Sri Lanka Medical Association – North America

2011 – Continuing Medical Education Program

November 12th, 2012

New York Hilton, New York USA

SLMANA—Continuing Medical Education Committee (2011):

- Sunil Wimalawansa, MD (Chairperson)
- Selvarani Richards, MD (Co-Chair)
- Aruna Seneviratne, MD
- Rohan Perera, MD
- Darshi Sunderam, MD

SLMANA

Scientific Session – I

November 12th, 2011

SRI LANKA MEDICAL ASSOCIATION OF NORTH AMERICA
EASTERN REGION INC.
PRESENTS

SLMANA EAST CHARITY BALL ANNUAL GENERAL MEETING & SCIENTIFIC SESSIONS ON NOVEMBER 12TH, 2011

NEW YORK HILTON AND TOWERS

1335 Avenue of The Americas New York, NY

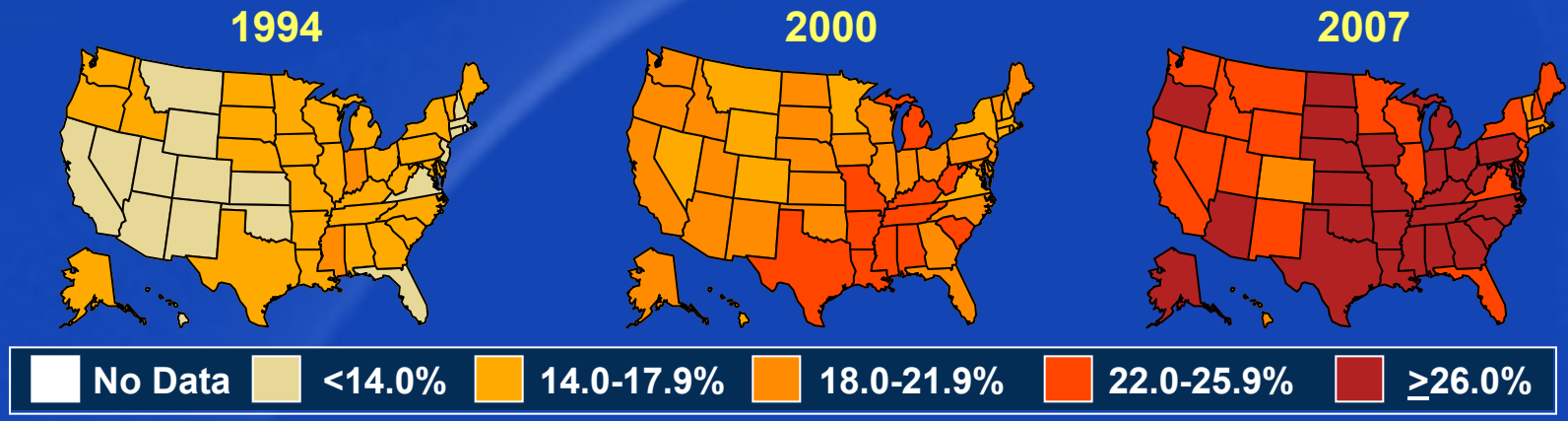
Targeting the Incretins System:

Can it Improve Our Ability to Treat Type 2 Diabetes?

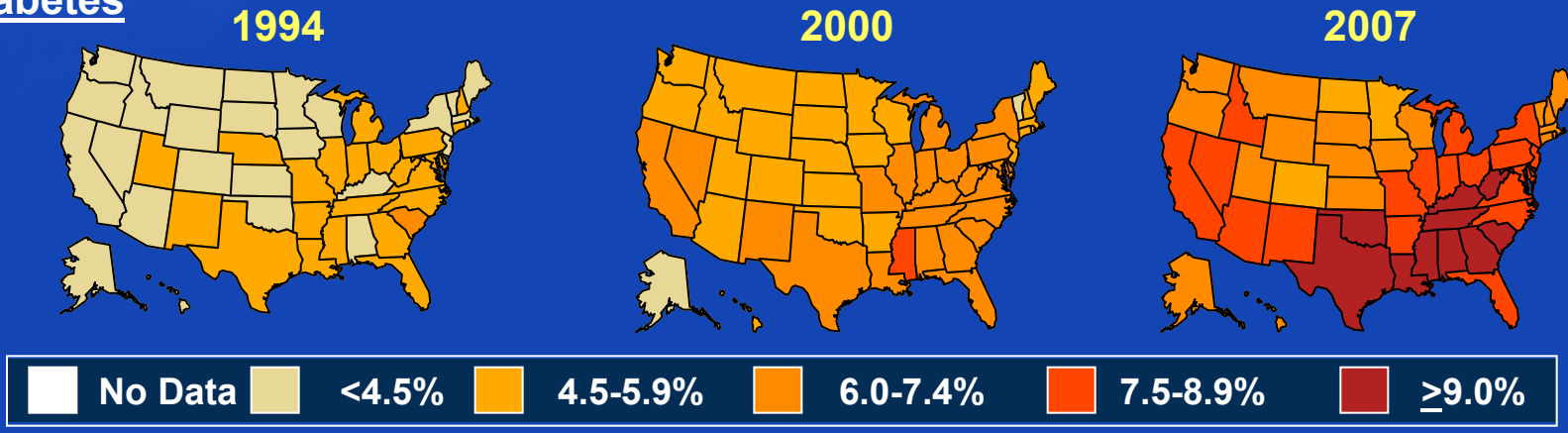
Darshi Sunderam, MD
Chief of Endocrinology
East Orange General Hospital

Age-adjusted Percentage of US Adults Who Were Obese or Had Diagnosed Diabetes

Obesity (BMI ≥30 kg/m2)



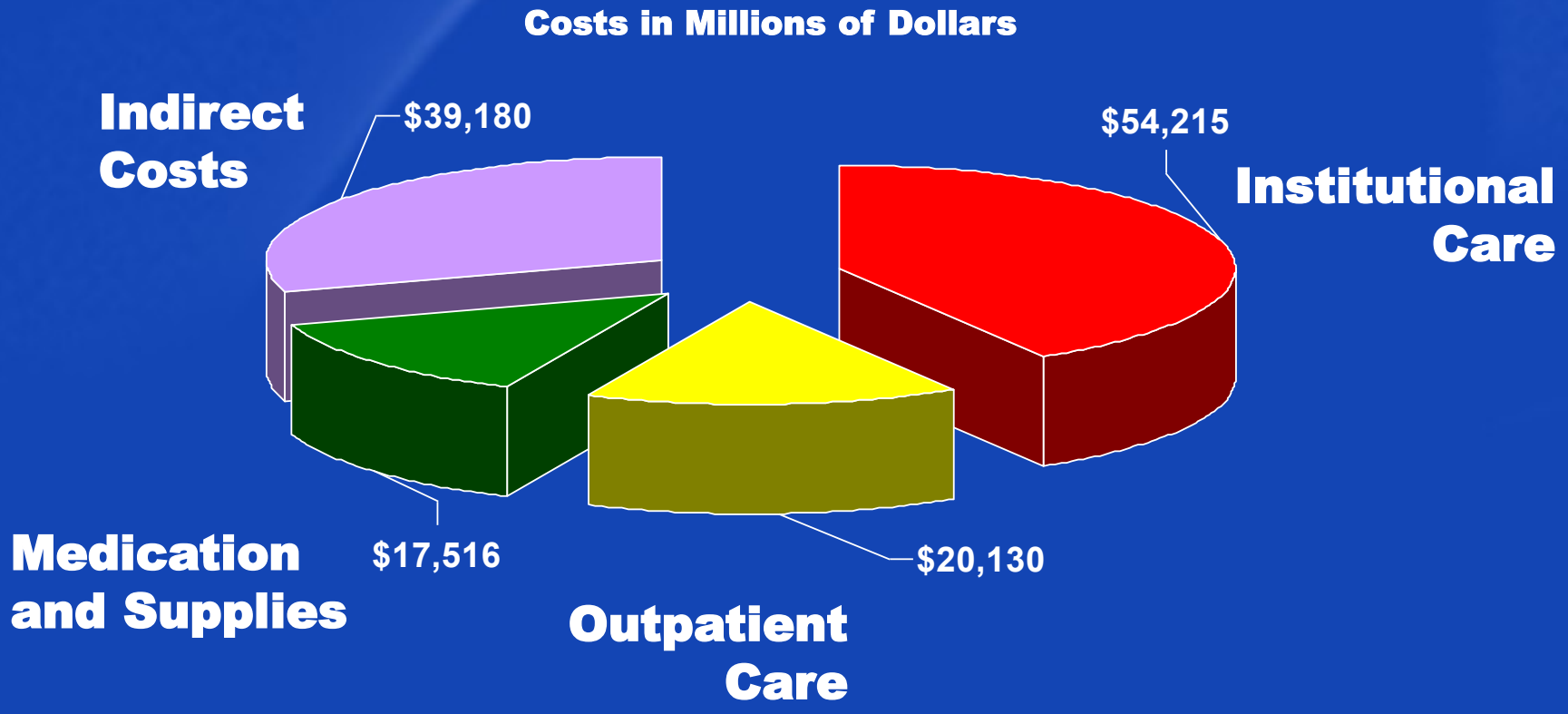
Diabetes



CDC's Division of Diabetes Translation. National Diabetes Surveillance System. http://www.cdc.gov/diabetes/statistics. Accessed October 30, 2008.

Diabetes is Costly

$132 Billion for Total Excess U.S. Cost Attributable to Diabetes in 2002



American Diabetes Association. *Diabetes Care* 2003;26:917-932.

...and Deadly

- **New Cases – 4,100**
- **Amputations – 230 (60% of non-traumatic amputations annually)**
- **Blindness – 55 (#1 cause)**
- **Kidney Failure – 120 (#1 cause)**
- **Deaths – 810 - >60% due to CVD**

Derived from NIDDK, National Diabetes Statistics fact sheet. HHS, NIH, 2005.

ADA Criteria for the Diagnosis of Diabetes

Diabetes Care,January 2010; 33:S62-S69

- **HbA1C ≥6.5% *OR***
- **FPG ≥126 mg/dl. Fasting is defined as no caloric intake for at least 8 h *OR***
- **2-h plasma glucose ≥200 mg/dl using 75 g glucose load *OR***
- **Random plasma glucose ≥200 mg/dl with classic symptoms of hyperglycemia or hyperglycemic crisis**

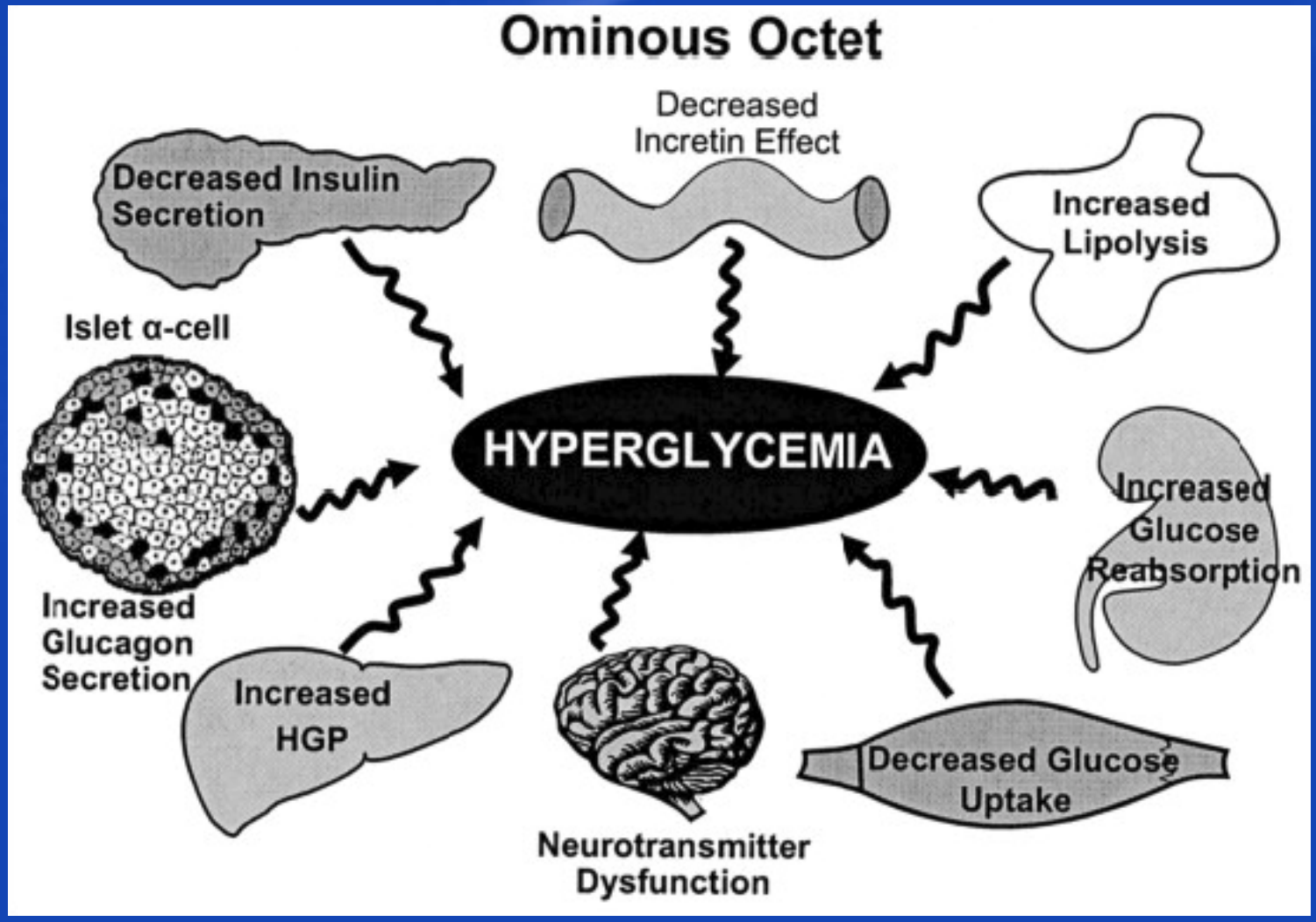
Goal of HbA1C

What is Safe?

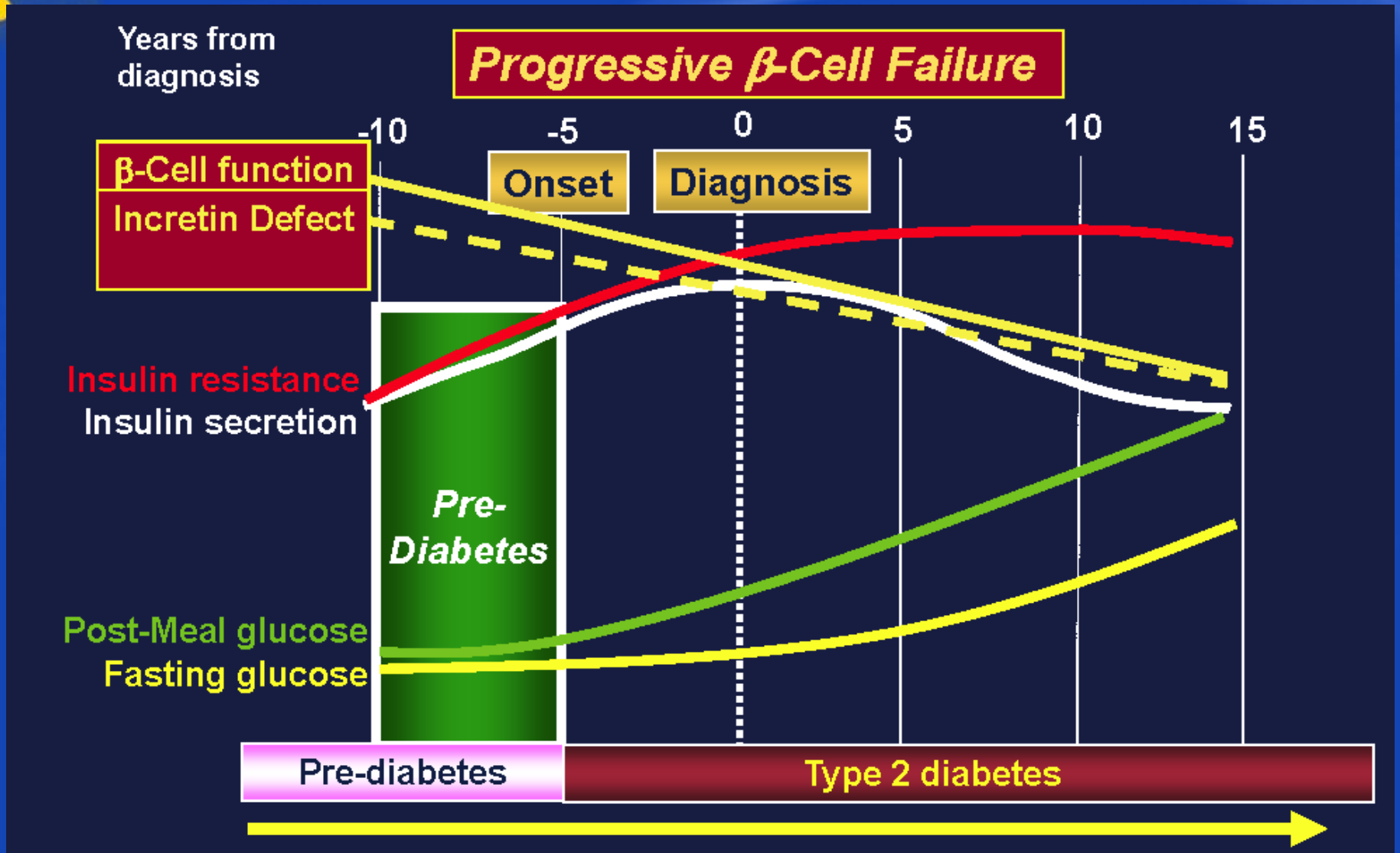
- Lower HbA1C decreases microvascular complications DM1 and DM2
- But, is tight control dangerous in type 2 diabetes with cardiovascular risks?

DeFronzo's Ominous Octet

DeFronzo RA. Am J Med. 2010 Mar;123(3 Suppl):S38-48.

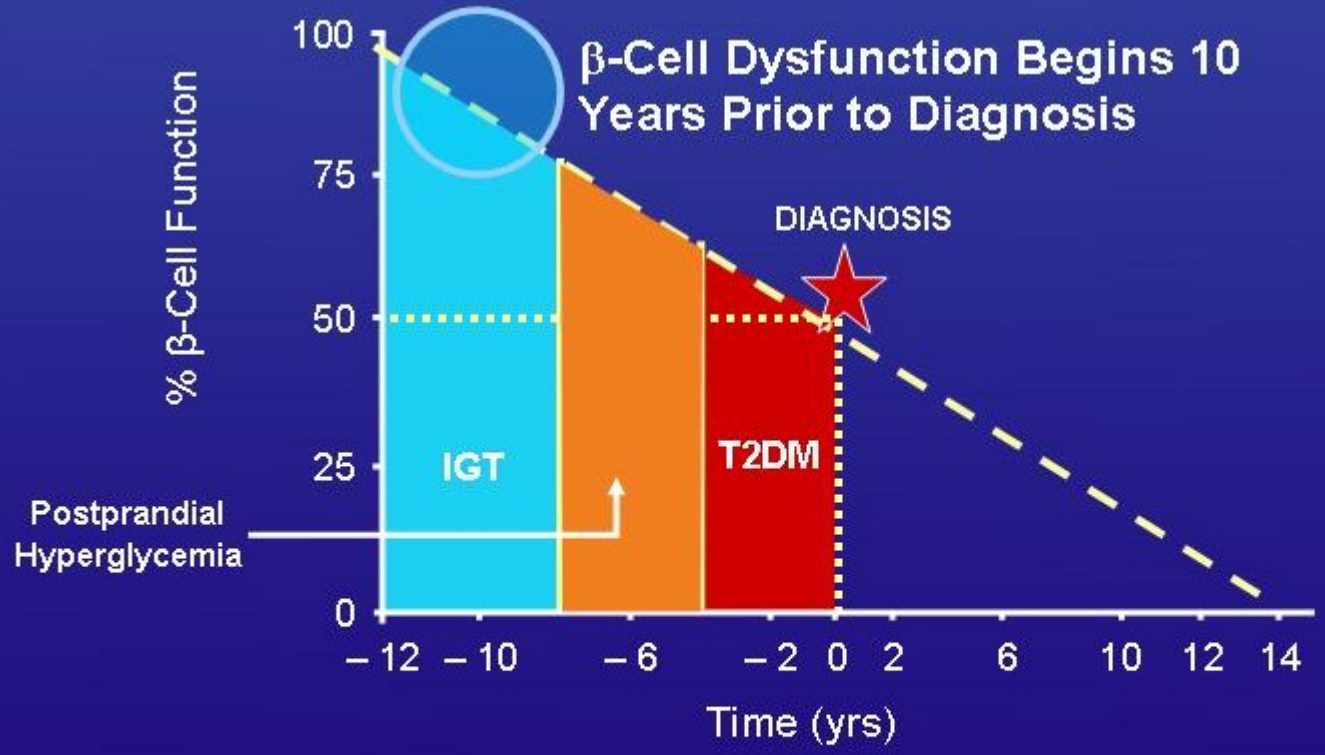


Natural History of Type 2 Diabetes



Ramlo-Halsted BA, Edelman SV. *Prim Care.* 1999;26:771-789; Nathan DM. *N Engl J Med.* 2002;347:1342-1349

β-Cell Dysfunction Begins 10 Years Prior to Diagnosis of Type 2 Diabetes



The Caring For Diabetes EDUCATIONAL FORUM

Lebovitz HE. *Diabetes Review*. 1999;7:139-153.

Introduction to Incretin Therapy in T2DM

Functional Definition of an Incretin

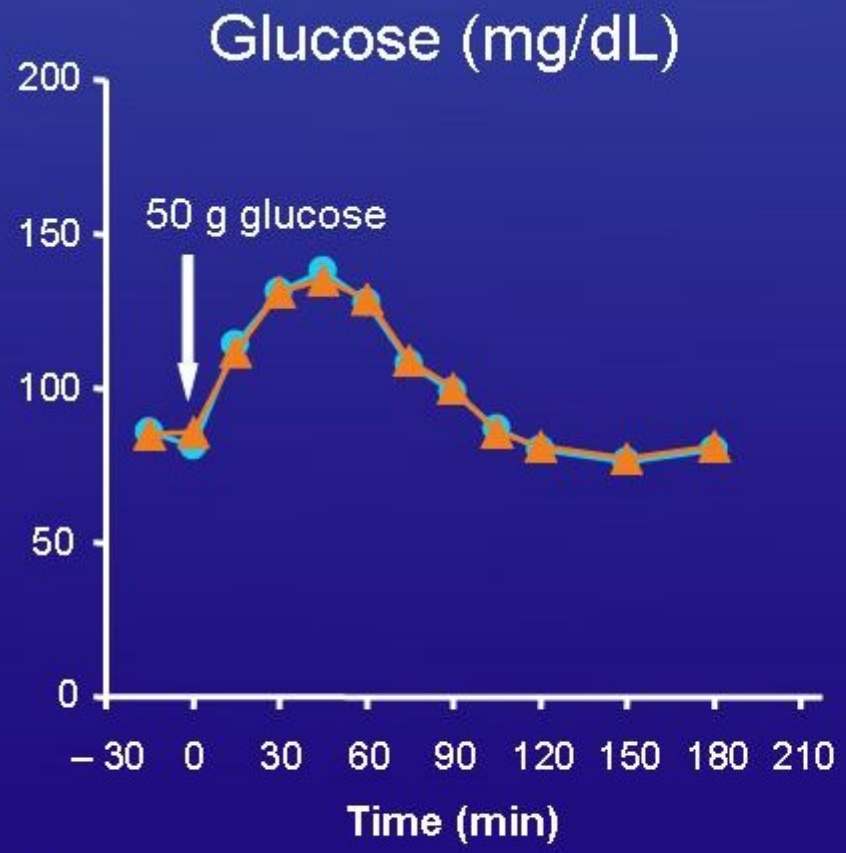
- Hormone(s) released during food ingestion
- Augment insulin secretion at physiologic concentrations
- Insulinotropic effects are glucose dependent

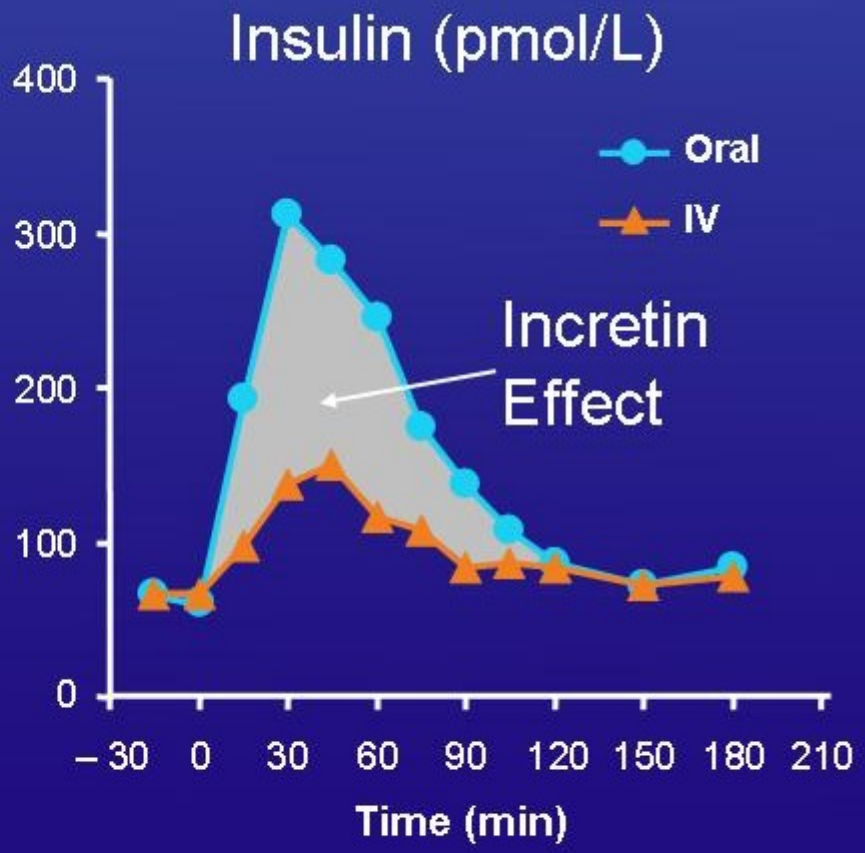
Intestinal Secretion of Insulin

The Caring For Diabetes EDUCATIONAL FORUM

Creutzfeldt WI. *Diabetologia*. 1979;16(2):75-85.

Measuring the Incretin Effect: OGTT and Matched IV Infusion





The Caring For Diabetes EDUCATIONAL FORUM

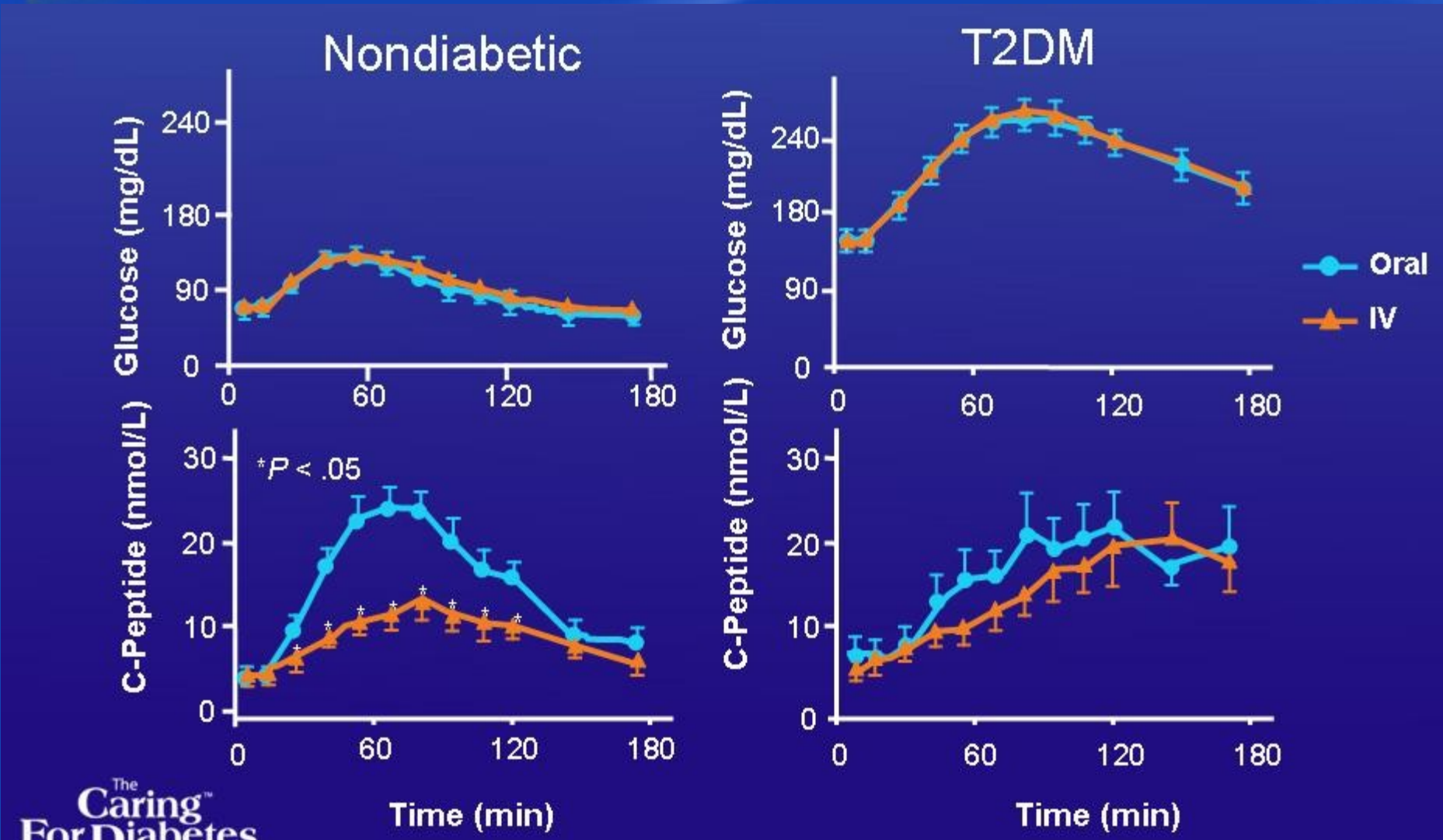
Nauck MA, et al. *J Clin Endocrinol Metab*. 1986;63:492-498.

Key Characteristics of Incretin Hormones Differ in Patients with Type 2 Diabetes

GIP	GLP-1
No defect in GIP secretion	Reduced GLP-1 secretion
Defective GIP response	Preserved GLP-1 response

Vilsbøll T, et al. *Diabetes*. 2001;50:609-613.
Toft-Nielsen M-B, et al. *J Clin Endocrinol Metab*. 2001;86:3717-3723.
Nauck MA, et al. *Diabetologia*. 1993;36:741-744.
Drucker DJ, et al. Lancet. 2006;368:1696-1705.

The Incretin Effect in Type 2 Diabetes



The Caring For Diabetes EDUCATIONAL FORUM

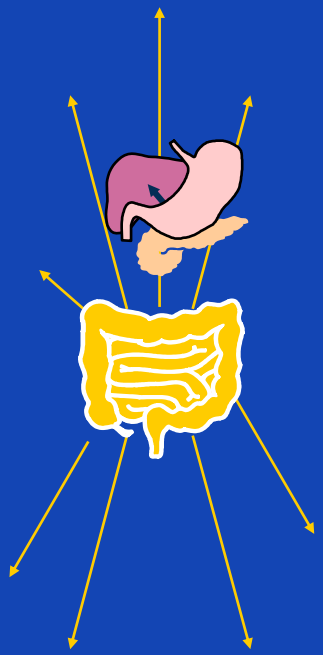
Nauck M, et al. *Diabetologia*. 1986;29:46-52.

GLP-1: Effects in Humans

After food ingestion…

GLP-1 is secreted from L-cells of the jejunum and ileum

That in turn…



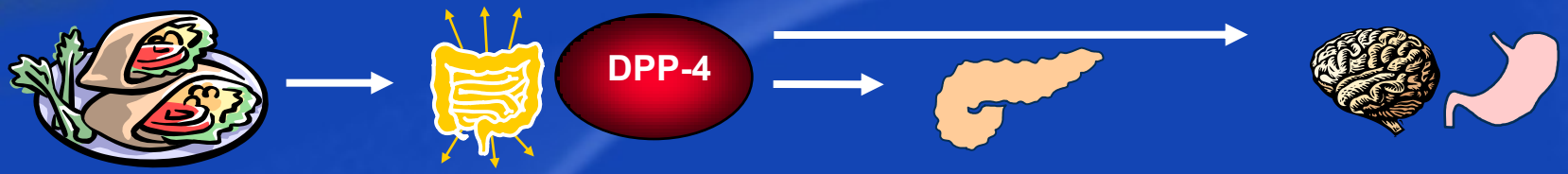
- Stimulates glucose-dependent insulin secretion
- Suppresses glucagon secretion
- Slows gastric emptying
- Leads to a reduction of food intake
- Improves insulin sensitivity

Long-term effects in animal models:

- Increase of β-cell mass and improved β-cell function

Drucker. Curr Pharm Des. 2001
Drucker. Mol Endocrinol. 2003

GLP-1 Secretion and Metabolism



Mixed meal eaten

GLP-1 released into bloodstream and rapidly degraded by DPP-4

Remaining GLP-1 enters pancreas

Remaining GLP-1 affects other systems

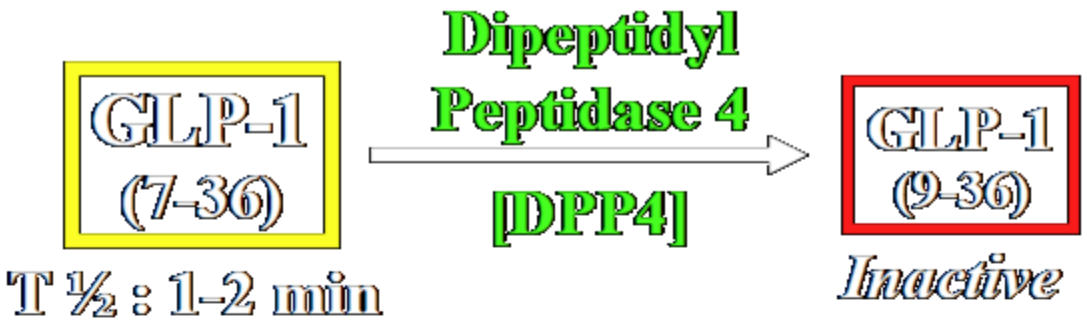
- >50% of secreted GLP-1 is degraded before it reaches the general circulation

- Stimulates insulin secretion
- Suppresses glucagon secretion

- Slows gastric emptying
- Enhances satiety and reduces food intake

Kieffer TJ, Habener JF. Endocr Rev. 1999;20:876-913.

Incretin-Based Therapy



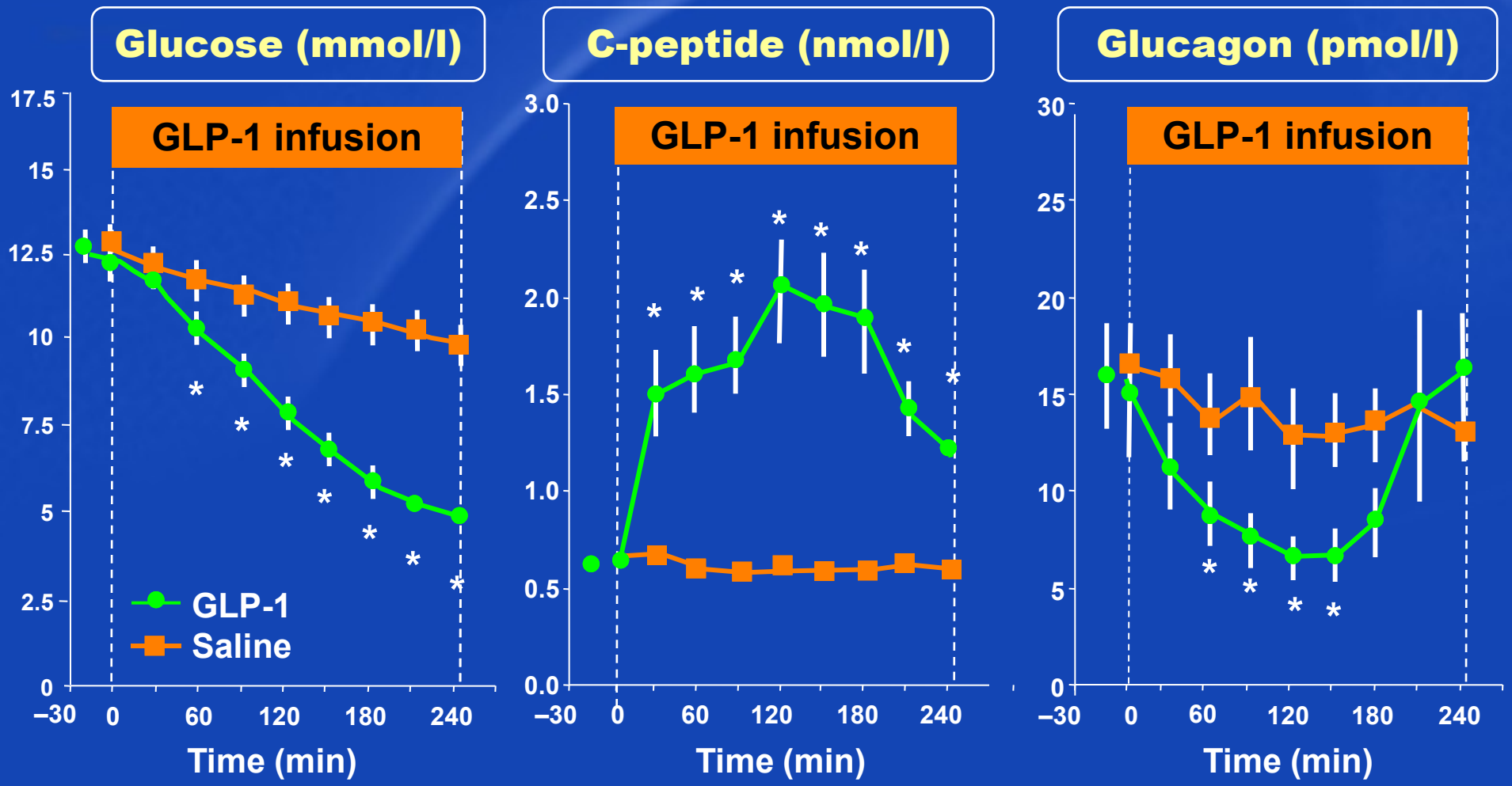
GLP-1 Analog / Agonist

- Resistant to DPP4 Action
- Prolonged Duration of Action

DPP4 Inhibitor

- Prevents Native GLP-1 Breakdown
- Prolongs Duration of Action of Native GLP-1

Therapeutic Effect of GLP-1 in People with Type 2 Diabetes



*$P<0.05$

Nauck et al. Diabetologia. 1993

Available Incretin Agents and Their Effect on A1C and Glucose Levels

GLP-1 enhancement

GLP-1 secretion is impaired in Type 2 diabetes

Natural GLP-1 has extremely short half-life

Add GLP-1 analogues with longer half-life:

- Exenatide (Byetta)
- Liraglutide (Victoza)
- Exenatide QW (Bydurion)

Injectables

Block DPP-4, the enzyme that degrades GLP-1:

- Sitagliptin (Januvia)
- Saxagliptin (Onglyza)
- Vildagliptin (Tradjenta)

Oral agents

Drucker. Curr Pharm Des. 2001; Drucker. Mol Endocrinol. 2003

GLP-1 Agent Therapy

Glycemic Effects

GLP-1 Agents	A1C %	FPG (mg/dl)	PPBG (mg/dl)
Exenatide	⇩ 0.8-1.5	⇩ 10-25	⇩ 126
Liraglutide	⇩ 1.0-1.5	⇩ 26-44	
Exenatide QW	⇩ 1.5-1.9	⇩ 42	

Buse J, Diabetes Care 2004; 27:2628-35
Kendall D, Diabetes Care 2005; 28:1083-91
DeFronzo R, Diabetes Care 2005; 28:1092-100
Drucker D, Lancet 2008;372:1240-1250
Klonoff DC, Curr Med Res Opin 2008;24:275-286
Aroda V, Am J Med 2010; 123:468
Diamant M, Lancet 2010; 375:2234-43
Bergenstal R, Lancet 2010; 376:431-9
Maiti M, Diabetes Med 2009; 26:268-78
Nauck M, Diabetes Care 2009; 32:84-90
Garber A, Lancet 2009; 373:473-81
Zinman B, Diabetes Care 2009; 32:1224-30
Russell-Jones D, Diabetologia 2009;52:2046-55
Buse JB, Lancet 2009; 374:39-47

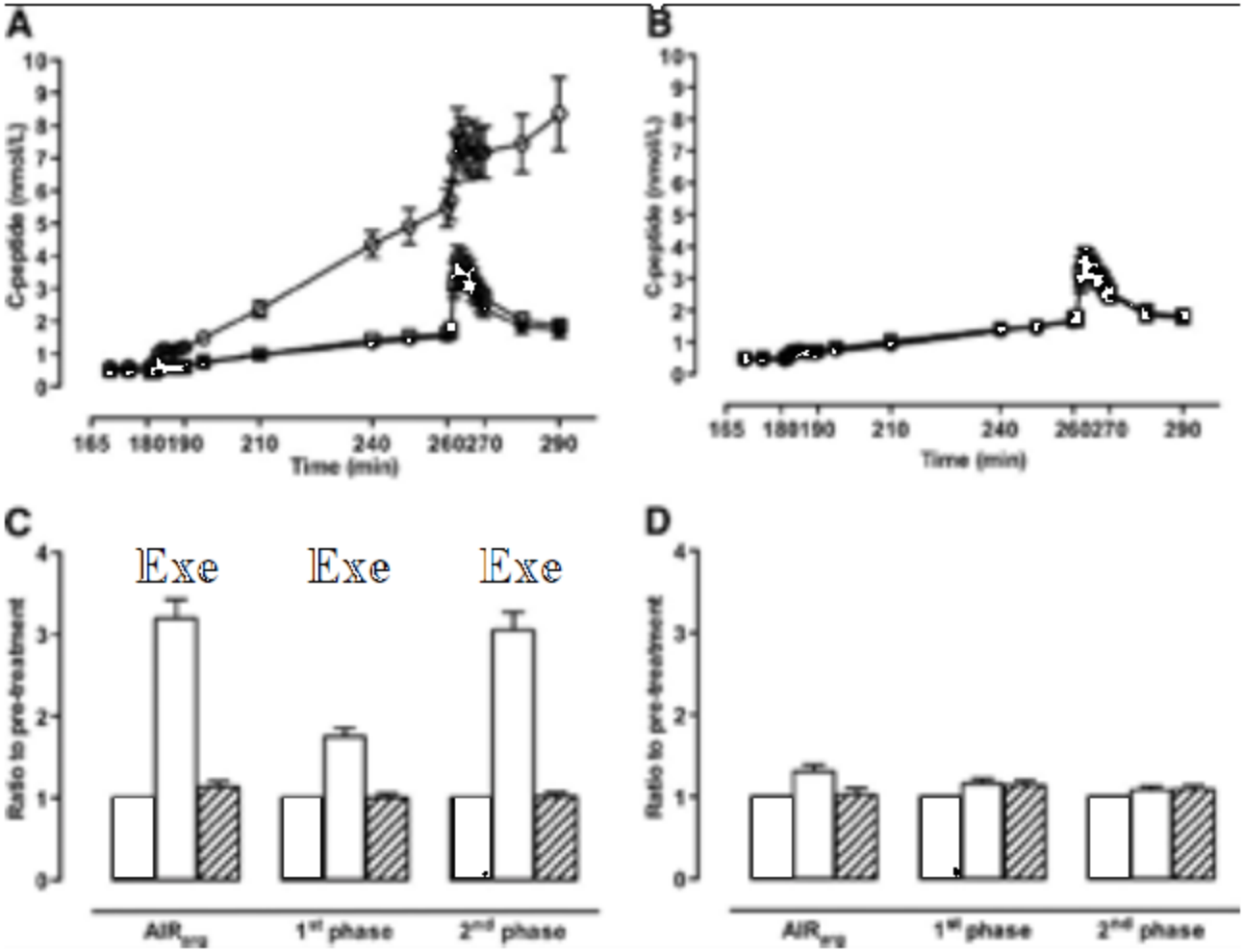
GLP-1 Agent Therapy

Weight Effects

GLP-1 Agents	Weight (kg)
Exenatide	↓ 1.6 5.3
Liraglutide	↓ 0.4 6.2
Exenatide QW	↓ 2.3 3.7

Buse J, Diabetes Care 2004; 27:2628 35
Kendall D, Diabetes Care 2005; 28:1083 91
DeFronzo R, Diabetes Care 2005; 28:1092 100
Drucker D, Lancet 2008;372:1240 1250
Klonoff DC, Curr Med Res Opin 2008;24:275 286
Apovian C, Am J Med 2010; 123:468
Diamant M, Lancet 2010; 375:2234 43
Bergenstal R, Lancet 2010; 376:431 9
Maure M, Diabetes Med 2009; 26:268 78
Nauck M, Diabetes Care 2009; 32:84 90
Gaber A, Lancet 2009; 373:473 81
Zinman B, Diabetes Care 2009; 32:1224 30
Russell Jones D, Diabetologia 2009;52:2046 55
Buse JB, Lancet 2009; 374:39 47

Exenatide Effect on β–Cell Function



During Treatment (1 Year)

⇑ 1st Phase Insulin

⇑ 2nd Phase Insulin

After Treatment

Back to Baseline

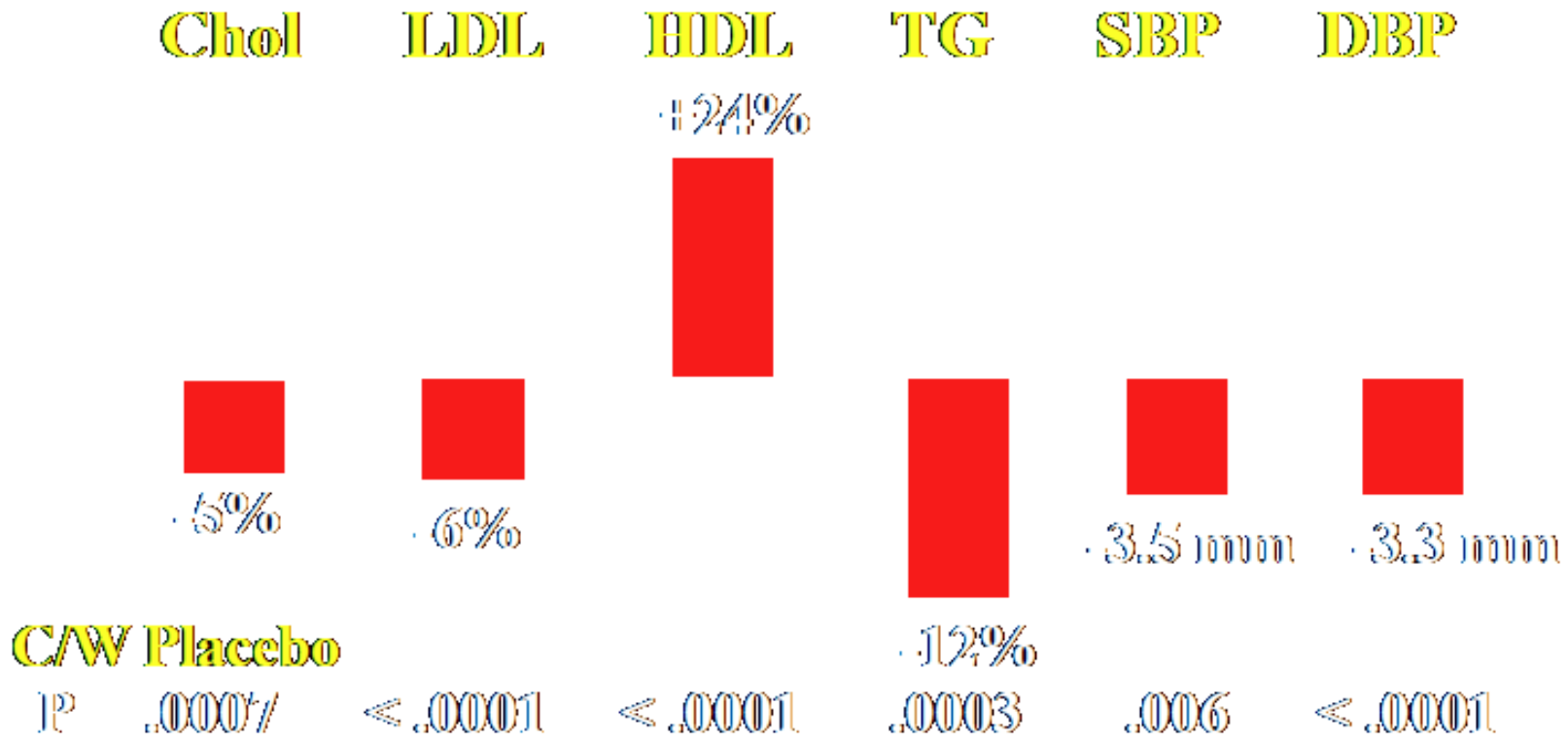
Bunck M, Diabetes Care 2009; 33:1734-7

Exenatide Therapy for 3 Years

Cardio-Metabolic Effects

Type 2 Diabetes Subjects (217)

3 Year Open Label Extension: Exenatide vs Placebo



Klonoff D, Curr Med Res Opin 2008;24:275-286

Incretin Mimetic Drugs: Safety Issues – CV Events

- **Meta-analysis of 12 randomized, controlled trials**
  - **12-52 weeks duration**
  - **Exenatide (5-10 µg bid) vs comparator (placebo or insulin)**
- **Patient characteristics at baseline (mean)**
  - **Age 56 y; BMI = 31-32 kg/m²; A1C = 8.3%-8.4 %**

	Exenatide (n=2279) 1063 patient-years	Comparator (n=1629) 780 patient-years	RR (95% CI)
CV event incidence (unadjusted)	2.0%	2.6%	0.69 (0.46-1.04)
Exposure-adjusted incidence (per 1000 patient-years)	43.7	54.4	0.80 (0.53-1.22)

Shen L, et al. Diabetes. 2009;58(suppl 1):A96.

DPP4 Therapy

Glycemic and Weight Effects

DPP4 Inhibitors	A1C %	FPG (mg/dl)	PPBG (mg/dl)
Sitagliptin	↓ 0.5 1.0	↓ 15 25	↓ 36 54
Saxagliptin	↓ 0.5 0.8		

DPP4 Inhibitors	Weight (kg)
Sitagliptin	No Δ
Saxagliptin	No Δ

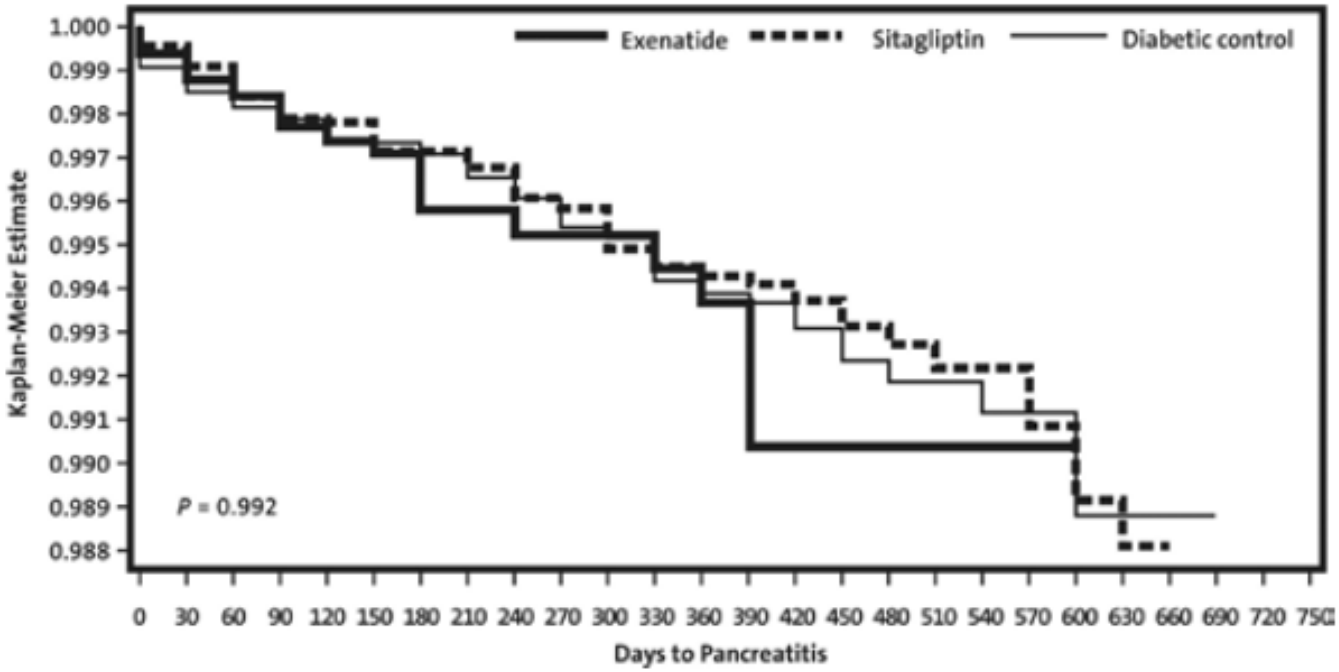
Goldstein B, Diabetes Care 2007;30:1979-87
Nauck M, Diab Obes Metab 2007; 9:194-205
Raz I, Current Med Res Opin 2008; 24:537-50
Visboll T, Diabetes Obes Metab 2010; 12:167-77

Acute Pancreatitis

Exenatide and Sitagliptin

Retrospective Cohort Study, Claims Database (~86,656 Patients)

Exenatide vs Sitagliptin vs Diabetes Controls



Pancreatitis

Exenatide

HR 0.9 (0.6 1.5)

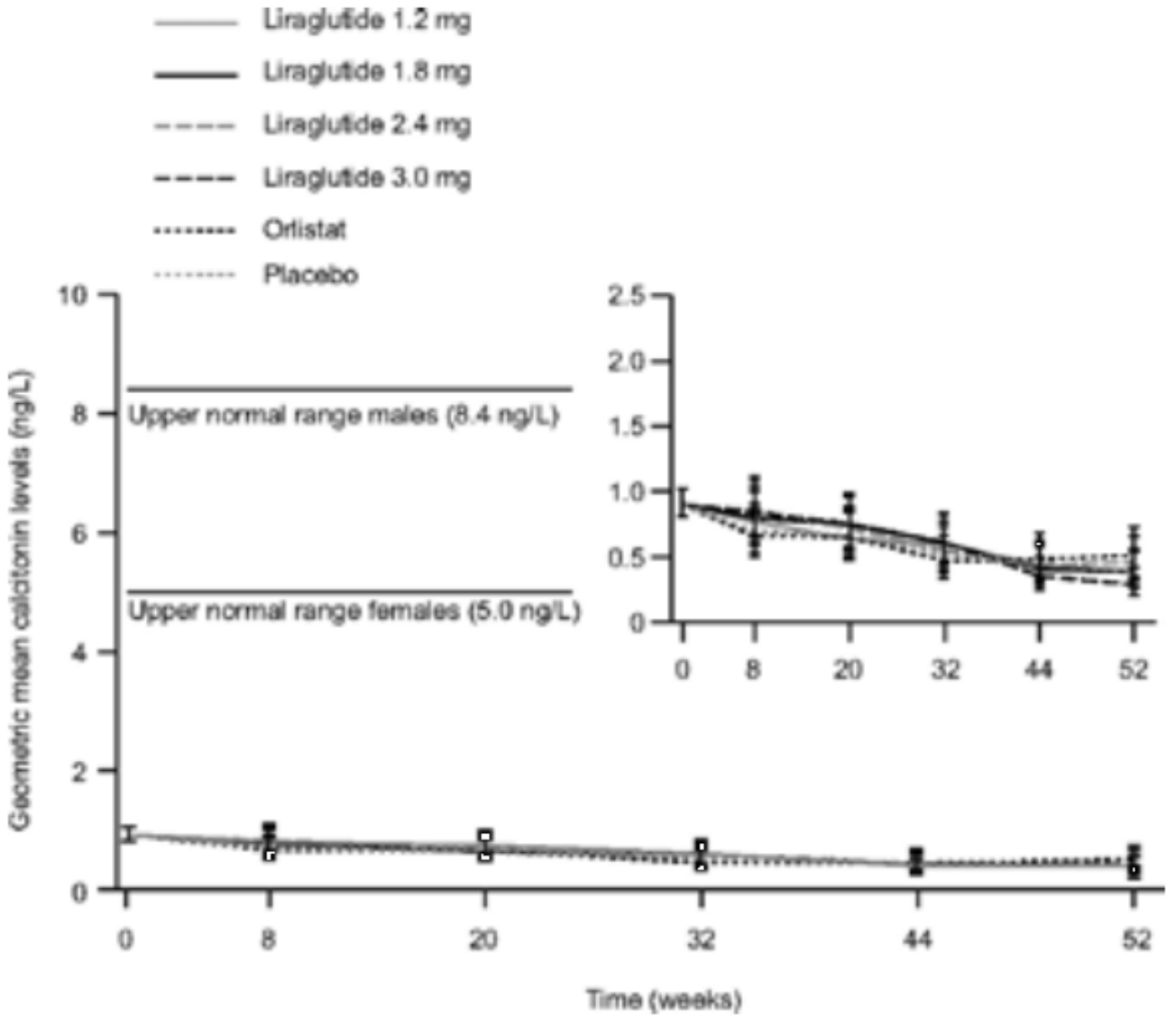
Sitagliptin

HR 1.0 (0.7 1.3)

Garg R, Diabetes Care 2010; 33:2349-54

Liraglutide and Medullary Thyroid Cancer

Calcitonin



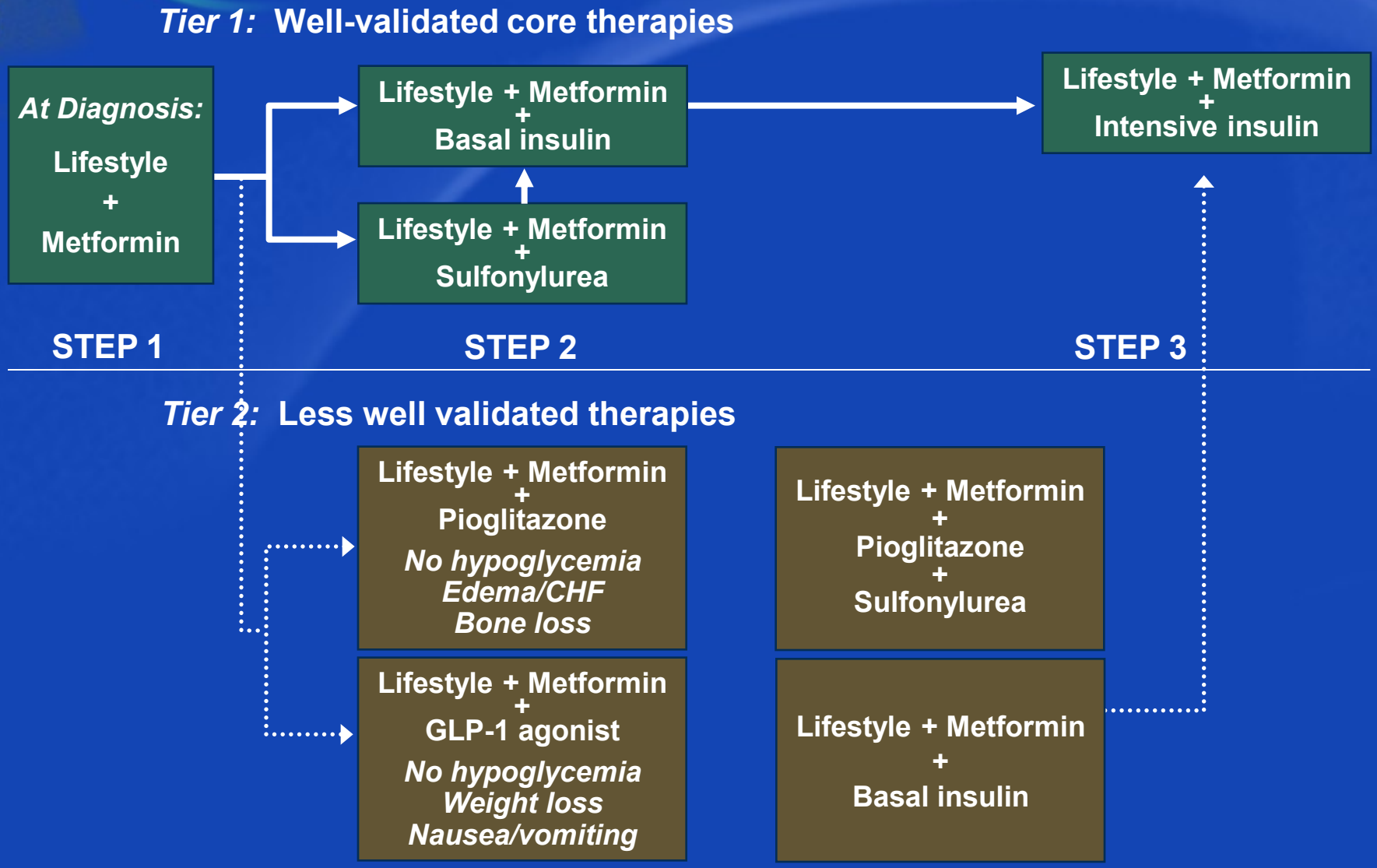
The Journal of Clinical Endocrinology & Metabolism

Hegedus L., J Clin Endocrinol Metab 2011; 96:853-60

Comparison of GLP-1 Receptor Agonists and DPP-4 Inhibitors

Effects/Parameters	GLP-1 receptor agonists	DPP-4 inhibitors
Route of administration	Subcutaneous injection	Oral
Dosing/timing of administration	Once or twice daily	Once daily
Insulin secretion	Enhanced	Enhanced
HbA1c reduction	-0.6% to -1.9%	-0.5% to -0.8%
Postprandial hyperglycemia	Reduced	Reduced
Glucagon secretion	Suppressed	Suppressed
Body Weight	Reduced	Neutral
Appetite	Suppressed	No effect
Gastric emptying	Slowed significantly	No Effect
Hypoglycemia	Low rates	Low Rates
GI AE's	Nausea, diarrhea	No significant GI AE's
CVD risk factors	Improved (with weight loss)	No consistent change

ADA/EASD Consensus Guidelines Treatment Algorithm



Reproduced with permission from Nathan DM, et al. [published online ahead of print October 22, 2008] Diabetes Care. http://care.diabetesjournals.org/cgi/reprint/dc08-9025v1. Accessed October 30, 2008.

Comparison of the ADA and Pathophysiologic-Based Algorithms

	ADA	Pathophysiologic-Based
Durability	**No**	**Yes**
β-cell Preservation	**No**	**Yes**
Hypoglycemia	**Yes**	**No**
Weight Gain	**Yes**	**No**

DeFronzo, Ralph A. From the Truimvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. Diabetes, Vol 58, April 2009.

Summary

- Type 2 diabetes is a progressive disease with multiple pathogenic defects
- Therapeutic approaches based on pathophysiology with multiple agents early in the disease state
- GLP-1 increases insulin secretion, decreases glucagon secretion in a glucose dependent manner
- GLP-1 has an effect on beta cell, liver, alpha cell, gut and brain.
- GLP-1 analogs provide long acting GLP-1 activity
  - improve glycemia with weight loss
  - Reduce blood pressure with improved lipid profile
- DPP-4 inhibitors prolong activity of native GLP-1
  - Improve glycemia and weight neutral
- GLP-1 analogs and DPP-4 inhibitors are effective alone and in combination with oral agents or with insulin

Remember

- Multiple pathogenic abnormalities
- At diagnosis only 20% of Beta Cell function is left
- Early diagnosis and aggressive treatment
- Protect remaining Beta Cell

Thank You

Q&A


LANKA MEDICAL ASSOCIATION OF NORTH AMERICA
EASTERN REGION INC.
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CHARITY BALL
NUAL GENERAL MEETING
&
SCIENTIFIC SESSIONS
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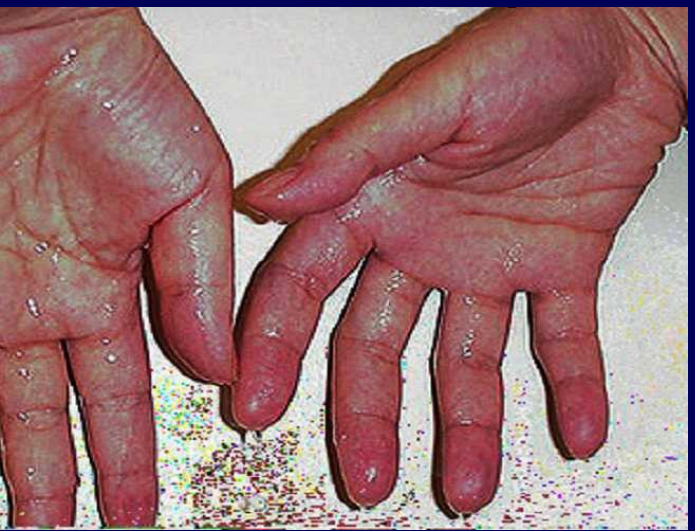
PRIMARY HYPERHIDROSIS

Disease or Anxiety



N. I. PERINPANAYAGAM M.D, FRCS, FACS
Professor of Neurosurgery
NYU Medical Center
New York, NY

PRIMARY HYPERHIDROSIS

Diagnosis of Primary HH - Start in the 1st or 2nd decades of life & should be Bilaterally Symmetrical

Occurs in 2.8% of the US population

Typically affects the hands, axillae, feet & less commonly the face (facial flushing)

INHERITANCE

- **Primary HH is reported to be inherited as an Autosomal dominant gene, with incomplete penetrance**

PRIMARY HH

- Has Psychological, Social, Economic & Occupational implications
- Most patients present in their teens and twenties
- Majority of pts. are on Anti-Anxiolytic drugs

TYPICAL PRESENTATION

- Palmar, Axillary & plantar HH
- Palmar HH only
- Axillary HH only, with or without Bromhidrosis
- Facial HH / Gustatory sweating with or without facial flushing
- Plantar HH

DIAGNOSIS

- Primary vs Secondary HH
- Endocrine work-up – Hyperthyroidism, Hyperpituitarism, Dumping syndrome, Alcohol & drug withdrawal, menopause, Diabetes, febrile illnesses, paraplegia, stroke, anxiety etc
- Objectively quantify degree/severity of HH & the impact on ADL
- Family history

PATIENTS WITH PRIMARY HH

- Excessive sweating independent of ambient temperature, worse with anxiety!
- Excessive hand sweating leaves puddles of sweat, avoid shaking hands
- Axillary sweaters change shirts 3-4 times/day, wear only darker clothes
- Plantar sweaters cannot wear sandals or slippers, wear thick sox & closed shoes

NON-SURGICAL TREATMENTS FOR PRIMARY HH

- Antiperspirants (Aluminum Chloride –Drysol)
- Anticholinergics – (Robinul)
- Iontophoresis
- Therapies based on Bio-feedback
- Botulinum toxin “A” Injection

IONTOPHORESIS (Drionic & Fischer)

- Immersing hands or feet in tap water through which a 15-20ma direct current is passed
- Iontophoresis to deliver anticholinergics
- Recom-20mts on days 1,2,4,7,10,15,22 & maintenance sessions every 4 wks
- Side effects burning, tingling, skin irritation, erythema

BOTULINUM TOXIN INJECTIONS

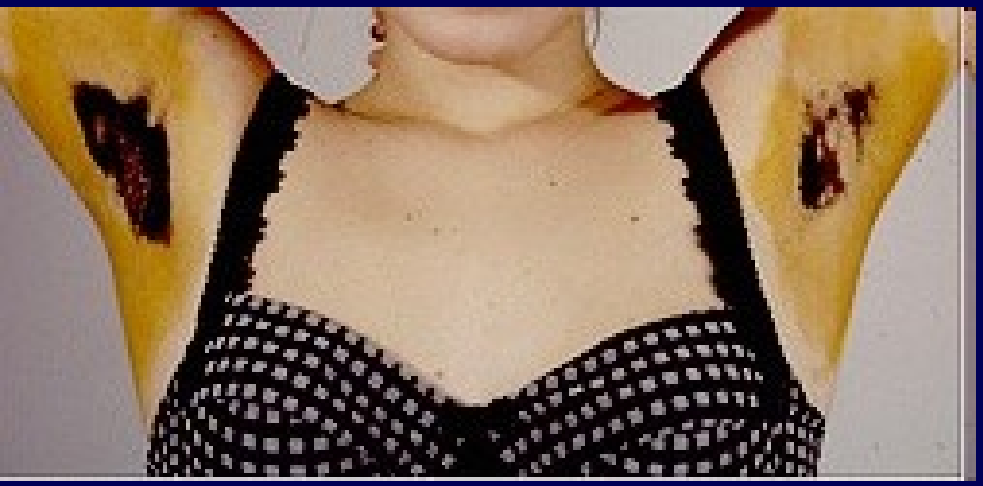
- Intra-dermal botox blocks the release of Ach
- The area to be treated is outlined using the “starch-iodine test” the area is marked out into 1.5cm squares and 2units of Botox is injected intradermally to each square

  (max dose 100units)
- Works best for axilla and less well in the hands and feet

MEDICAL MANAGEMENT

- Antiperspirants – 1st line of Rx -Palmar, Plantar, Axillary HH (Drysol- Aluminum based)
- Iontophoresis – non-responsive to above Palmar & Plantar
- Anticholinergics – Robinul (1mg tid) palmar, plantar, axillary (1st line in whole body HH & facial HH)
- Botox Injections – Axillary HH not responsive to 1 & 2 (not recom. In palmar – muscle wasting & hand weakness)

STARCH IODINE TEST SHOWING LOCATION OF EXCESSIVE SWEATING



SURGICAL TREATMENT OF PRIMARY HH

- Excision of Apocrine glands –Axilla (liposuction)
- Radio-frequency lesioning of the Sympathetic ganglia (Imprecise)
- Endoscopic Thoracic Sympathectomy

THORACIC SYMPATHECTOMY FOR HH

- Isolates the sympathetic supply to the sweat glands
- Immediately stops sweating, hands after sympathectomy slightly warmer & pink
- Approaches –

  Supra-clavicular; Trans-axillary

  Postero-lateral thoracic (midline approach)

  Endoscopic Thoracic Sympathectomy

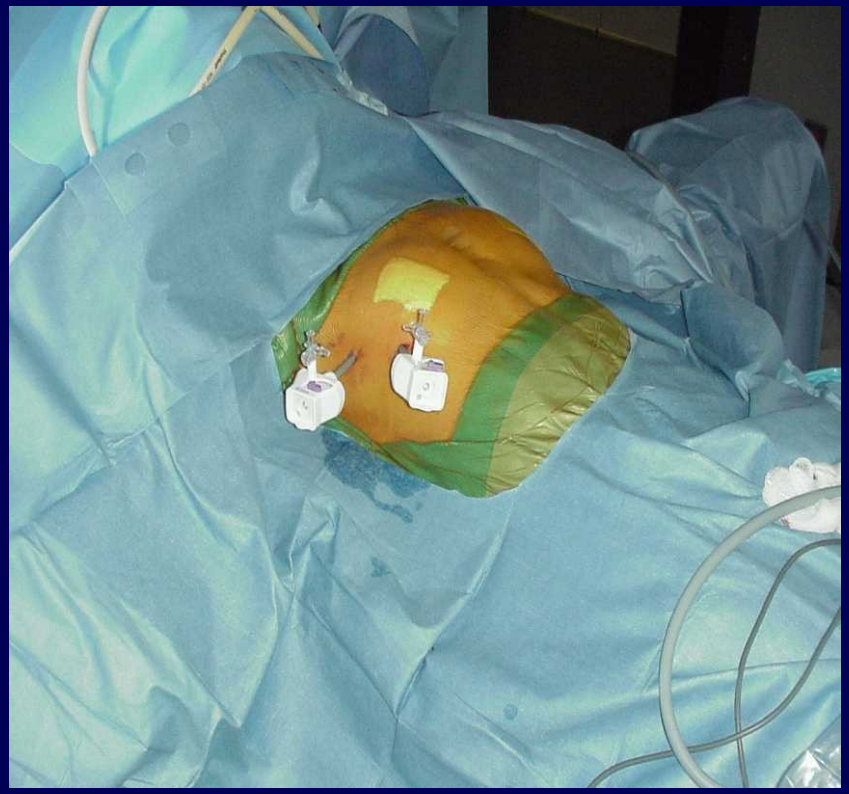
INTERNATIONAL NOMENCLATURE FOR SYMPATHECTOMY SURGERY(ISSS)

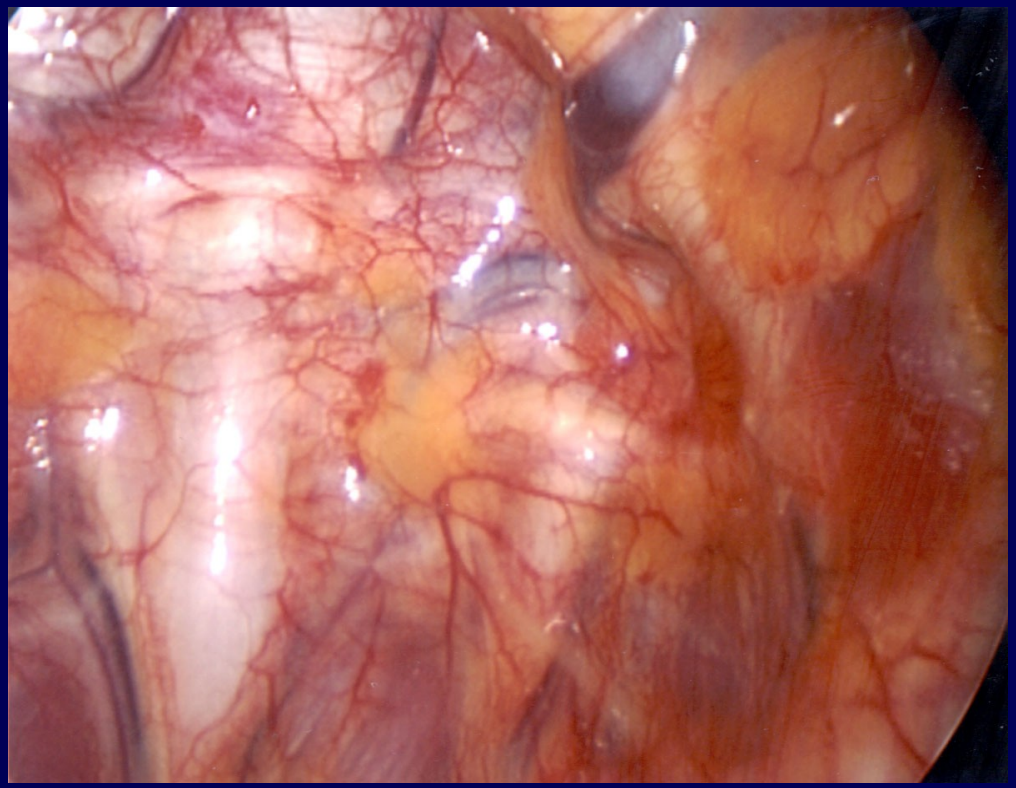
- Notation of level or levels where sympathetic chain isolated
- Rib based - R2, R3, R4, R5
- Ganglion based – G2 (R2-3) G3(R3-4), G4(R4-5), G5(R5-6)
- Old terminology – Sympathicotomy / T2, T3, T4, T5 Sympathectomy.
- T2 – (R2R3/G2), T3 – (R3,R4/G3),
  T4-(R4,R5/G4), T5 – (R5,R6/G5)

INDICATIONS FOR ENDOSCOPIC THORACIC SYMPATHECTOMY(ETS)

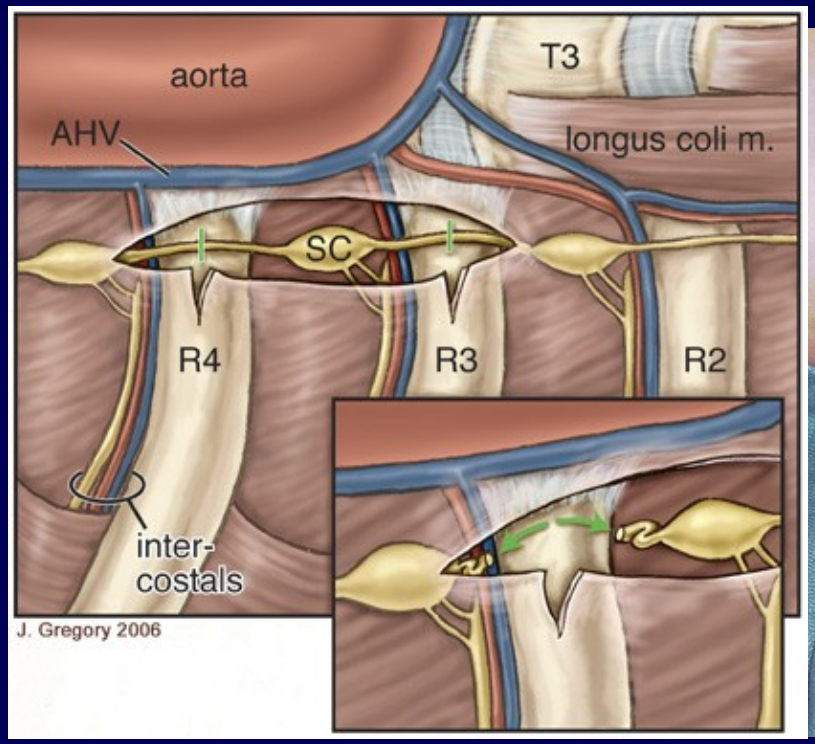
- Severe Palmar with Mod. Axillary, & Plantar Hyperhidrosis (failed medical Rx)
- Isolated Axillary
- Facial Flushing or Redness
- Reflex Sympathetic Dystrophy (CRPS)
- Raynaud's Syndrome
- Idiopathic cardiac arrythmias-children

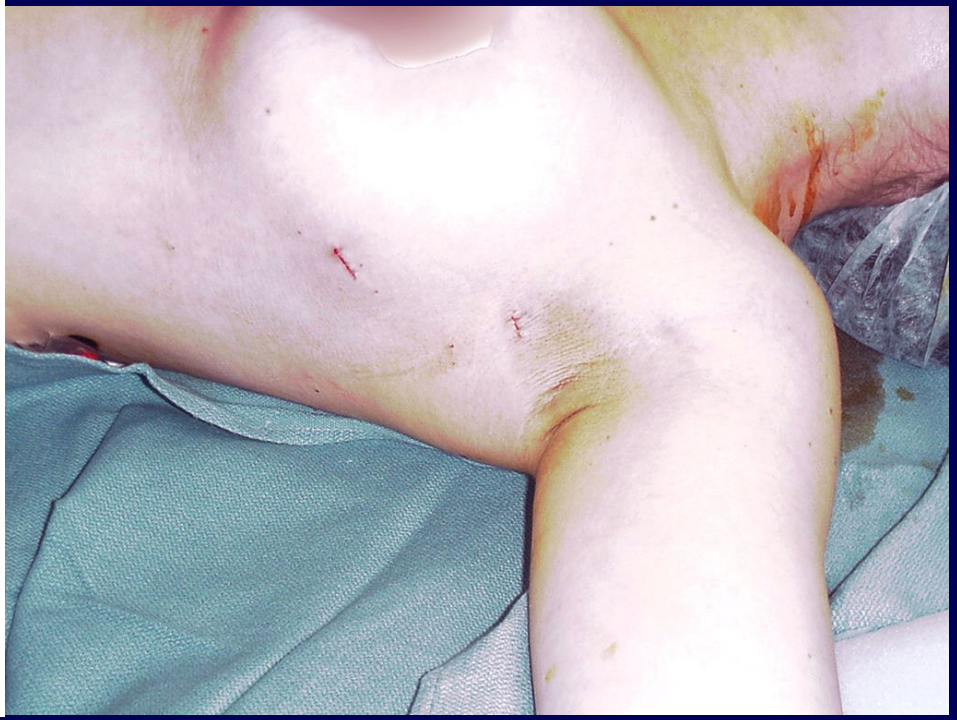
BILATERAL ENDOSCOPIC THORACIC SYMPATHECTOMY-ETS





DIVISION OF THE TRUNK AT R3,R4 ISOLATES THE 3rd GANGLION





CLINICAL MATERIALS & METHODS

- **Retrospective review of 185 patients for a total of 370 sympathectomies.**
- **138 patients were available for follow-up**
  (very mobile young Pt. population)

Chwajol M, Barrenechea IJ, Chakraborty S, Ichiba T, Lesser JB, Connery CP, Perin NI, **Impact of symptomatic improvement, recurrence and compensatory hyperhidrosis on patient satisfaction after endoscopic thoracic sympathectomy**. *Neurosurgery*. 2008; 64:511-518.

RESULTS - 1

- ETS for HH - 182pts,
- ETS for facial Flushing - 3pts.
- Avg. time from ETS to questionnaire - 1.3yrs
- Of the 138 patients, 81 females (59%) &
  57 males(41%)
- Age range 10 - 67yrs. (mean 28, SD 8.9)

RESULTS WITH ETS FOR HH

- 98% reduction of sweating in Palmar HH
- 80% Reduction in Axillary HH
- 60% Reduction in Plantar HH
- Facial Flushing / Facial sweating inconsistent response
- Recurrence 1-2% (Higher in patients treated for Axillary HH)

COMPENSATORY HYPERHIDROSIS

- Major source of dissatisfaction after ETS for HH
- Occurrence - All Pts. have some degree of compensatory HH following ETS, especially during exercise and hot weather
- However Intractable Compensatory HH, occurs in less than 5% of patients
- Incidence of the severe Intractable CHH has decreased with going to lower levels in the chain (R3,R4-3G,R4,R5-4G)

COMPENSATORY HH SEVERITY SCALE

- Grade: 0 - No CH
- Grade: 1 – CH seldom noticeable, does not interfere with daily activities
- Grade: 2 – CH noticeable but tolerable & does not interfere with daily activities
- Grade: 3 – CH Intolerable & Interferes with daily activities

OCCURRENCE OF COMPENSATORY HH

- Almost all Pts. experienced some degree of CHH during exercise & hot weather(130 of 138 = 94%)
- CHH occurred mostly in the back, lower chest, abdomen & thighs
- 18 had one body area affected, 41 had two areas, 35 three areas & 36 had four areas affected

SEVERITY OF COMPENSATORY HH & POSSIBLE PREDISPOSITION

- Age of the patient-Tendency older pts
- Pre-operative BMI-Tends higher with higher BMI
- # of levels of the sympathetic chain /ganglion divided- Tends higher with more levels
- Occurrence of Compensatory HH related to upper versus lower ganglion isolation

  Shown to reduce severe CHH (T2 to T3 & T4)

CURRENT PROTOCOL FOR SYMPATHECTOMY IN HH

- **Presently all patients with Palmar HH receive a T3 Ganglion isolation**

  (R3,R4/3G)

- **Patients with Palmar & Axillary HH – T3G & T4G (R3-R4/3G, R4-R5/4G)**
- **Patients with facial HH & Facial Flushing – T2G (R2-R3/2G)**

SATISFACTION RATES REPORTED ON THE QUESTIONNAIRE

- Very Satisfied 88 pts (64%)
- Somewhat Satisfied 36 pts (26%)
- Somewhat Unsatisfied 9 pts (7%)
- Regretted having the surgery 5pts (3%)

Satisfaction rates highest in patients with severe palmar HH, and lowest in patients with isolated severe Axillary HH

Results in Facial flushing & facial sweating inconsistant

Some improvement in Plantar HH (60%)

REVERSIBILITY

- Cutting or Clipping of the Sympathetic chain
  Possible to remove the clips in very severe Compensatory HH to revert to original state – Inconclusive evidence of reversal
- Nerve Grafting for reversal (sural vs Intercostal nerve for grafting)-

Latif MJ, Afthinos JN , Connery CP, Perin NI, Bhora FY, Chwajol M, Todd GJ, Belsley SJ,
Robotic intercostal nerve graft for reversal of thoracic sympathectomy: a large animal feasibility model. *Int J MedRobotics Comput Assist Surg*. 2008; 4:258-226.

ROBOTIC INTERCOSTAL NERVE GRAFT

IRB to perform - Robotic Intercostal nerve to sympathetic trunk grafts, to reverse Intractable compensatory sweating.

CONCLUSION

- Sympathectomy for intractable Palmar HH is a very effective treatment
- There was a 98% reduction of hand sweating, an 80% reduction of Axillary sweating & a 60% reduction of plantar sweating after upper Thor.ETS
- 94% of patients in our series developed some degree of CHH. There was a statistically significant association between advancing age & CHH(p=0.02), Higher BMI showed a trend towards increased CHH (p=0.14)

CONCLUSION

Higher satisfaction rates were noted in Pts. treated for Palmar (100%) even with asso. CHH vs. Axillary HH(73%). Overall satisfaction rate in both groups was 92% at one year.

- With sectioning of the Sympathetic trunk from T2G to T3G & T4G for palmar HH &, T4G,T5G for axillary HH has significantly reduced the incidence of severe CHH

Q&A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PRESENTS
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NUAL GENERAL MEETING
&
SCIENTIFIC SESSIONS
ON
NOVEMBER 12TH, 2011
NEW YORK HILTON AND TOWERS
1335 Avenue of The Americas New York, NY

Endocrine and Metabolic Challenges in Baby Boomers

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Nov 12 2011

Objectives & Disclosures

- Review - selected perspectives of endocrine & metabolic health in relation to Baby boomers

- Disclosures – None

TROUBLING demographics

- For next 19 years, *additional* 10,000 Baby Boomers/ daily in USA, become 65 yrs !
- In 2010 T2 DM - 26 million , by 2050 1/ 3 rd of US population
- 79 million in USA currently have PRE-Diabetes
- USA spent 17 % of GDP on health in 2010
- Childhood obesity, T2DM, processed / Na laden/ fatty foods, soda-pop with cheap calories, *rampant and fast-growing across the globe*

Biggy,Easy,Couchy & roundy

- **BMI TABLE**

	Caucasians	Asians
Normal	< 25	< 23
Overweight	25 –29.9	23 –29.9
Obese	30–39.9	30 –39.9
Morbid Obesity	≥ 40	≥ 40
Super Morbs	> 60	> 60

Morbidity in impending Baby Boomers

- **2007 USA**
  - 64% of , 50 - 64 yr olds(pre-boomers),
    (35 million people),
  - have at least one chronic health condition > CAD, HTN, DM
  - Geriatric changes start early as 50 yrs age

(Analysis of the Medical Expenditure Panel Survey 2007 by N. Tilipman and B. Sampat of Columbia University for The Commonwealth Fund.)

!

The birds of a feather flock together

- **Endocrine and Metabolic problems almost,**

" never occur alone! "

Boomer metabolic Fraility

- **State of reduced physiological reserves associated with increased susceptibility to disability** ***(William's Text of Endocrinology 11 ed)***

- **Boomer's presentation can be ATYPICAL -** ***Fatigue/Lethargy/loss of libido/cyclothymia/social withdrawal***

Biochemical Aging theories that impact Endocrine system

- 1. oxidation by free radicals
- 2. non-enzymatic glycosylation
- 3. epigenetic changes such as DNA methylation and histone acetylation
- 4. widely distributed deterioration of signal transduction efficiency

BMR decline in –Boomers and beyond

- Gradually occurs after 2 nd decade
- Multi-factorial - major endocrine contributions from Thyroid , Adrenal
- CANNOT totally be explained by sole changes in body composition
- lower fat-free mass (FFM) and sarcopenic states aggravates decline and increases mortality

Normal Aging

- Some hormone secretions ***altered*** with age, but changes are,

  -much less predictable -andropause

  -not well-defined by age-adjusted normal values. Eg: Hyperparathyroidism, DM 2, hypo/hyperthyriodism

- Some hormone secretion ***decreases*** with age

  - increased other hormone secretion *may or may not* compensate eg; Testosterone *(decreased secretion, increased LH, reduced metabolism)*

Metabolic aging stages

1. **First change** - progressive loss of reserve capacity
   - basal labs relatively unchanged –FBS
   - compensatory homeostatic attempts occur

     eg. Drop in Testosterone increases LH
2. **Second change** - reduced adaptability to environment when stressed, safety valve fails (greater rise in bld sugar at OGTT)
3. **Final change** – organs fails at rest (without been stressed)

Differentiate " normal Aging" from "disease"

- **Normal Aging** - Impaired Homeostasis

- **Disease** - added insult exponentially aggravates homeostasis

Aging with related metabolic ILLNESS

- highly prevalent
- occasionally asymptomatic
- distinction ***very subtle and easily miscalculated***
- does not make therapeutic intervention mandatory (***Best example*** - GH and IGF-1 levels drop dramatically ; despite supplementing GH or IGF-1 does ***not*** restore rejuvenation)

Altered presentation of Endo disease in elderly - symptoms and signs

- Non-specific > wt loss, fatigue, constipation,depression , weakness
- Psychomotor retardation, Atr Fib, exacerbated existing CHF – apathetic Hyperthyroidism
- Hyperosmotic non-ketotic coma - DM
- Confusion – due to hypercalcemia – hyperparathyroidism
- Manifestations altered/masked by existing co-morbidites/polypharmacy

Easily discernible Endocrine derangements in Boomers

- Menopause
- Apathetic thyrotoxicosis
- Hyperosmolar non-ketotic state

Problem with current " normal" reference values in boomers

- Age adjusted " normal" ranges rarely available
- "normals" historically calculated for young/middle age
- "normals" more "cross-sectional" vs. Longitudinal (reducing applicability and accuracy)
- "normals" confounded by multiple ***SICK-elderly*** in validation cohorts

"Normal range " Sodium of 145 in the elderly – "may not reflect normalcy for given patient"

- Hyponatremia relatively more common in elderly
  - occult adreno-cortical insufficiency
  - more hypothyroidism, CHF, Cirrhosis, edema states
  - high risk of beer drinkers potomania/hyperglycemia
  - lower intake from salt poor diets
  - tubular conservation of sodium is impaired
  - CKD and conditions that predispose to SIADH more common
  - multiple therapeutics including loop diuretics Thiazides,Metolazone

" U-shaped curve" relation for CAD and ***ALL-cause mortality*** vs. LDL-C

- **In the oldest of old , decrease in baseline LDL-C > linked with increased mortality**

- **Exact Threshold for optimal TC or LDL-C in elderly > undefined**

Statin Rx in seniors -*very controversial*

- Optimum LDL /TG levels not clearly defined (ATP 3 gives no special values)
- Multiple confounders + high mortality - preclude accurate conclusions
- Statin Rx - " NO age ceiling "that limits CAD benefits
- Dieting induced wt-loss to reduce lipids – may increase mortality
- Therapeutic life style as sole lipid control - practically unachievable

Principles of Rx Geriatric Endo

- **Treatment plan - consider**

  -co-existing illness/meds

  - target organ changes in sensitivity

  (WHI – Estrogens had different outcomes for immediate post-menopausal women Vs. Older women)

- **Dosing - adjust to GFR**
- **Start lowest effective dose/go slow > *but go***

Principles of Rx Geri-Endo

- **Review doses frequently > titrate / taper-off/monitor once therapeutic goals met**

- **Increase *concurrent physical and cognitive activity-* to *minimize* body /mind decline**

Bottom line for boomer Metabolic Rx

- EBM for Boomers -therapeutic /healthy life style changes definitely benefit

- Artificial " hormonal supra-physiological supplementation " – may do more harm

Supplementation in boomers

- Vit D RDA - 1000-2000 IU with upper tolerable limit of 4000 IU

  (AACE 2011 recommends Vit D levels at 30-50 ng/ml)

- Calcium RDA - Elemental calcium – in divided doses to avoid constipation

  Women > 50 yr = 1200 mg with upper tolerable limit of 2000 mg

  Men > 50 yr = 1000 mg with upper tolerable limit of 2000 mg

- Problems - higher risk of kidney stones with higher doses of calcium, dosing needs to be timed separately from other meds

  (Source - IOM report + AACE Recommendations 2011)

Endocrinologists solely cannot meet demand

- Demand for Endocrinologists will Exceed Supply
- Senior endocrinologists are retiring rapidly -PCP s will have to assume burden
  (AAMC Work-Force Study Aug 2011 p. 12)
- Decreasing funding and manpower for allopathic health
- **Rising life expectancy**
  -overwhelming rise in > 50 yr (AARP) age
  metabolic and endocrine diseases

Potential remedies for Boomer Metabolics in 21st century America + Globe

- Increasing collaboration of Endocrinologists with PCP
- ? ACA act of 2010
- ACO - Accountable Care Organization
- PCMH – Patient Centered Medical Home
- Integrated Metabolic & Dietetic Health Education/Health Literacy/ Preventive Health
- Tele-medicine & Care Coordination
- Health exchanges to incentivize therapeutic behavior
- Medical Foster Home (VA model)
- Global collaboration in taming metabolic disease tide

Acknowledgements

- Lilamani Romayne Kurukulasuriya MD,FACE
  Associate Professor, Division of Endocrinology, Diabetes & Metabolism, University of Missouri, Columbia, MO 65212

- Dale Melloway - Internal Medicine Department of IT , University of Missouri at Columbia, MO 65212

- Diane E Johnson - Chief Librarian, Otto Health Science Library, School of Medicine, University of Missouri at Columbia, MO 65212

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- American Geriatric Society –Geriatrics at Your Fingertips- 13 th edition 2011
- Williams Textbook of Endocrinology – 11 th Ed 2008
- DynaMed
- UptoDate


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Vitamin D:
All You Need to Know

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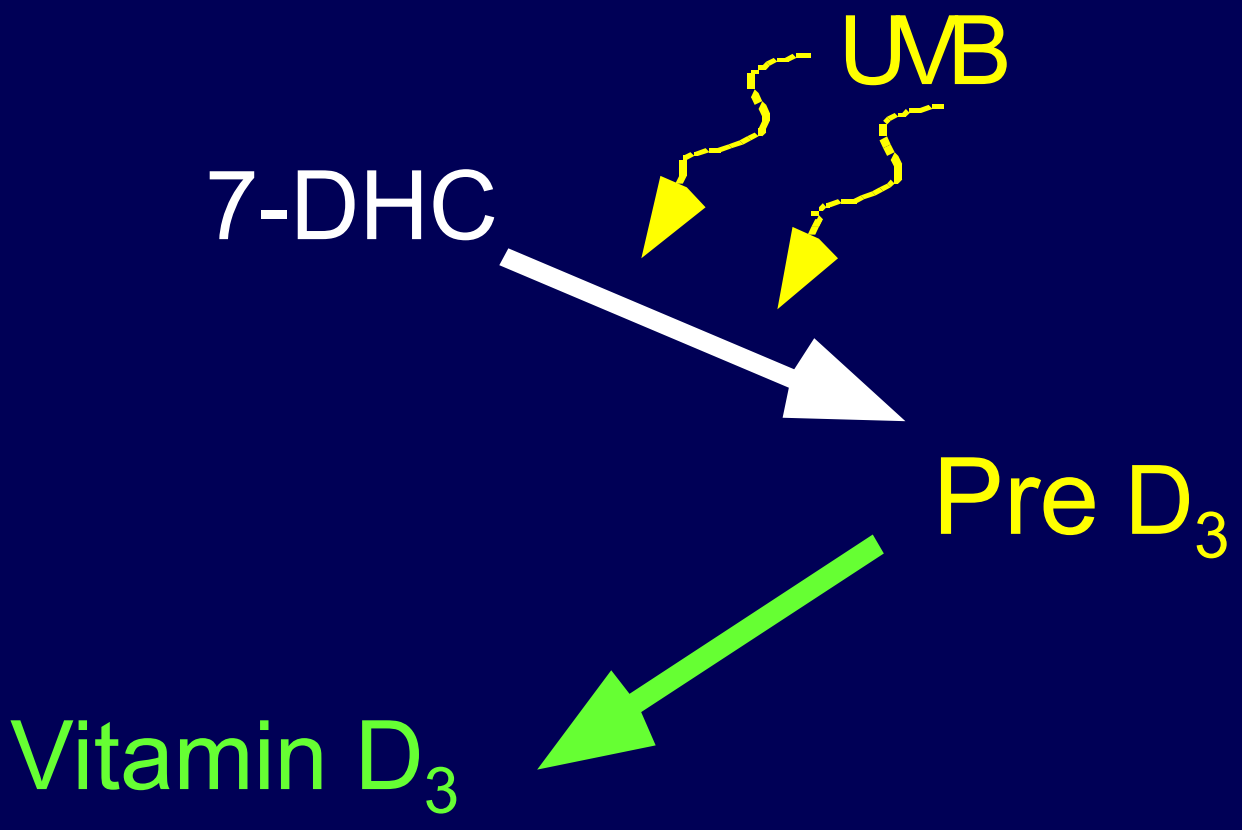
Professor of Endocrinology Metabolism & Nutrition
UMDNJ-RWJ Medical School
New Brunswick, New Jersey

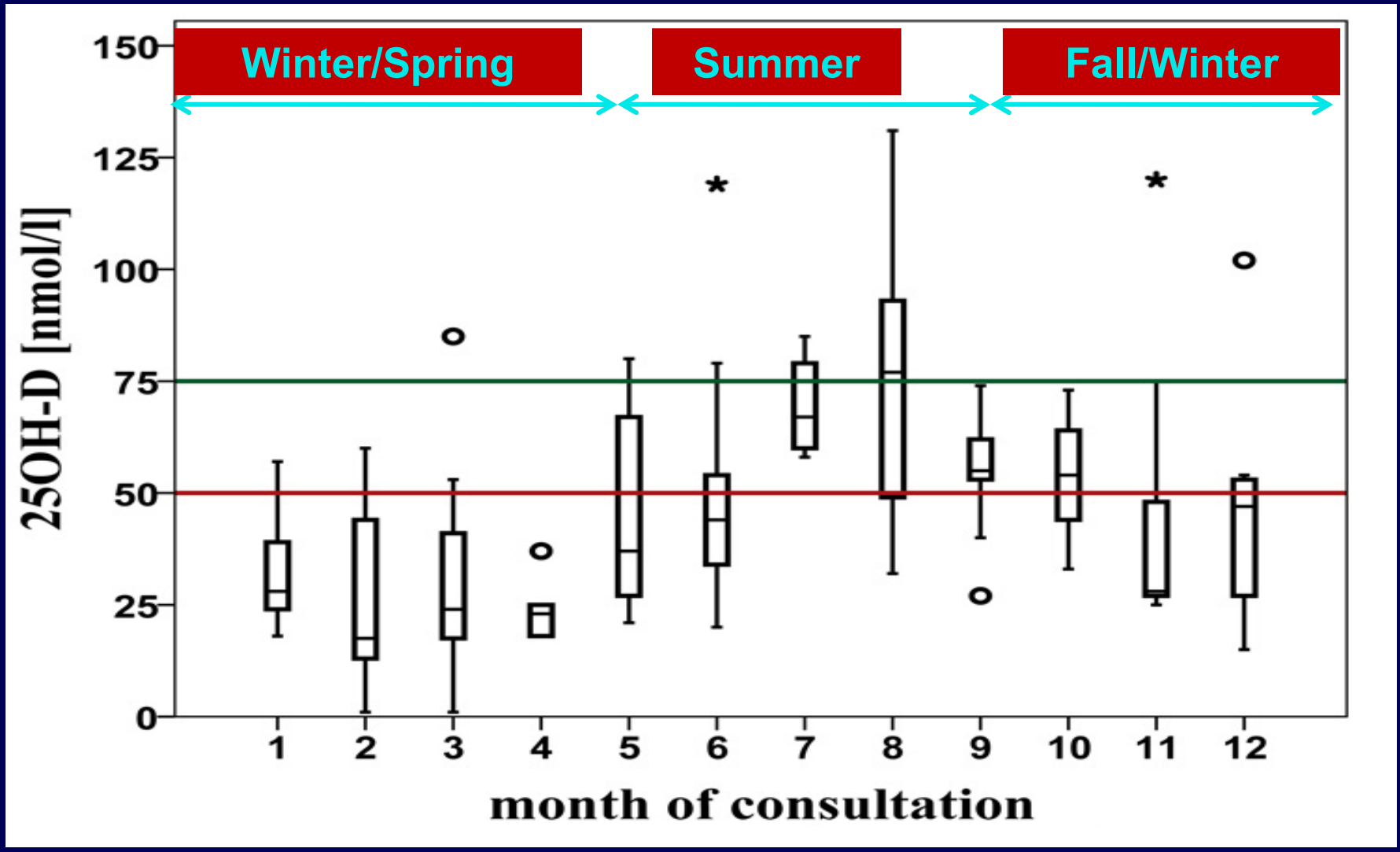
Outline of Vitamin D

- Basics: structure and production
- Prevalence of vitamin D deficiency
- Consequences of low vitamin D status
  - Skeletal and Non-Skeletal diseases
- Toxicity due to vitamin D
- How to replace /supplement vitamin D

Historically, Humans Obtained Vitamin D from the Sun

UVB (~280–315 nm) Produces Vitamin D

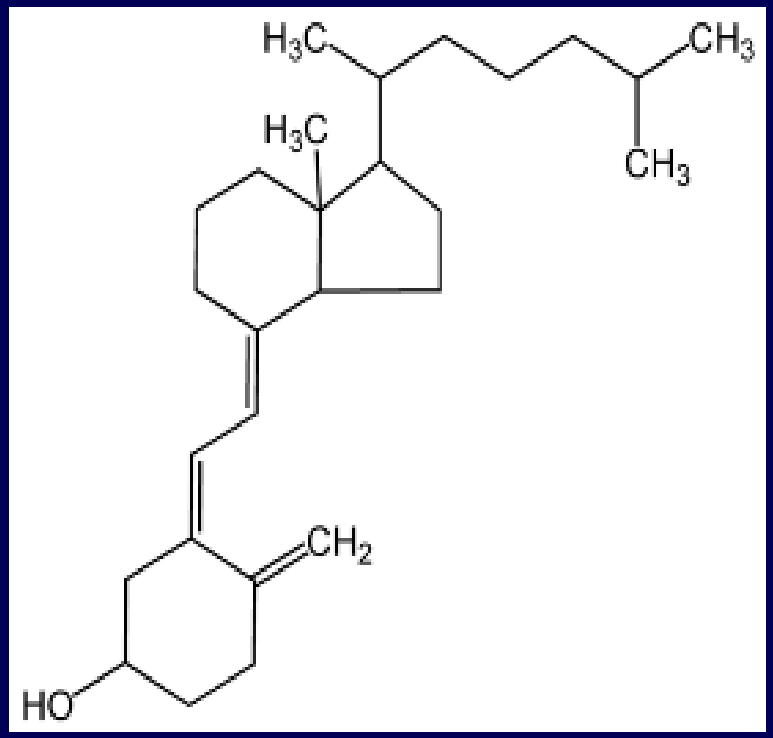




A marked seasonal variability of 25D levels is observed since UV light exposure is essential for vitamin D biosynthesis in the skin. Only during the months of July, August and September were 25(OH)D levels sufficient for most patients.

J.M, Ballinari P, Mullis PE, Flück CE. High prevalence of vitamin D deficiency in children and adolescents with type 1 diabetes. Swiss Med Wkly. 2010 Sep 3;140:w13091.

Vitamin D_2 versus D_3?



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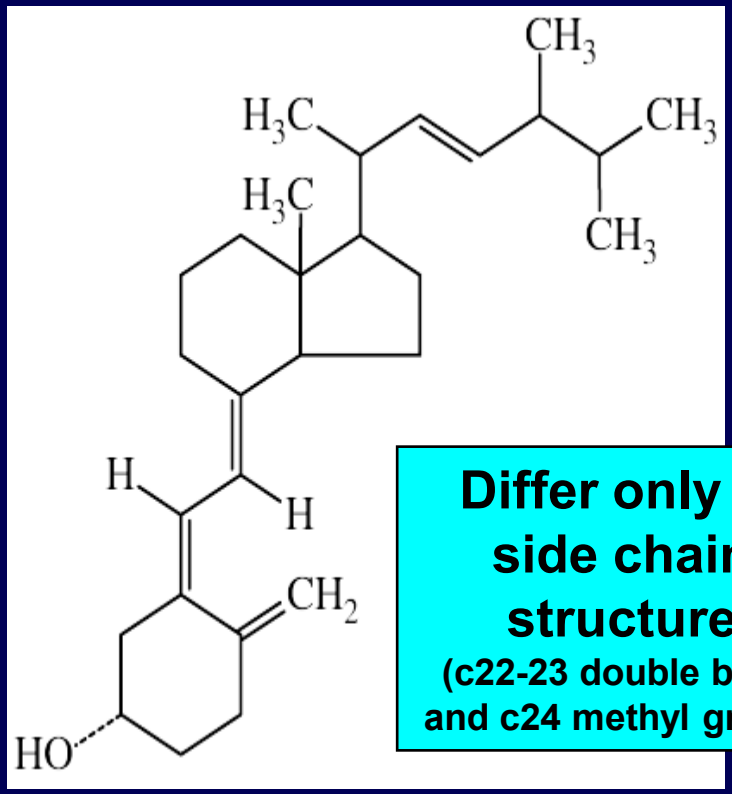
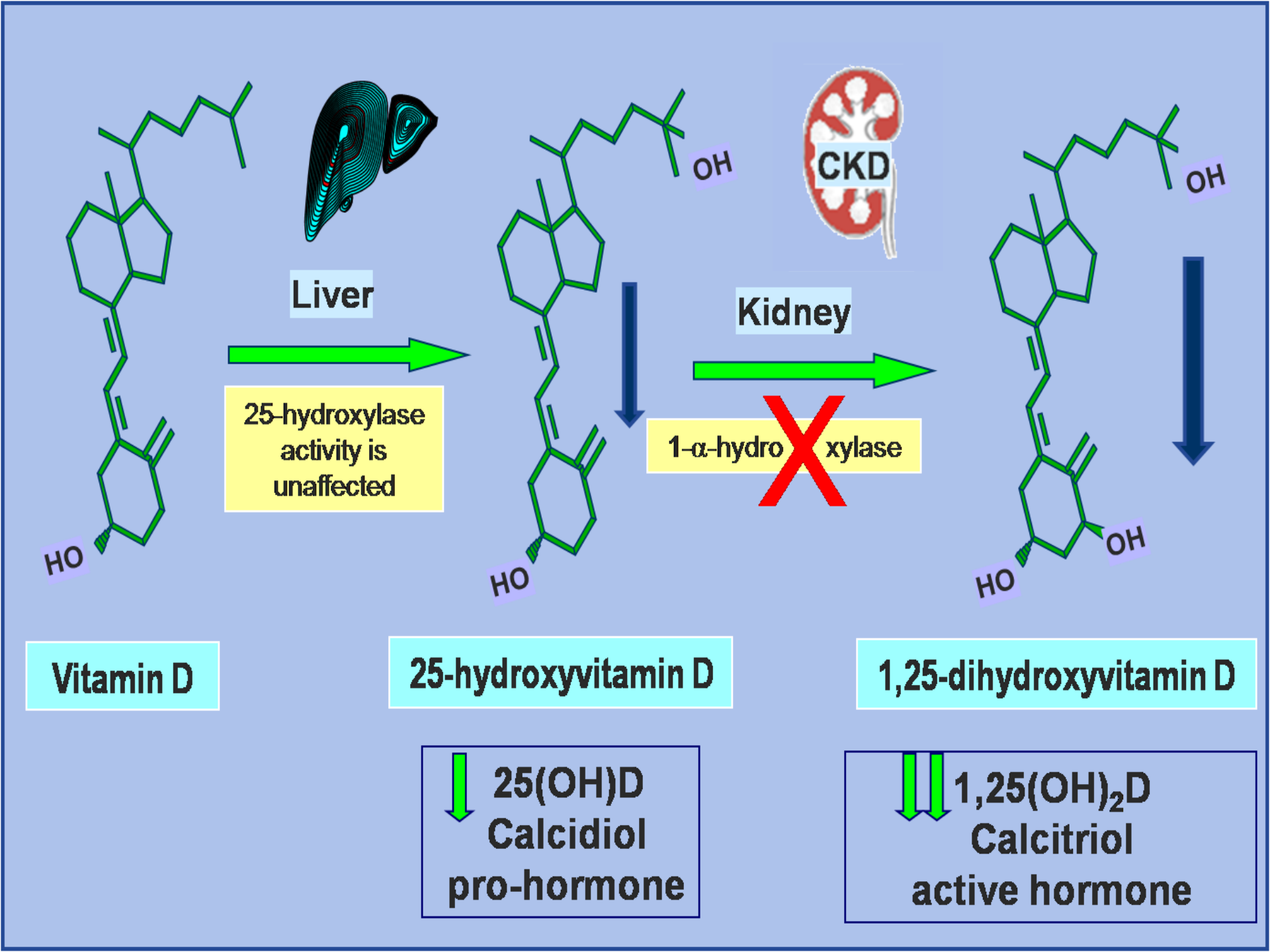
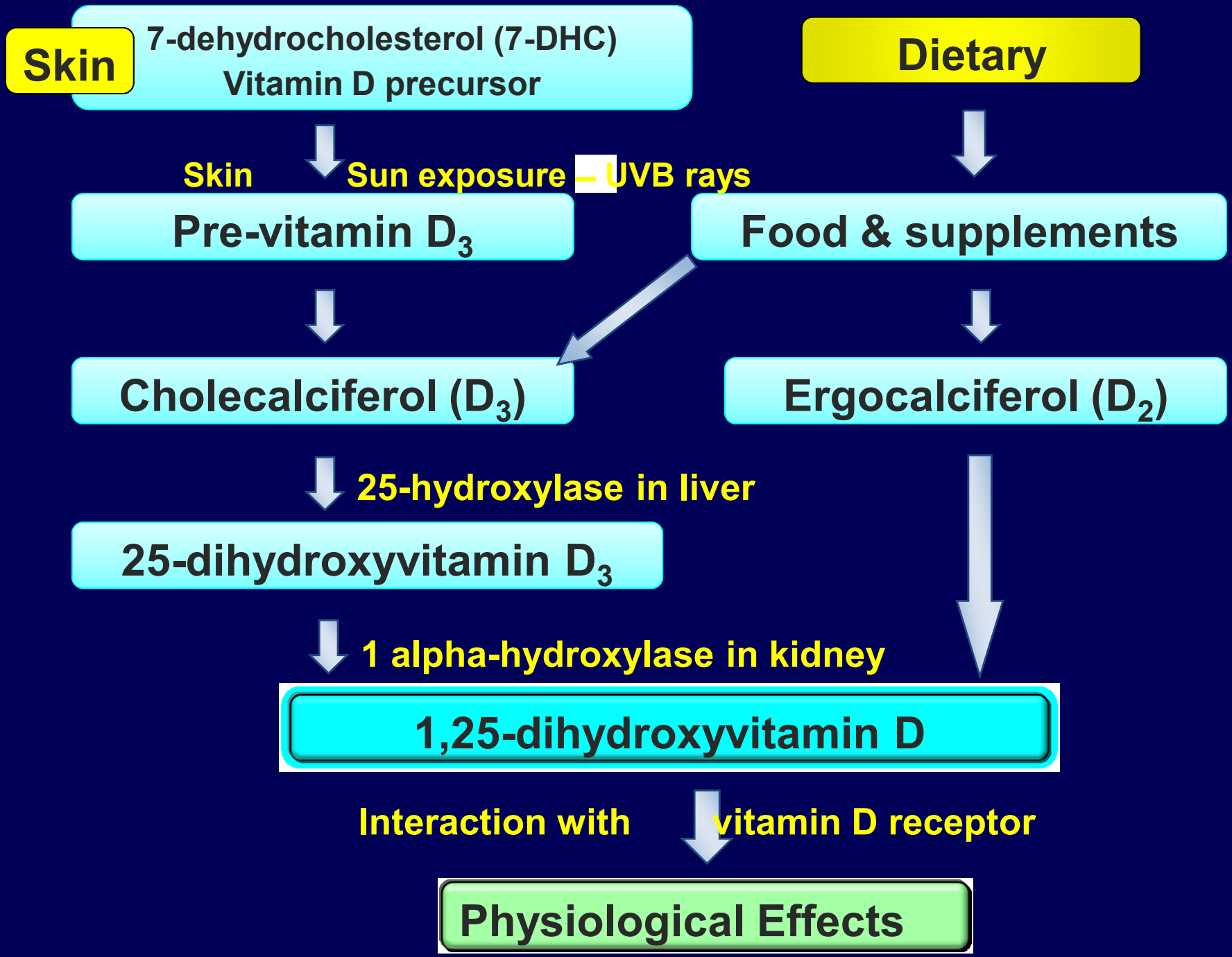


Differ only in side chain structure
(c22-23 double bond and c24 methyl group)

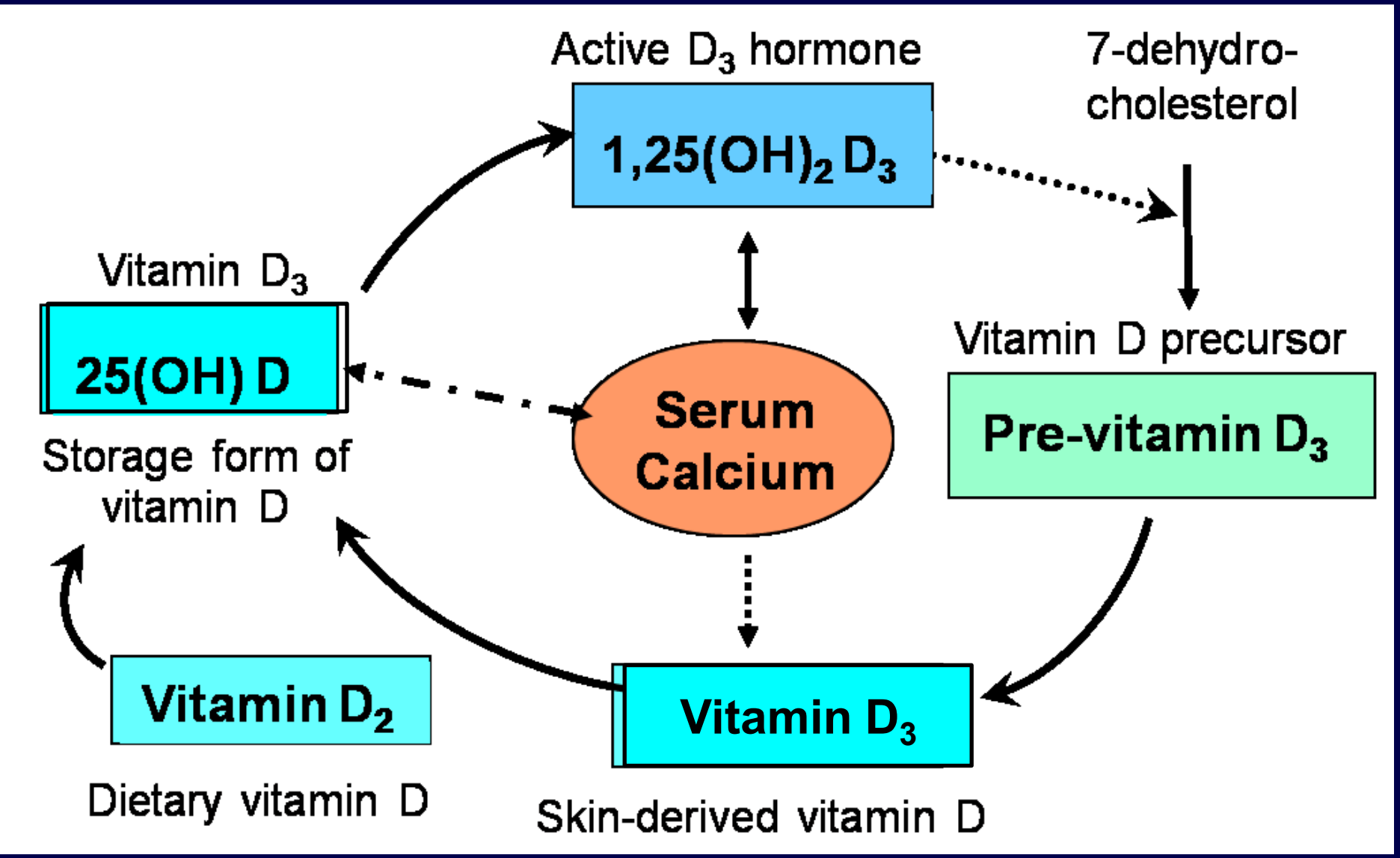
Cholecalciferol
Vitamin D_3

Ergocalciferol
Vitamin D_2


Liver
25-hydroxylase activity is unaffected
CKD
Kidney
1-α-hydro X xylase
OH
HO
OH
OH
HO
Vitamin D
25-hydroxyvitamin D
1,25-dihydroxyvitamin D
25(OH)D
Calcidiol
pro-hormone
1,25(OH)2D
Calcitriol
active hormone


Skin
7-dehydrocholesterol (7-DHC)
Vitamin D precursor
Dietary
Skin
Sun exposure – UVB rays
Pre-vitamin D_3
Food & supplements
Cholecalciferol (D_3)
Ergocalciferol (D_2)
25-hydroxylase in liver
25-dihydroxyvitamin D_3
1 alpha-hydroxylase in kidney
1,25-dihydroxyvitamin D
Interaction with
vitamin D receptor
Physiological Effects

Generation of Vitamin D



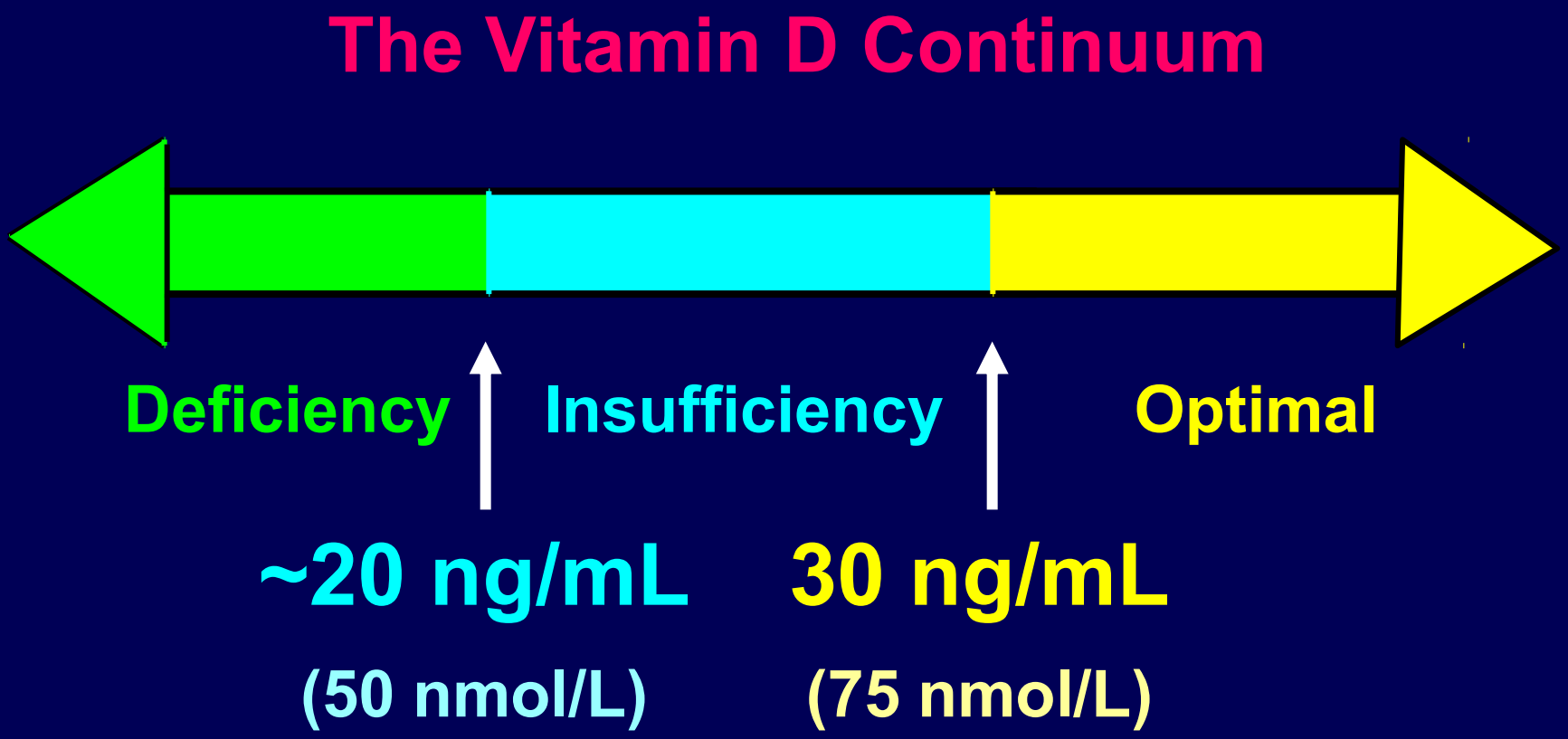
Vitamin D Deficiency

- The most common disorder in the world
- With supplements, it is easy to correct vitamin D deficiency
- Deficiency:
  - in children leads to rickets
  - in adults leads to osteomalacia
- Is associated with increased falls, osteoporosis and fractures
- Also associated with many other diseases

Vitamin D Facts and Figures

- Vitamin D is essential for survival
- Major portion of our vitamin D requirement is made in the skin
- Most common cause of vitamin D deficiency is lack of exposure to sunlight
- Measurement of serum vitamin D levels makes the diagnosis

Measurement of Serum 25(OH)D is the Way to Assess Vitamin D Status



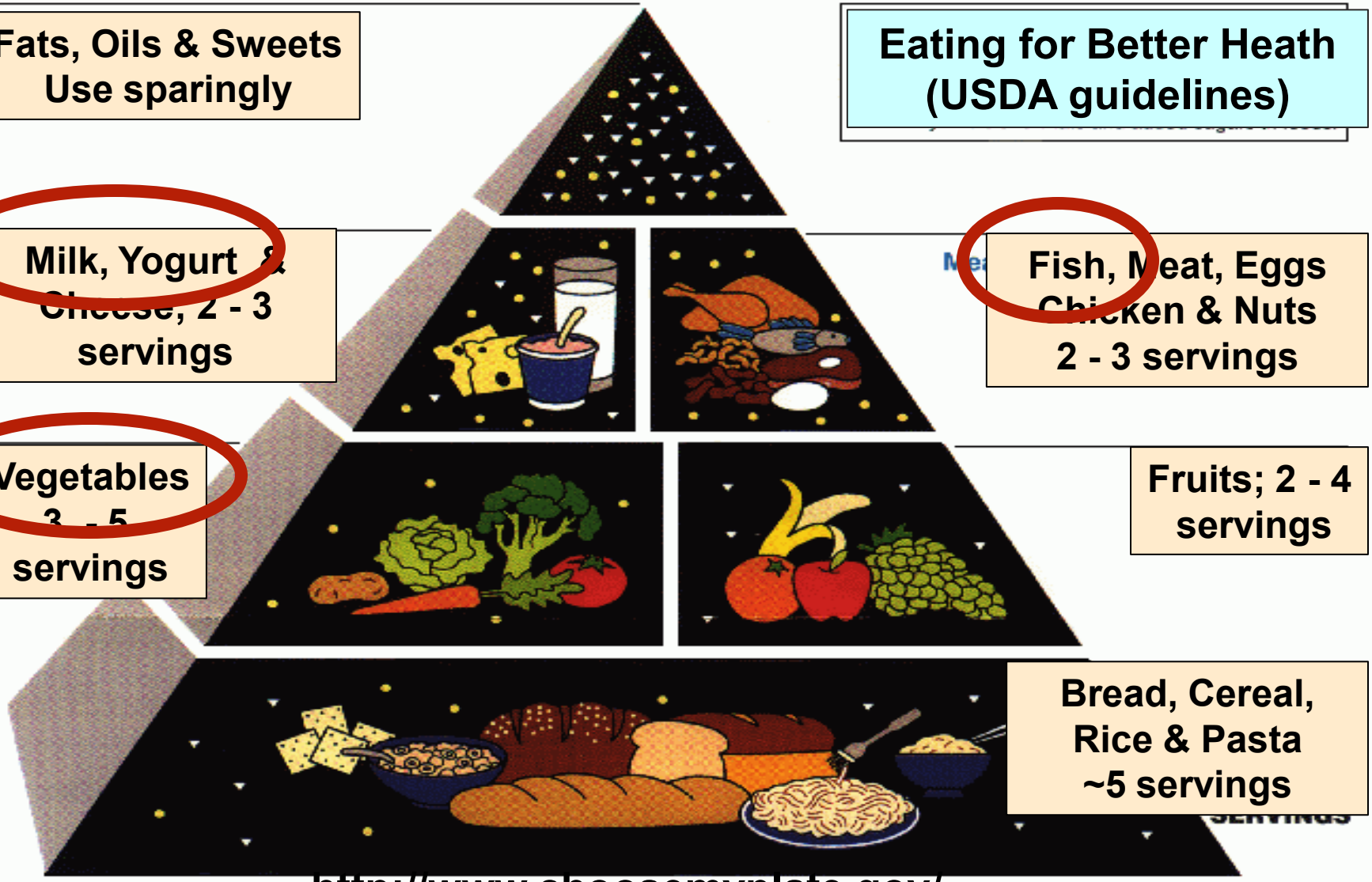
Total daily requirements of Calcium and Vitamin D

Age	Calcium	Vitamin D
4 to 8	800 mg	600 IU
9 to 18	1,300 mg	1,000 IU
19 to 50	1,000 mg	1,000 IU
≥ 50	1,200 mg	1,000 IU
Pregnancy/Lactation	1,300 mg	2,000 IU
Postmenopausal	1,300 mg	1,000–2,000 IU

Main Sources of Vitamin D

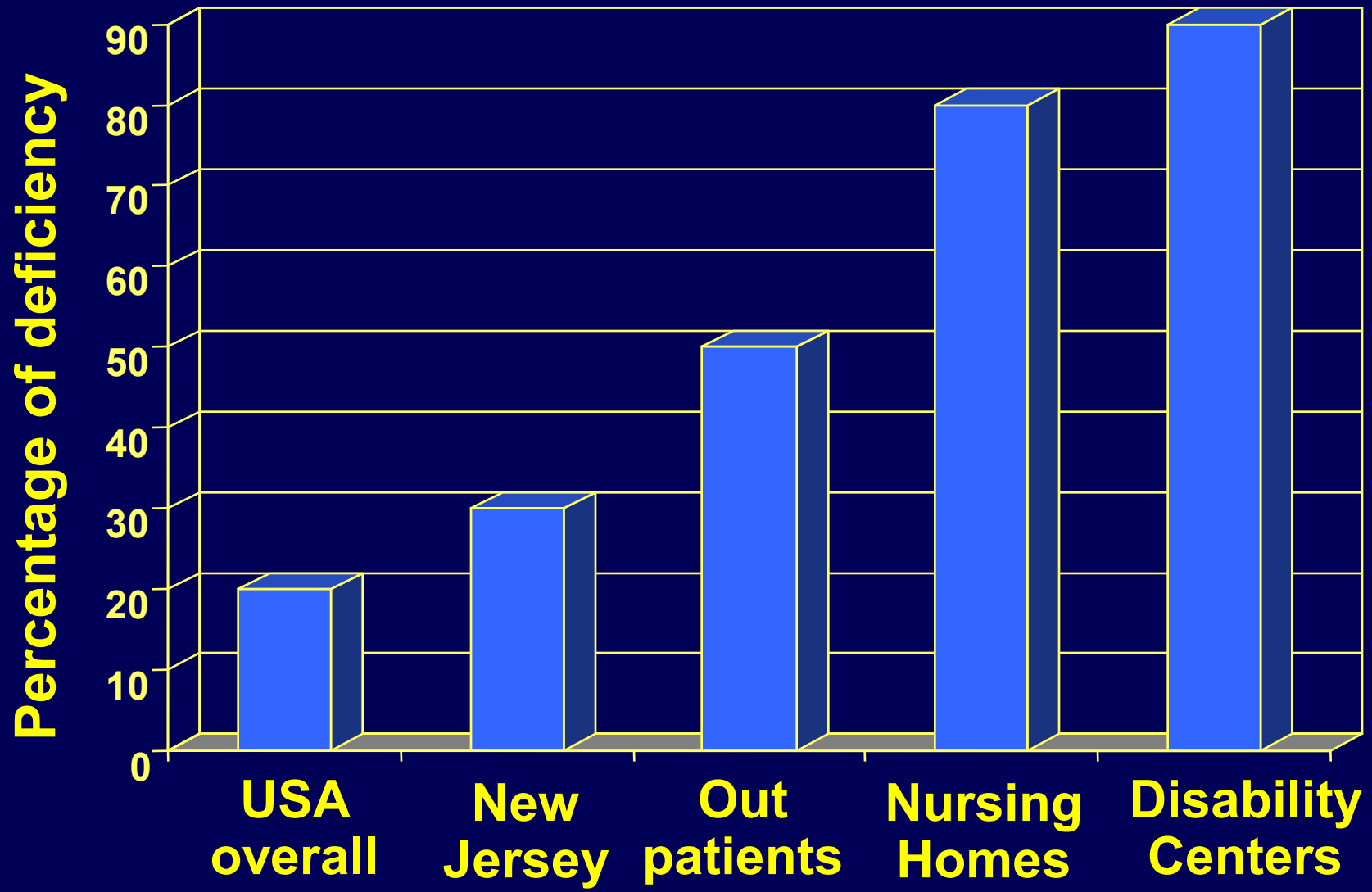
- Sun-light
- Food that contain high content of vitamin D
  - Fortified milk and cereal
  - Mushroom
  - Oily fish; salmon, sardines, mackerel, tuna
  - Cod-liver oil

Nutrition and Bone Health

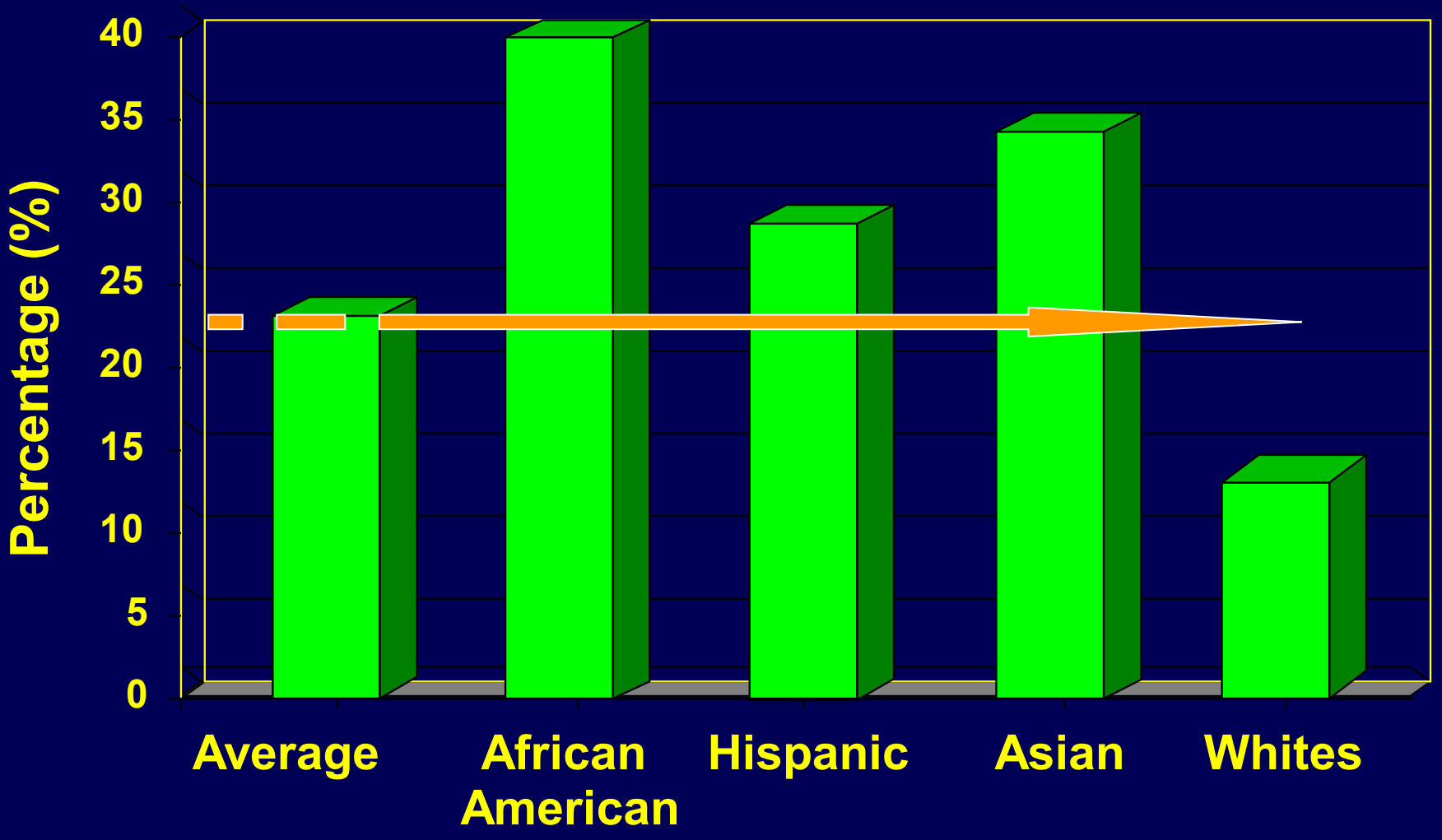


http://www.choosemyplate.gov/

Prevalence of Vitamin D Insufficiency

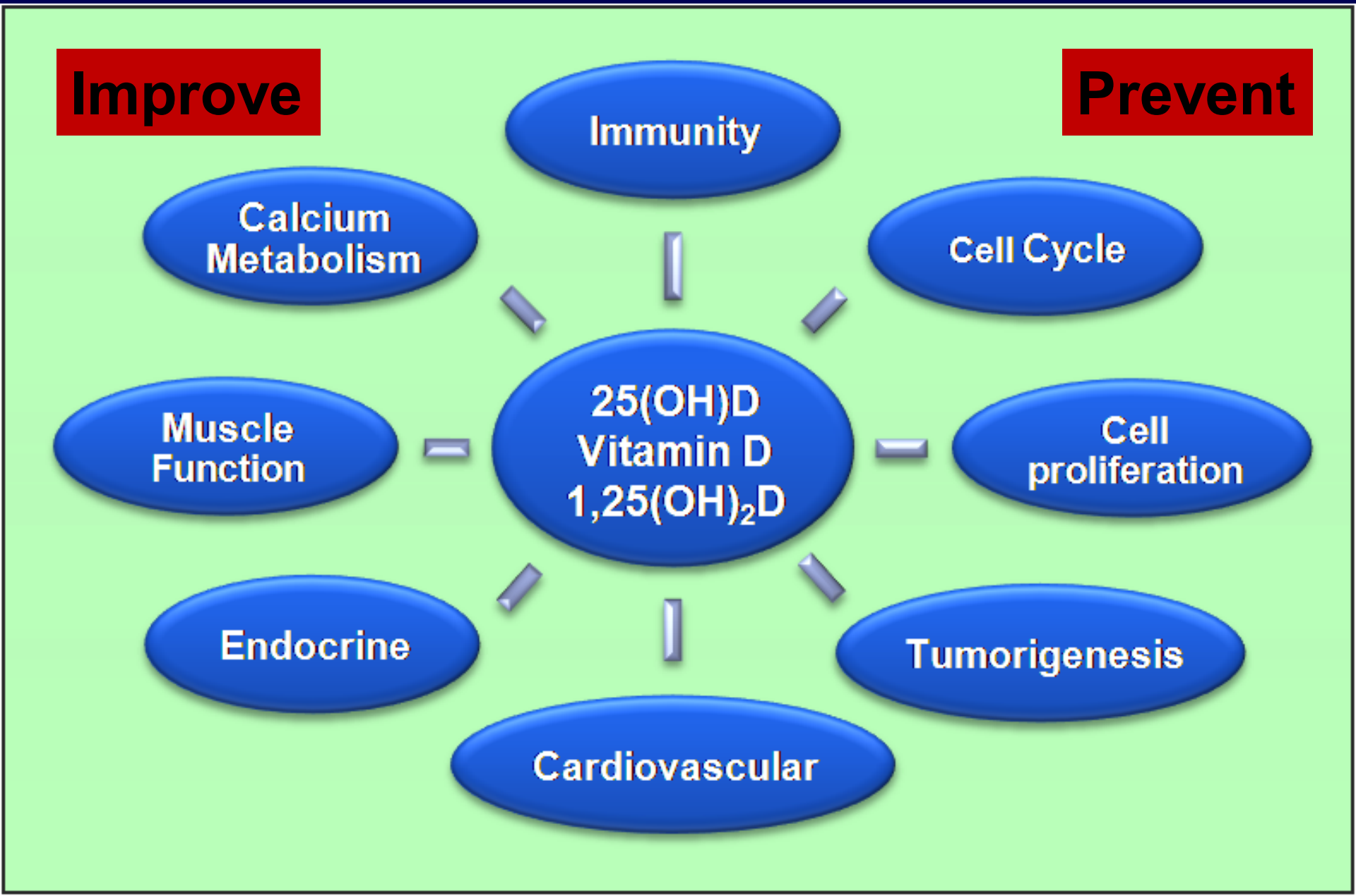


Prevalence of Vitamin D Insufficiency by Ethnicity



“In a person with a lighter skin, exposure to sunshine for 20 minutes can prevent vitamin D deficiency.”

Potential Beneficial Effects of Vitamin D



Beneficial Effects of 25(OH) Vitamin D

Classical effects:

- Calcium metabolism (Calcium absorption, bone mineralization, etc.)

Non-classical functions:

- Neuromuscular functions
  - Balance and muscular coordination/reflexes
  - Prevention of falls/fractures
- Immune system and immunity
- Prevention of diseases
- Reproduction and sexual functions

Potential Benefits of Vitamin D

- **Skeletal effects:**
  - Calcium homeostasis
  - Gastrointestinal absorption of calcium
  - Bone mineralization
  - Avoidance of rickets and osteomalacia
  - Prevention of osteoporosis
- **Non-skeletal effects:**
  - Immune system
  - Nervous system
  - Cancer prevention
  - Balance and muscular system (sarcopenia)
  - Type 2 diabetes
  - Improved survival

Vitamin D and Diabetes?

"A major practical conclusion on vitamin D and diabetes is:

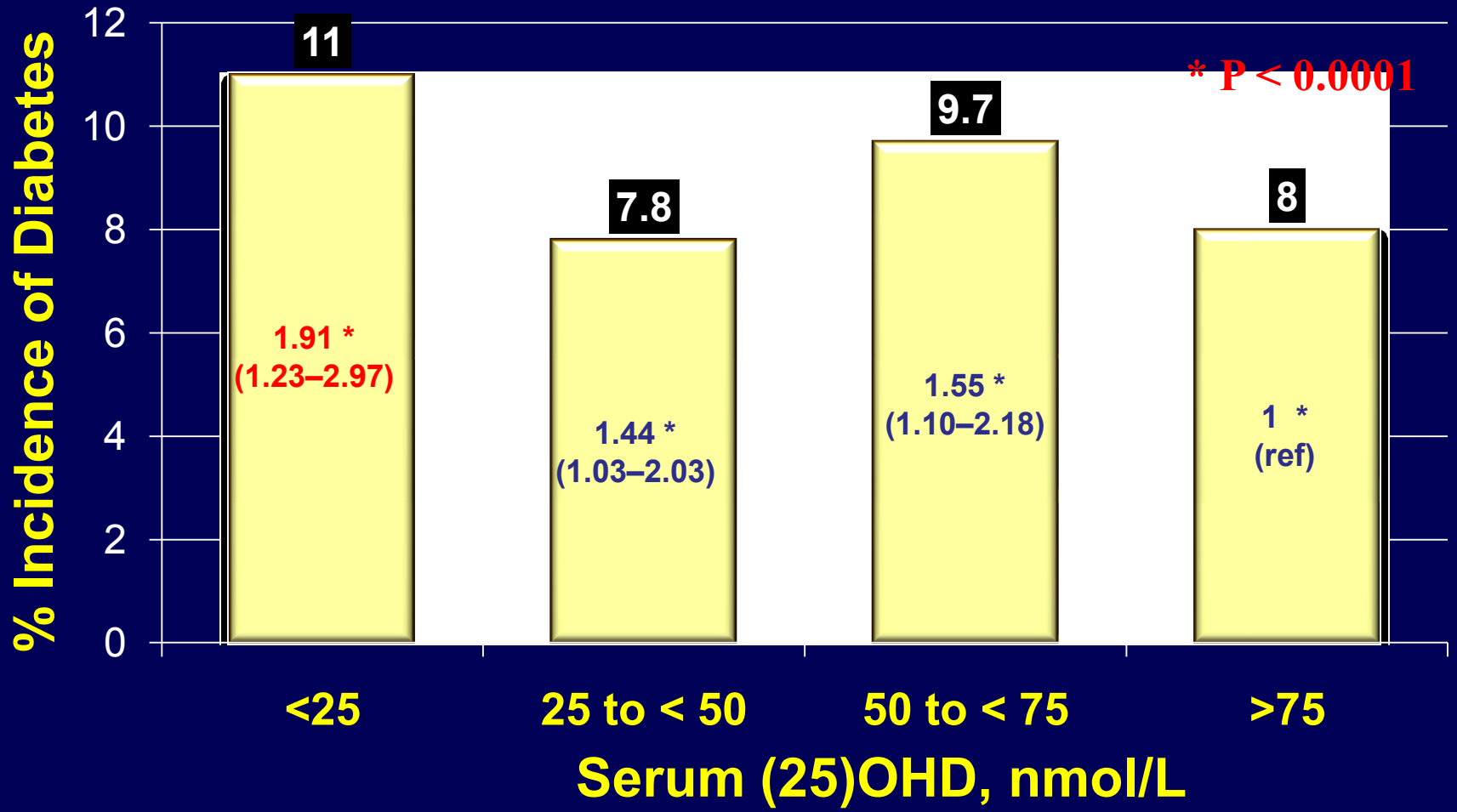
Vitamin D deficiency is undesirable, not only for calcium absorption and bones, but also for glucose metabolism."

Mathieu et al., *Diabetologia,* 2005; 48:1247-1257

Vitamin D and Diabetes?

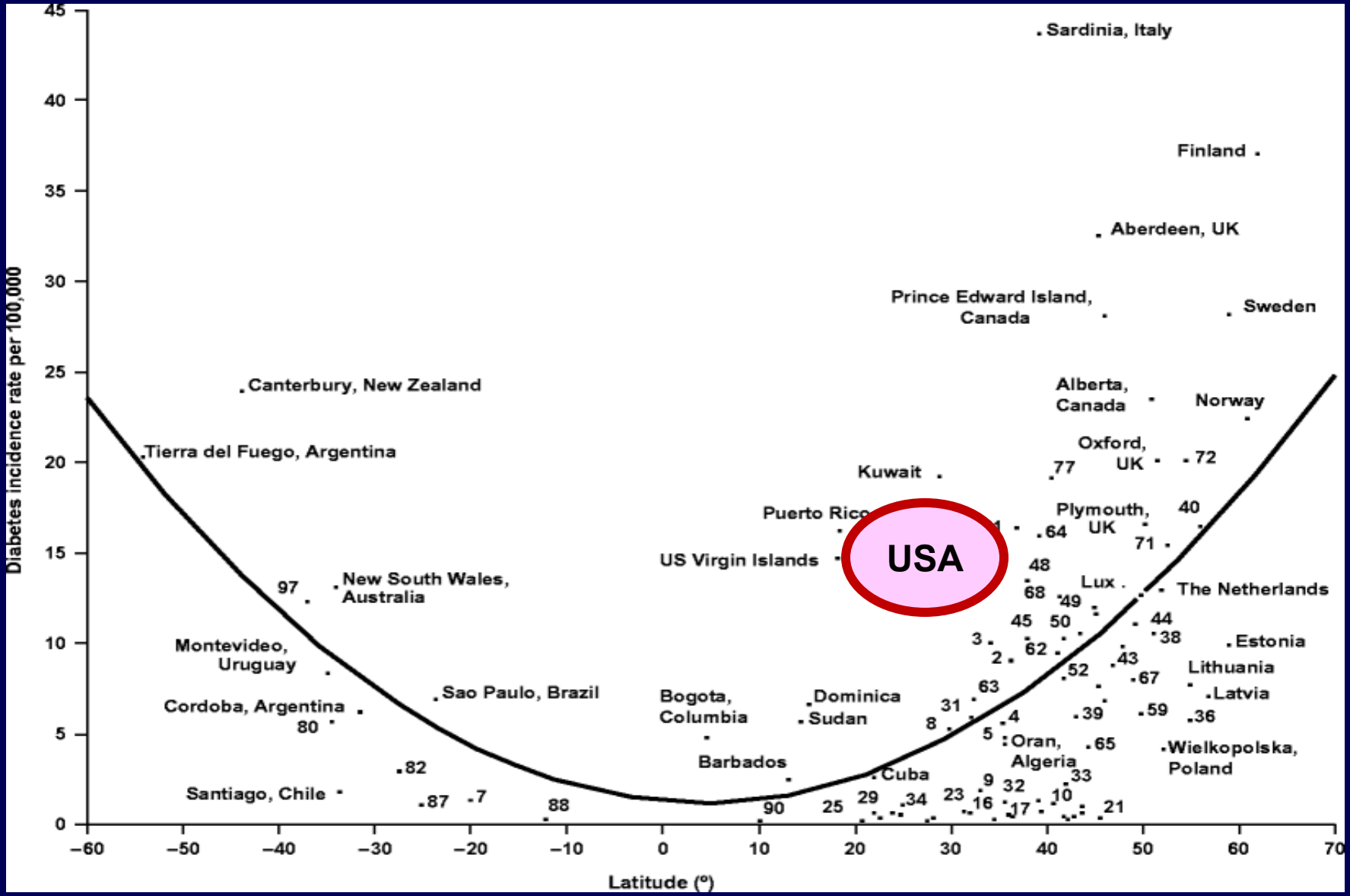
- Beta cells contain the vitamin D receptor
- $1,25(OH)_2D$ stimulates insulin release
- Insulin release is reduced in vitamin D-deficient animals
- $1,25(OH)_2D$ prevents development of diabetes in the NOD mouse
- Recent meta-analyses associate low vitamin D status with increased risk of type 1 and type 2 diabetes

Incidence of Diabetes by Serum Vitamin D Levels



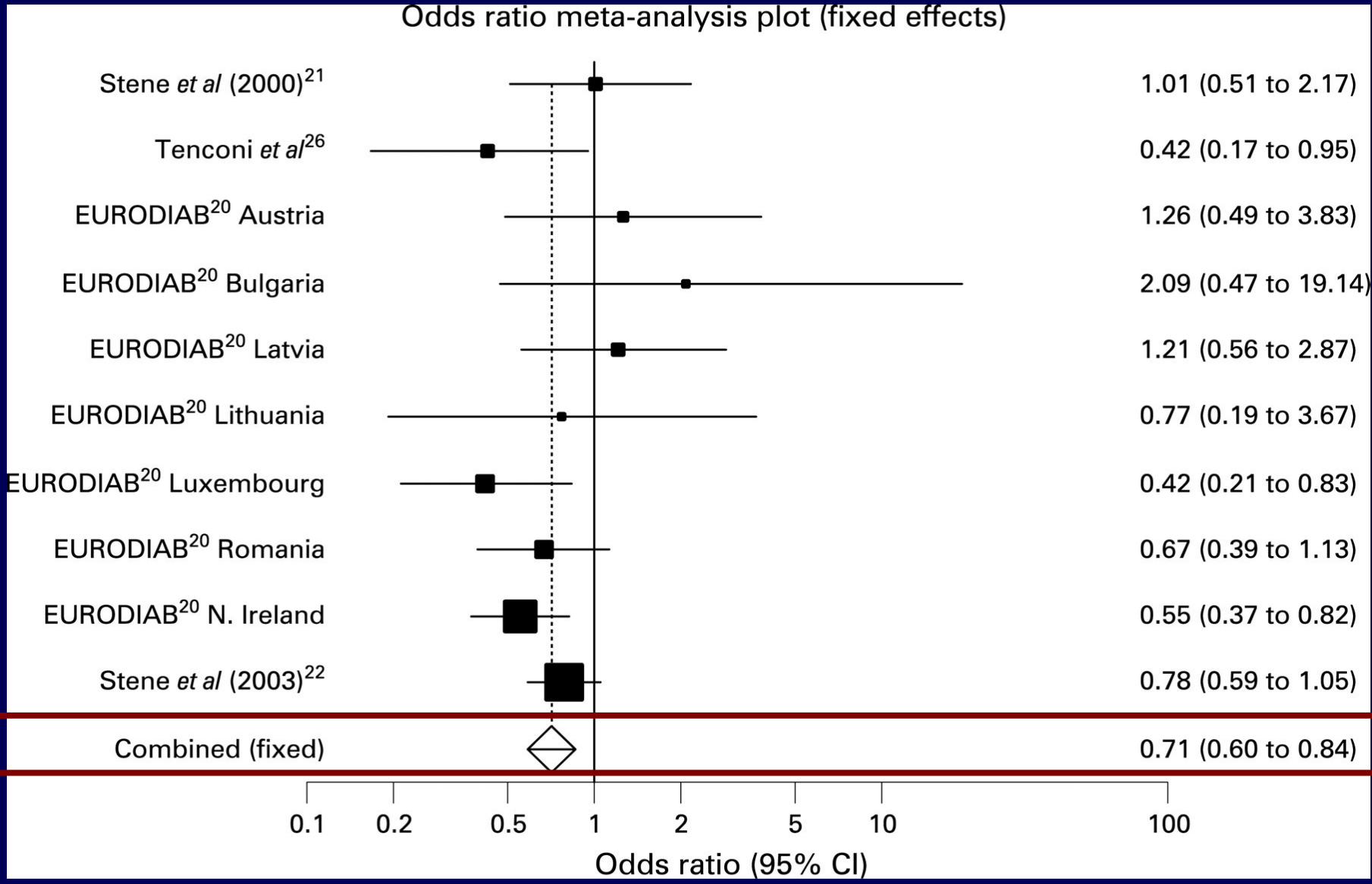
Choi ,HS, Kim KA, Lim CY, et al. Low serum vitamin d is associated with high risk of diabetes in Korean adults. J Nutr. Aug 2011;141(8):1524-1528.

Incidence of type 1 Diabetes by Latitude



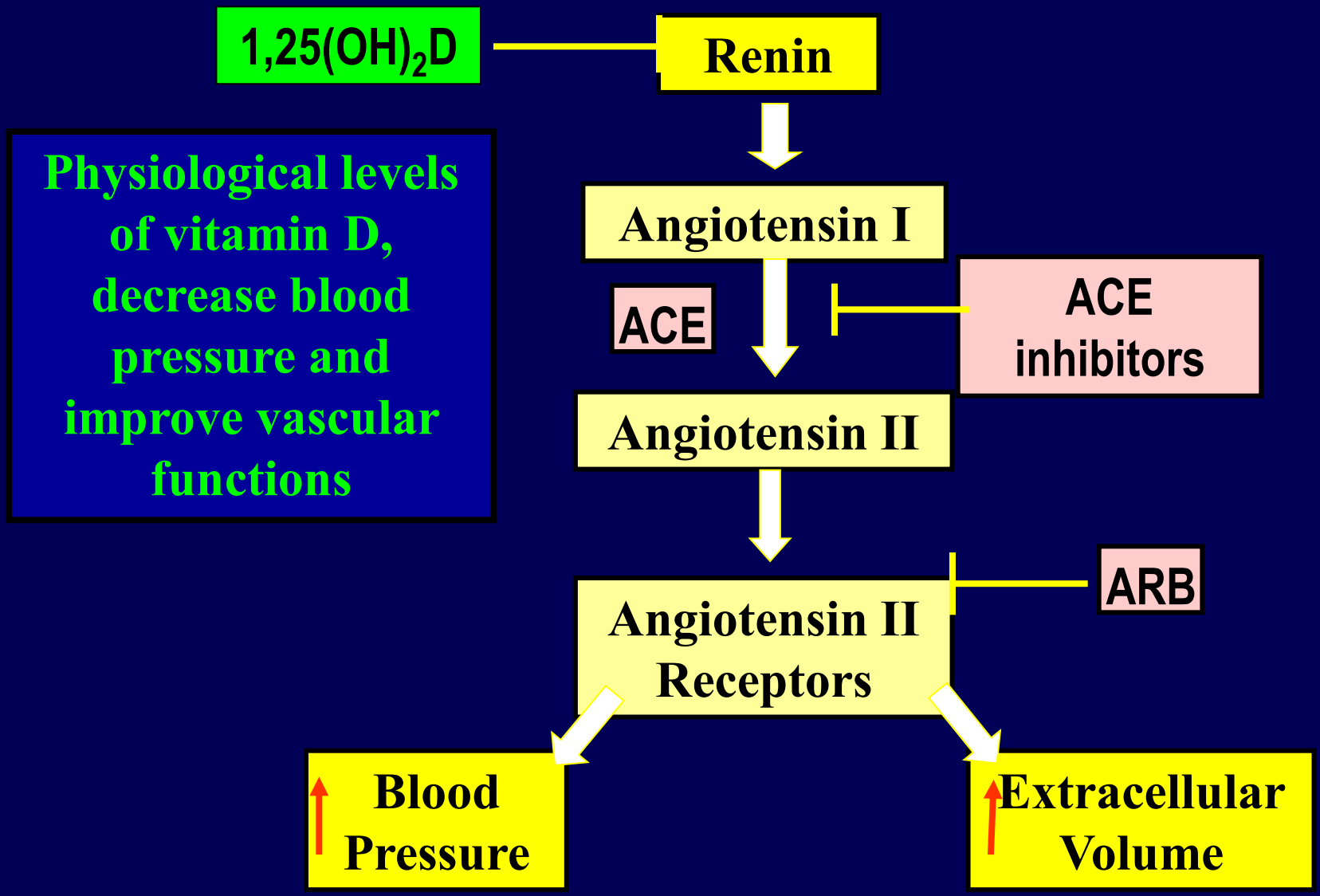
Mohr, Diabetologia 2008

Vitamin D Supplementation and Development of Type 1 Diabetes (observational studies)



Zipitis, C S et al. Arch Dis Child 2008;93:512-517

Effect of Vitamin D on the Renin/Angiotensin System



Vitamin D and Vascular Disease?

- Vitamin D decreases inflammation
- CVD death rate increases with latitude
- Higher CVD deaths in winter months
- Vitamin D receptors in myocytes
- Vitamin D impacts renin-angiotensin and blood pressure

Vitamin D and Muscle

The Lancet 1999; **353**:806

DOI:10.1016/S0140-6736(98)10206-4

A woman who left her wheelchair

MD, Dr G Mingrone [a], MD AV Greco [a], MD M Castagneto [b] G Gasbarrini [a]

–"After 3 weeks she could walk again, and muscle weakness and bone pain disappeared."

- **Myocytes possess vitamin D receptors**
- **D deficiency associated with myopathy**
  - **32-year-old woman with progressive muscle weakness and diffuse bone pain**
  - **Fat malabsorption; s/p bowel resection**
  - **25(OH)D = 2.4 ng/ml**
- **Treated with $1,25(OH)_2D_3$**

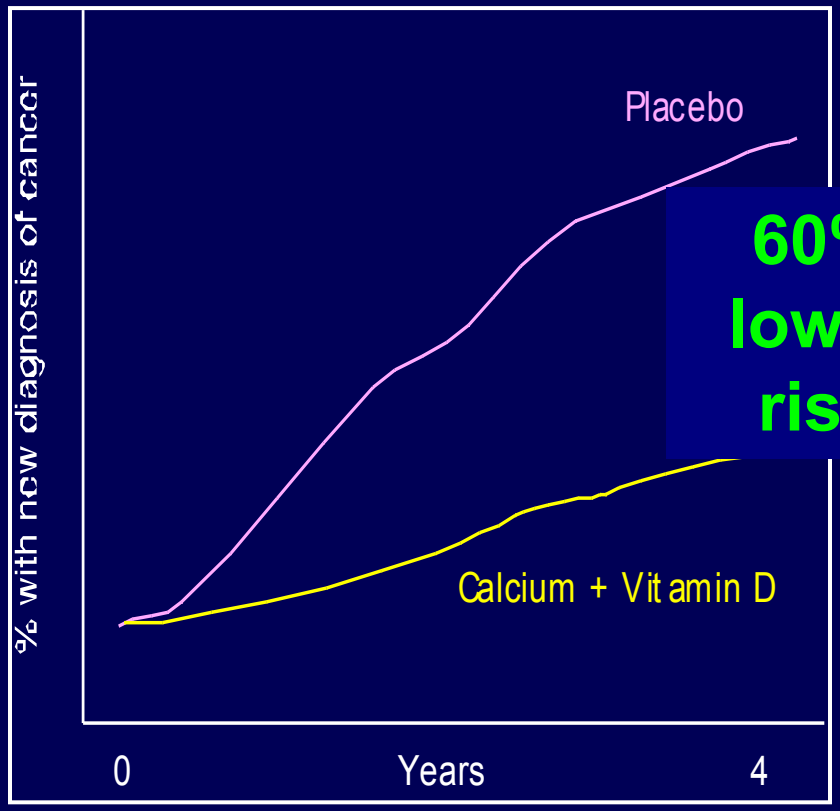
Boonen et al., *Calcif Tissue Int*, 78:257-270, 2006

Sorenson et al., *Clin Sci*, 56:157-161, 1979

Vitamin D Reduces Cancer Risk

1179 women avg age 67 years; 4-year study placebo, calcium 1500 mg or calcium + vitamin D 1100 IU

25(OH)D increased from 28 ng/ml to 38 ng/ml



60% lower risk

"..improving vitamin D nutritional status substantially reduced all-cancer risk in postmenopausal women."

Lappe et al., *Am J Clin Nutr*, 85:1586-1591, 2007

Those with Vitamin D Insufficiency or Deficiency Need Supplemental Vitamin D Therapy

There are Several Ways of Replacing Vitamin D

Treating Vitamin D Insufficiency / Deficiency

- 50,000 IU of Vit.D once a week, for 8-12 weeks
- Followed by 50,000 IU Vitamin D every 2-4 weeks
- Or 2,000 IU Vitamin D every day
- The dosage will raise 25OH D level to sufficient levels 30-50 ng/ml with no adverse effects
- Vitamin D dose in multivitamin ~ 400 IU.
  Too low to raise 25 OH D level

Two simple and practical therapeutic regimens for supplementation of vitamin D

Regimen A:

Serum vitamin D below 10 ng/mL, administer 50,000 IU three times a week; between 11 and 20 ng/mL, administer 50,000 IU twice a week; and between 21 and 29 ng/mL, administer 50,000 IU once a week for 12 weeks;

Regimen B:

A loading therapeutic dose of vitamin D (one time high dose, or 50,000 IU 1 to 5 times/week), followed by 50,000 IU, once or twice a week (Table 12).

Vitamin D Conclusions

- Vitamin D inadequacy is very common
- No downside to aiming for 25(OH)D ≥ 30 ng/ml
- Need at least 1,000-2,000 IU/day
  - Not everyone needs the same dose
  - Prudent to recommend D_3
  - These "higher" doses are safe
- "Casual" sun exposure is not enough
- Vitamin D may not be the fountain of youth
- Vitamin D adequacy will reduce osteoporotic fractures, falls, cancer, and potentially a multitude of other diseases

Conclusions

- **Important public health implications**
  - **Vitamin D and calcium insufficiency are common**
  - **Both interventions can be implemented easily and inexpensively**
- **Vitamin D and calcium homeostasis seem to play a role in development of type 1 and type 2 diabetes and cardiovascular diseases (based on observational studies)**

Conclusions

- Supplementation with vitamin D (and calcium) may have a role in the prevention of type 1 and type 2 diabetes and reduction of cardio-vascular deaths in high-risk individuals

Reducing the Risk of Osteoporosis and Fracture, Falls, and Cancer is Good Enough for me to Treat My Patients with Vitamin D

Thank you..

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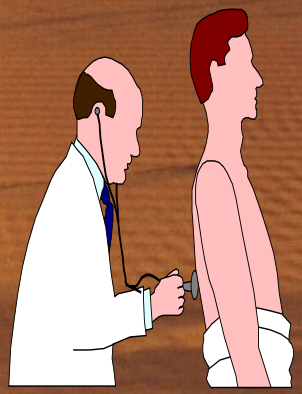


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