l (72 mg/dl); **≤3.1 mmol/l (56 mg/dl)

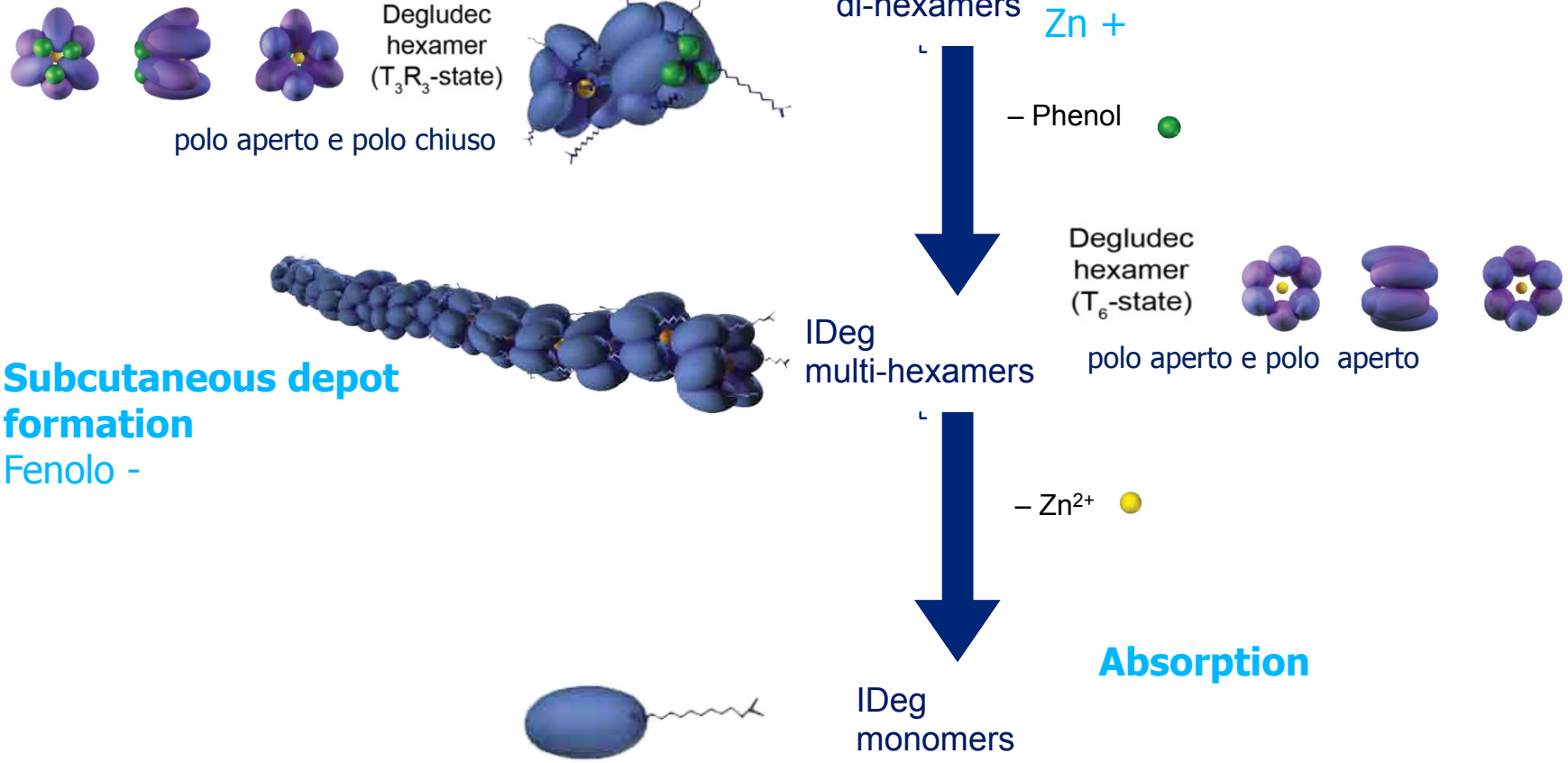
Adapted from Riddle M, et al. Diabetes Care 2003;26:3080–86.

insulina **DEGLUDEC**: struttura



Jonassen et al., Pharm Res 2012 – Published online April 2012 DOI 10.1007/s11095-012-0739-z

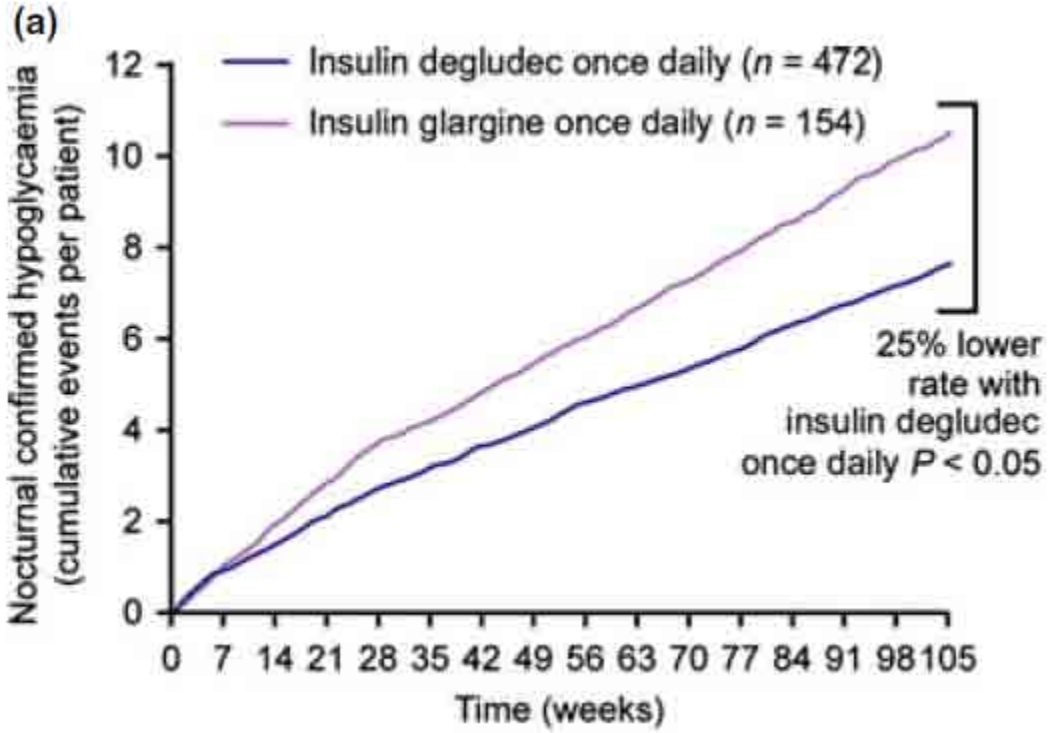
dall'iniezione all'assorbimento...



Jonassen et al., Pharm Res 2012 – Published online April 2012 DOI 10.1007/s11095-012-0739-z

Insulin degludec improves glycaemic control with lower nocturnal hypoglycaemia risk than insulin glargine in basal–bolus treatment with mealtime insulin aspart in Type 1 diabetes (BEGIN® Basal–Bolus Type 1): 2-year results of a randomized clinical trial

B. W. Bode[1], J. B. Buse[2], M. Fisher[3], S. K. Garg[4], M. Marre[5], L. Merker[6], E. Renard[7], D. L. Russell-Jones[8], C. T. Hansen[9], A. Rana[9] and S. R. Heller[10] on behalf of the BEGIN® Basal–Bolus Type 1 Trial Investigators*



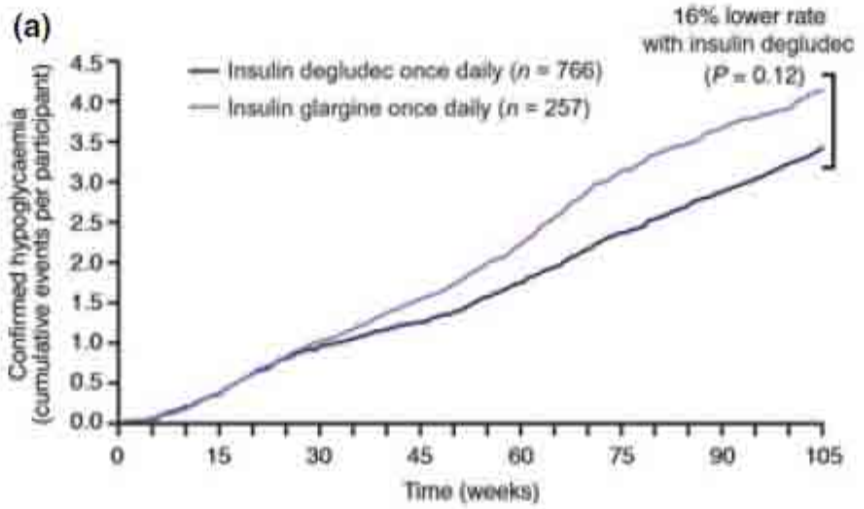
Diabet. Med. 30, 1293–1297 (2013)

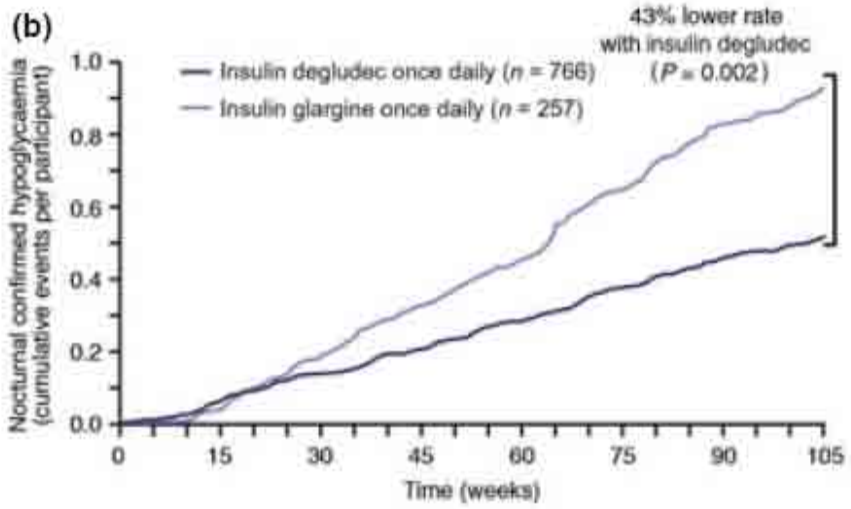
Tresiba nel T1DM

Comparison of insulin degludec with insulin glargine in insulin-naive subjects with Type 2 diabetes: a 2-year randomized, treat-to-target trial

H. W. Rodbard[1], B. Cariou[2], B. Zinman[3], Y. Handelsman[4], A. Philis-Tsimikas[5], T. V. Skjøth[6], A. Rana[6] and C. Mathieu[7] on behalf of the BEGIN Once Long Trial Investigators*

Diabet. Med. 30, 1298–1304 (2013)





Tresiba nel T2DM

TABLE 2. **Comparison of GLP-1 Receptor Agonists and DPP-4 Inhibitors**[a]

Effects/parameters	GLP-1 receptor agonists	DPP-4 inhibitors
Route of administration	Subcutaneous injection	Oral
Dosing/timing of administration	Once or twice daily[b]	Once daily
Insulin secretion	Enhanced[c]	Enhanced
HbA_{1c} reduction	–0.6% to –1.9%[c]	–0.5% to –0.8%
Postprandial hyperglycemia	Reduced[c]	Reduced
Glucagon secretion	Suppressed[c]	Suppressed
Body weight	Reduced	Neutral
Appetite	Suppressed[c]	No effect
Gastric emptying	Slowed significantly[c]	No effect
Hypoglycemia	Low rates	Low rates
GI AEs	Nausea, diarrhea	No significant GI AEs
CVD risk factors	Improved (with weight loss)	No consistent change

[a] AEs = adverse events; CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase 4; GI = gastrointestinal; GLP-1 = glucagon-like peptide 1; HbA_{1c} = hemoglobin A_{1c}.

[b] Exenatide once weekly has been submitted to the US Food and Drug Administration for regulatory review.

[c] In head-to-head clinical studies, exenatide or liraglutide had a greater effect on these parameters than did the DPP-4 inhibitor sitagliptin.[53,58,59]

Information derived from Nathan et al,[22] Buse et al,[52] DeFronzo et al,[53] Drucker et al,[54] Kendall et al,[55] Madsbad,[56] and Triplitt et al.[57]

A review of newer treatment approaches for type-2 diabetes: Focusing safety and efficacy of incretin based therapy

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Regin Elsa George, Siby Joseph

Comparison of safety studies

Drug	Body weight	Hypoglycemia	More reported events	Rare events
Sitagliptin	Neutral (monotherapy) Increasing (With insulin and sulfonylureas) (Scott et al., 2007; Raz et al., 2006; Rosenstock et al., 2007a; Charbonnel et al., 2006; Hermansen et al., 2007; Arjona Ferreira et al., 2008)	None (monotherapy) (Barzilai et al., 2009; Raz et al., 2006; Rosenstock et al., 2007a; Rosenstock et al.) Increasing (with insulin and sulfonylureas) (Nauck et al., 2007; Hermansen et al., 2007; Vilsboll et al., 2010)	Headache, upper respiratory tract infection, nasopharyngitis (Chan et al., 2008)	Pancreatitis, hypersensitivity reactions (Ahrén, 2010)
Vildagliptin	Neutral (Bosi et al., 2007; Bolli et al., 2008; Garber et al., 2007; Pratley et al., 2006; Scherbaum et al., 2008; Schweizer et al., 2007)	None (monotherapy) Increasing (with insulin) Kalra, 2011	Nausea, headache nasopharyngitis, dizziness, cough, constipation (Pratley et al., 2006; Scherbaum et al., 2008)	Mild liver enzyme elevation (Kothny et al., 2009)
Linagliptin	Neutral or decreased (monotherapy) Del Prato et al., 2011; Taskinen et al., 2011; Forst et al., 2010; Owens et al., 2011; Lewin et al., 2010; Kawamori et al., 2011 Increasing (with glitazones) Gomis et al., 2011	Increasing (with insulin, sulfonylureas and insulin secretagogues) (Forst et al., 2010; Owens et al., 2011; Lewin et al., 2010; Gallwitz et al., 2011)	Urticaria, angioedema or bronchial hyperreactivity (Del Prato et al., 2011; Taskinen et al., 2011; Forst et al., 2010; Owens et al., 2011; Gomis et al., 2011; Tradjenta, 2011)	-

Comparison of safety studies				
Drug	Body weight	Hypoglycemia	More reported events	Rare events
Exenatide	Decreased (Bergenstal et al., 2012; Gallwitz et al., 2012b)	Mild episodes (Bergenstal et al., 2012; Buse et al., 2004)	Nausea, diarrhea and upper-respiratory-tract infection (Bergenstal et al., 2012; Gallwitz et al., 2012b)	Injection-site erythema, pruritus, urticaria and rash (Buse et al., 2004)
Liraglutide	Neutral or decreased (Pratley et al., 2010; Zinman et al., 2009; Russell-Jones et al., 2009; Nauck et al., 2009; Marre et al., 2009)	None Garber et al., 2009; Zinman et al., 2009; Buse et al., 2009; Nauck et al., 2009; Marre et al., 2009; Seino et al., 2010; Kaku et al., 2010	Nausea, vomiting, diarrhea and constipation (Garber et al., 2009; Pratley et al., 2010; Zinman et al., 2009; Russell-Jones et al., 2009; Nauck et al., 2009; Marre et al., 2009; Seino et al., 2010; Kaku et al., 2010)	Acute pancreatitis and increase in calcitonin level (Russell-Jones et al., 2009; Nauck et al., 2009; Marre et al., 2009)

Mario Schifano Coca Cola (smalto su carta povera)

grazie!