Identification and Treatment of Type 1 Diabetes in AI/AN Populations

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Objectives

To review and discuss:

1. The Natural History of and Laboratory Tests for Diagnosis of Type 1 Diabetes
2. Laboratory Tests that Differentiate Type 1 from Type 2 Diabetes
3. Important Considerations in AI/AN patients with Type 1 Diabetes
4. Current Treatment Guidelines
5. One Recommended Change You Can Make in Your Practice.

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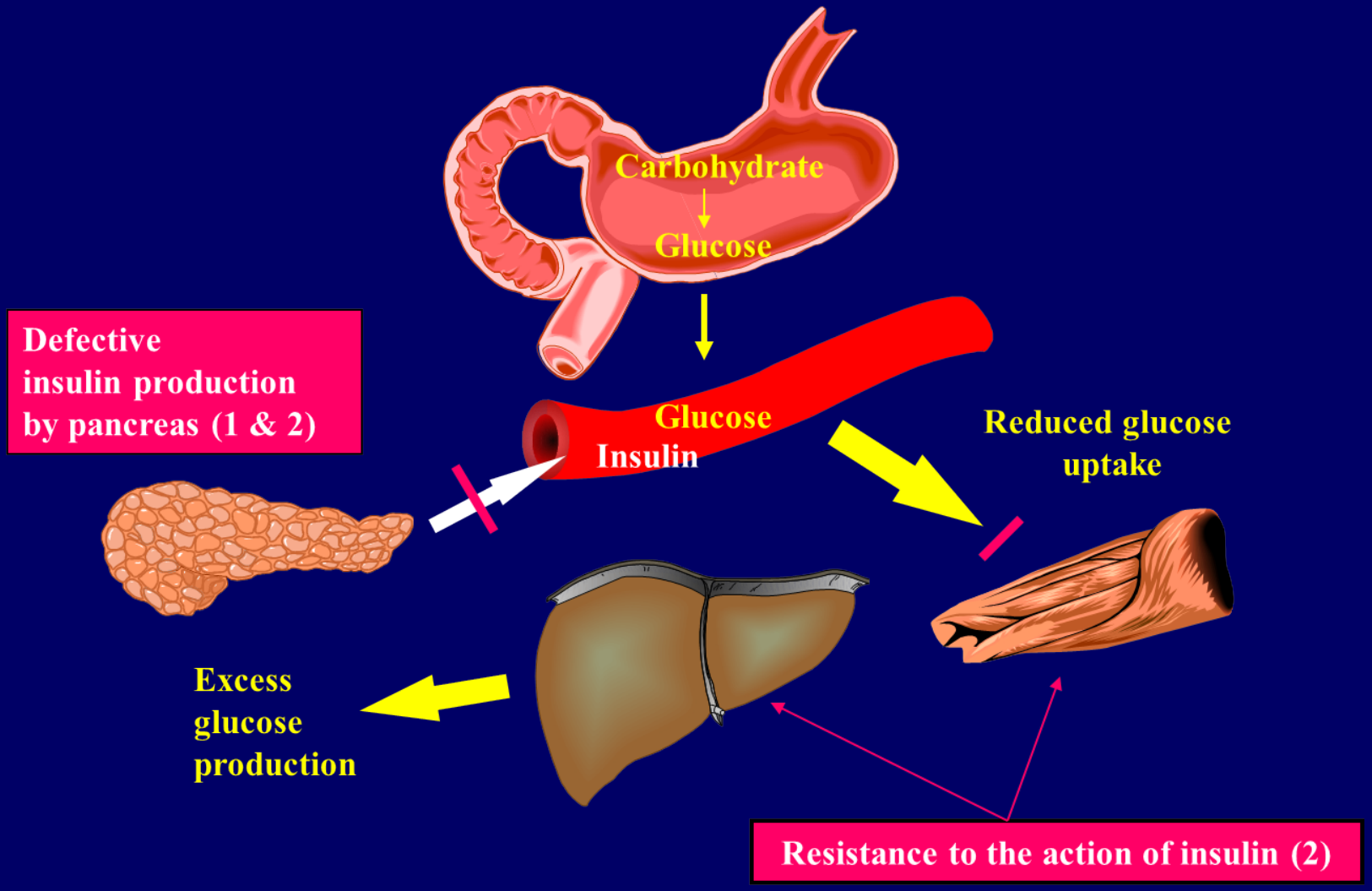
The Causes of Diabetes



Type 1 Diabetes: Family Risks

- Most case of Type 1 DM are sporadic; only 10 percent to 15 percent of affected individuals have a first-degree relative Type 1 DM at the time of diagnosis.
- The risk of developing Type 1 DM if 5 percent if a first degree family member is also affected with Type 1 DM, compared with a general population risk of 0.4 percent – i.e., about a 20-fold increase.
- The offspring of a father with Type 1 DM has a 4-6 percent chance of becoming diabetic, whereas the risk for an offspring of a Type 1 mother is 2-3 percent.
  - This may reflect a higher spontaneous early abortion rate both the fetus and the mother carry the Type 1 genes.

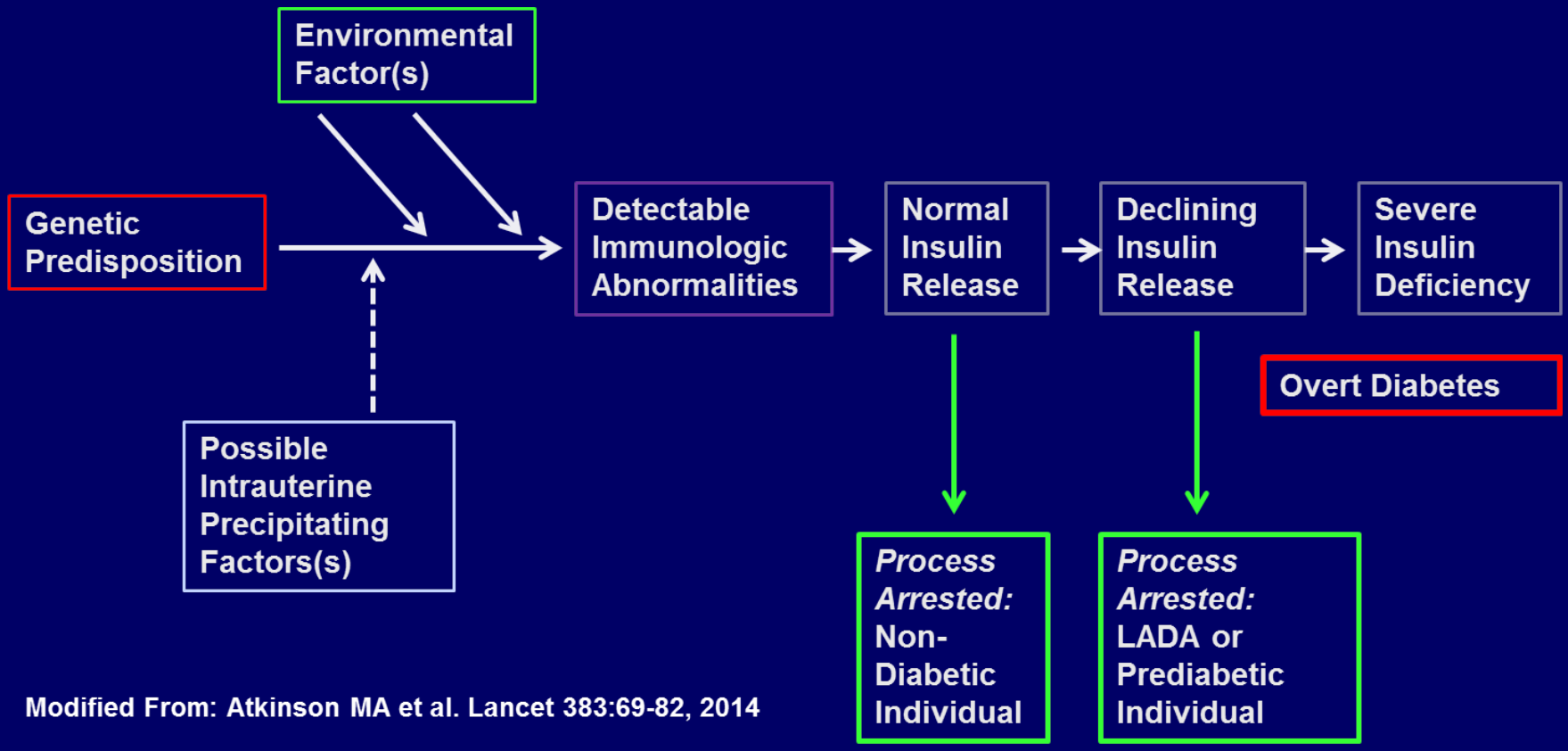
Type 1 Diabetes: Family Risks

Concordance Rates With Types of Diabetes:

Type 1 Diabetes in Identical Twins:	50%
Type 2 Diabetes in Identical Twins:	70-90%
Type 1 Diabetes in Siblings with 1 parent affected:	5%
Type 2 Diabetes in Siblings with 1 parent affected:	30%

This indicates that there is a powerful environmental component(s) interacting with the genetic component to confer risk of Type 1 Diabetes.

Natural History of Type 1 Diabetes



Modified From: Atkinson MA et al. Lancet 383:69-82, 2014

Type 1 Diabetes: Auto-antibodies

- At clinical onset of Type 1 DM, less than 10 percent residual β-cell mass remains and humoral and cellular abnormalities are present.
- In humans, islet cell infiltration by lymphocytes (mainly CD8+ cells) is found in patients newly-diagnosed with the disease.
- As a result of T-cell lymphocyte-mediated attack, islet cell cytoplasmic antibodies (ICAs) are formed against proteins in the β-cell.

Type 1 Diabetes: Auto-antibodies

- 90 percent of persons with newly diagnosed type 1 diabetes have one or more associated autoantibodies
- *Commonest of these are:*
  - Islet cell ab (ICA)
  - Insulin ab (IAA)
  - Glutamic Acid Decarboxylase 65 ab (GAD65)
  - PTP-related Islet Antigen 2 ab (IA-2A)
  - Zinc Transporter 8 Ab (ZnT8A)
- One Positive Ab confers a 5-year risk of 5 percent for Type 1 Diabetes
- Four Positive Abs confers a 5-year risk of 80 percent for Type 1 Diabetes

Siljander HT et al. Diabetes 58:2835-2842, 2009

Winter WE et al. Diabetes Technol Ther 4:817-839, 2002.

Type 1 Diabetes: Environmental Factors

Actual Precipitant(s) Unknown - Factors for which there is some supporting evidence include:

- Exposure to viruses (rubella, mumps, coxsackie B) or other microbial pathogens
- Early exposure to cow's milk
- Diminished breast milk consumption
- Early exposure to cereals, with or without wheat gluten
- Lack of Vitamin D supplementation in infancy
- "Clean" Environment

Possible mechanisms for these include:

- "mimicry" of components of the islet cell by components of these agents, such that the immune response turns on the islet component
- Inadequate immune system priming early in life to train it to distinguish "self" from "non-self"

Eringsmark Regnell S & Lernmark A. Diabet Med 30:155-160, 2013.

Virtanen SM & Knip M. Am J Clin Nutr 78:1053-1076, 2003.

Norris JM et al. JAMA 276:609-614, 1996.

Genetics of Type 1 DM and HLA Haplotypes

Susceptibility:

High

DRB-1: 0401, 0402, 0405, 0301

DQA-1: 0301, 0501

DQB-1: 0302, 0201

Moderate

DRB-1: 0801, 0101, 0901

DQA-1: 0401, 0101, 0301

DQB-1: 0402, 0501, 0303

Protection:

High

DRB-1: 1501, 1402*, 0701

DQA-1: 0102, 0101, 0201

DQB-1: 0602, 0503, 0303

Moderate/Weak

DRB-1: 0401, 0403, 0701, 1101

DQA-1: 0301, 0201, 0501

DQB-1: 0301, 0302, 0201

* Found more commonly in Native Americans

Genetics of Type 1 DM and HLA Haplotypes

- Type 1 Diabetes is also associated with other auto-immune endocrine diseases, e.g., Hashimoto's thyroiditis, adrenal insufficiency, etc.
- A patient with type 1 DM has about a 30 percent lifetime risk of autoimmune thyroid disease (>90 percent of which will be Hashimoto's disease leading to hypothyroidism), a 4 percent risk of adrenal insufficiency and a 1 percent or lower risk of premature gonadal failure, hypoparathyroidism or pernicious anemia and others.

Umpierrez GE et al. Diabetes Care 26:1181-1185, 2003.

Atypical Forms of DM that May Resemble Type 1

ADA Etiologic Class III – Types A-H

A. Genetica Defects of β-cell funtcion:

MODY types 1-6 and Mitochondrial DNA

B. Genetic Defects in Insulin Action:

Type A insulin resistance, Lipoatrophic DM, Rabson- Mendenhall Syndrome, Leprechaunism

C. Exocrine Pancreatic Disorders:

Pancreatitis, Trauma, Pancreatectomy, Neoplasia, Cystic fibrosis, Hemochromatosis, *Tropical calcific pancreatitis, Cassava toxicity*

D. Secondary to Endocrinopathy:

Acromegaly, Cushing's Syndrome, Glucagonoma, Pheochromocytoma, Hyperthyroidism, Somatostatinoma, Aldosteronoma

Atypical Forms of DM

ADA Etiologic Class III – Types of A-H (continued):

E. Drug of Chemical Induced:

Vacor, Pentamidine, Nicotinic Acid, Glucocorticoids, Thyroid hormone, Diazoxide, β-Adrenergic agonists,Thiazides, Dilantin, α-Interferon

F. Infections:

Congenital Rubella, Cytomegalovirus

G. Immune Mediated:

Stiff-Man Syndrome, Anti-insulin receptor anitbodies

H. Other Genetic Syndromes:

Down's Syndrome, Klinefelter's Syndrome, Turner's Syndrome, Wolfram's Syndrome, Friedreich's Ataxia, Huntington's Chorea, Laurence-Moon-Biedl Syndrome, Dystrophia Myotonica, Porphyria, Prader-Willi Syndrome

Atypical Forms of DM

- ADA Etiologic Class IV:

Gestational Diabetes Mellitus (GDM)

Defined as diabetes mellitus first recognized during pregnancy

Most will be true GDM

Some will be previously unrecognized Type 2 DM

A very few will be evolving Type 1 DM

Rarely, atypical (Class IV) DM will be picked up at this time.

Therefore, diabetes must be re-evaluated and reclassified after delivery.

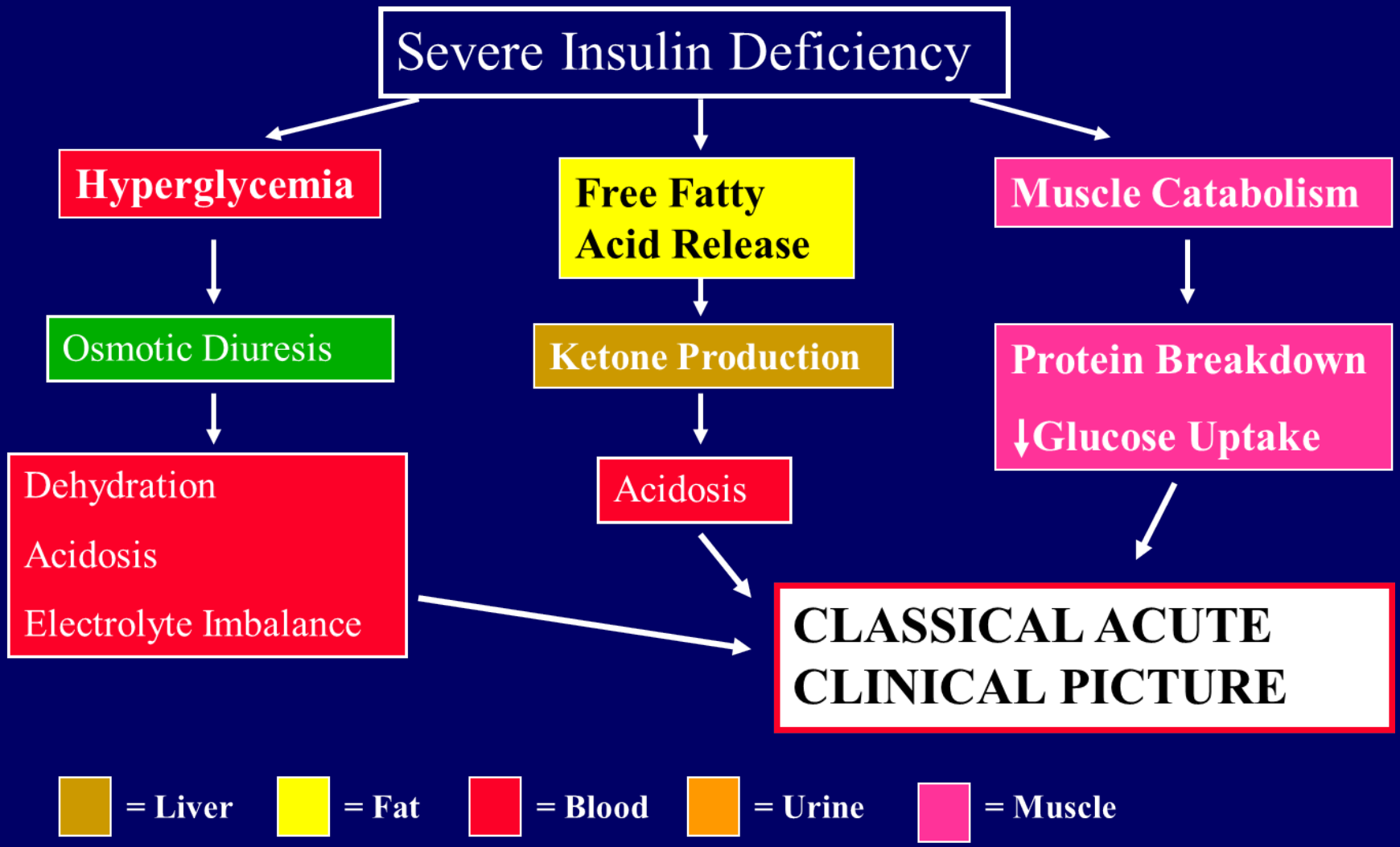
Prevention of Type 1 DM

No intervention has been conclusively shown to be effective in preventing Type 1 DM

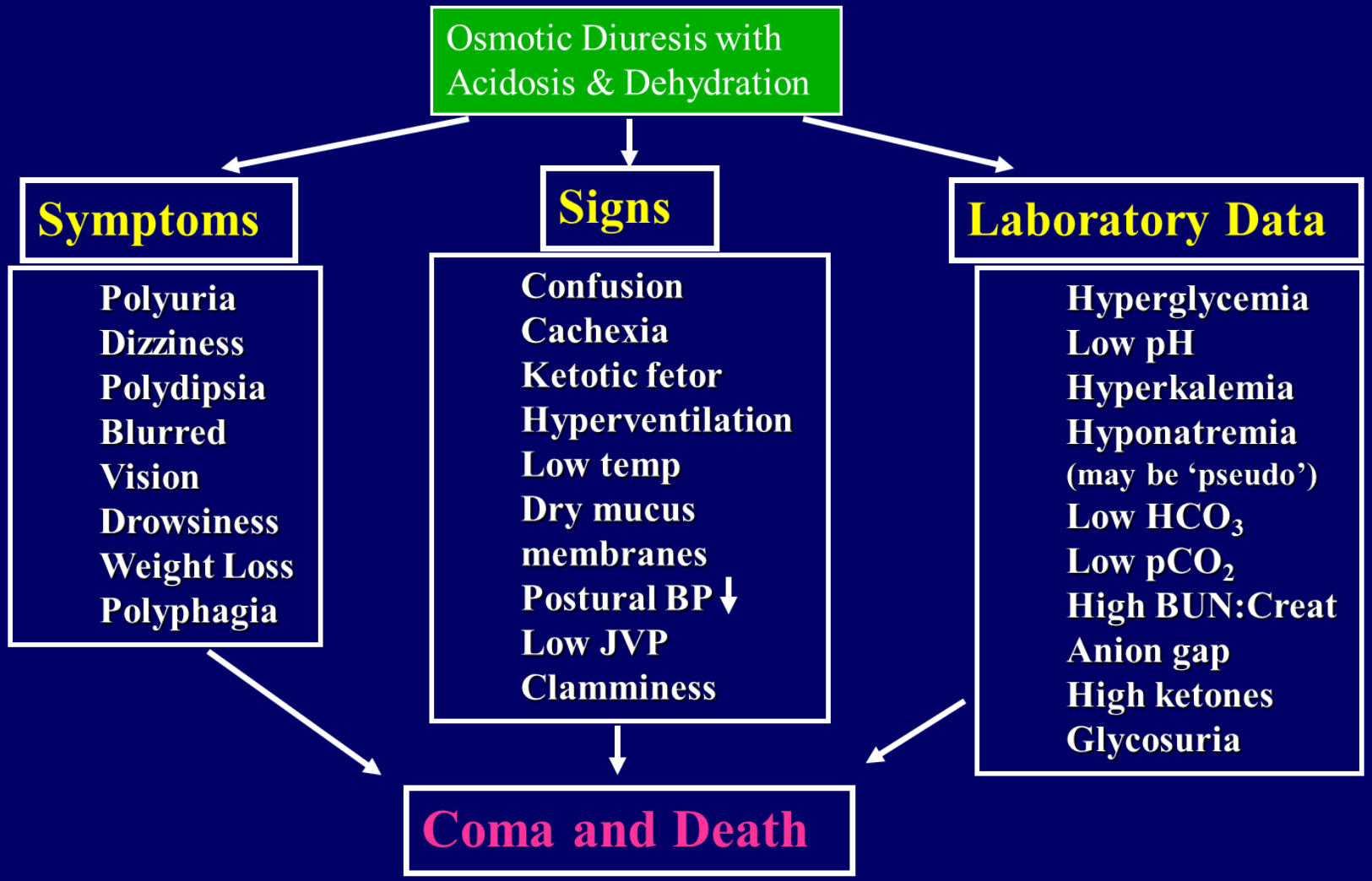
- European Nicotinamide Diabetes Intervention Trial 'ENDIT' – treatment of >500 high risk subjects with high-dose nicotinamide was ineffective;
- Diabetes Prevention Trial (DPT) – treatment of high-risk subjects with oral or parenteral insulin was ineffective;
- Avoidance of cow's milk products – inconclusive, probably ineffective;
- Multiple infections in early childhood and preschool daycare have shown a protective effect against Type 1 DM.
- Canadian/European and French Cyclosporin studies showed insufficient benefit to justify cyclosporin toxicity.
- Trials with azathioprine, linomide, BCG vaccine and oral insulin were ineffective.
- Protégé Study – Phase 3 trial with anti-CD3 antibody tepluzimab. Some beneficial results, but primary outcome measure was not met.
- Trials with anti-CD20 ab rituximab and anti-T lymphocyte abatacept have shown early promise.

McKinney PA et al. Diabetes Care 22:928-932, 1999.
Sherry N et al. Lancet 378:487-497, 2011
Gale EA et al. Lancet 363:925-31, 2004.
Pescovitz MD et al. Diabetes Care 37:453-459, 2014
Orban T et al. Diabetes Care 37:1069-1075, 2014
Schatz DA and Bingley PJ. J Pediatr Endocrinol Metab. 14(Supp 1):619-22, 2001.

Metabolic Consequences of Type 1 DM

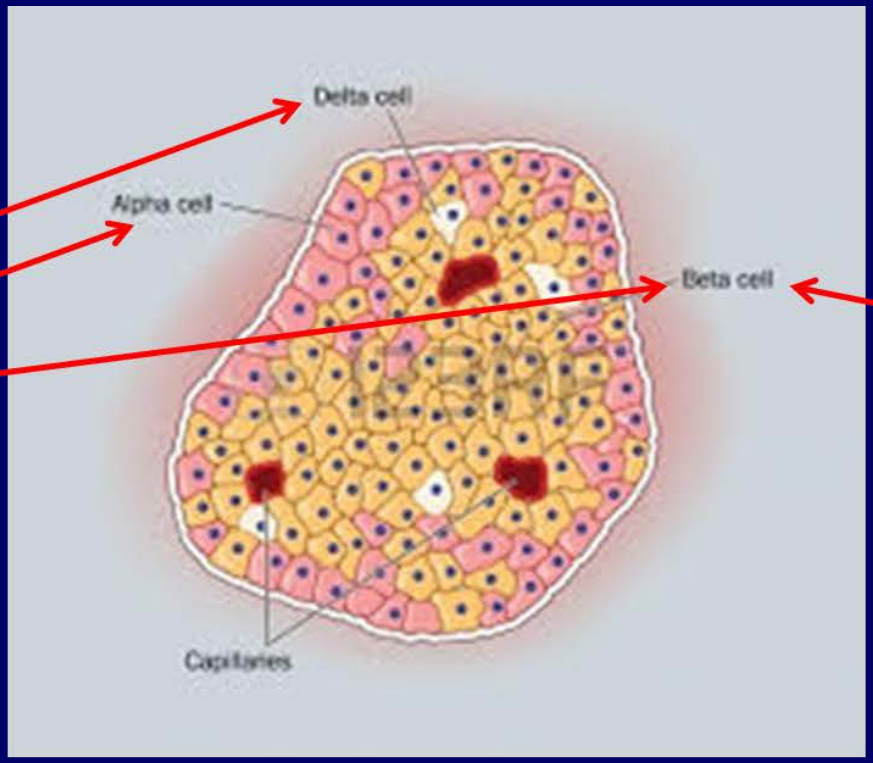


Classical Acute Clinical and Laboratory Picture of Type 1 DM Diabetic Ketoacidosis (DKA)



Unique Features of Non-Immunologically Mediated "Pseudo-Type 1 DM"

Pseudo-Type 1 DM: All Islet Cell Types are damaged



Type 1 DM: Beta Cell is specifically targeted for destruction

Net Result: Loss of both insulin and glucagon = very brittle diabetes and usually exocrine insufficiency & malabsorption.

Net Result: Loss of insulin production only

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Distinguishing Type 1 from Type 2 DM

As a practical issue, this is actually less important than it sounds.

Why?

1. Because the principle of therapy is to treat hyperglycemia with the least aggressive, most convenient modalities that will achieve stable target glycemia and to treat all detected cardiovascular risk factors.
2. Because many patients have features of both Type 1 and Type 2 diabetes in varying degrees, all of which must be addressed.
3. Because diabetes is a spectrum ranging from classic type 1 through intermediate forms to classic type 2.
4. It is often not possible to give a patient a label with certainty.

Distinguishing Type 1 from Type 2 DM

Features that do not differ between Type 1 and Type 2 DM with sufficient frequency to be diagnostically helpful:

History/Symptoms/Signs:

Polyuria

Polydipsia

Nocturia

Polyphagia

Weight loss

Dizziness

Blurred vision

Obesity

Family history

Laboratory Data:

Hyperglycemia

Acidosis

Hyperkalemia

Low HCO_3

High BUN: Creatinine

Glycosuria

Distinguishing Type 1 from Type 2 DM

Features that differ between “Classic” Type 1 and Type 2 DM:

Feature	Type 1	Type 2
Ketoacidosis	Yes	No
Autoantibody positive	Yes	No
Low c-peptide	Yes	Np
Anion gap	Yes	No
High triglycerides	No	Yes
Low HDL	No	Yes
Hypertension	No	Yes
Lean	Yes	No

Generally, the diagnosis is made when multiple classic features are present, but there is “required” number of criteria.

Distinguishing Type 1 from Type 2 DM

Exception to ketoacidosis as a reliable diagnostic criterion for Type 1 DM:

MODY in African-Americans

- 10 percent of African-Americans with youth onset diabetes
- Presents with weight loss, ketoacidosis, insulin-dependence
- Later generally follows a non-ketosis prone insulin-independent course for many years of follow up.
- 50 percent of affected patients are obese.

Ketoacidosis generally indicates severe, virtually complete, insulin deficiency, but can occur in the setting of moderately severe insulin deficiency with extreme insulin resistance.

Winter WE et al. Endocrinol Metab Clin North Am 28:765-785, 1999

Distinguishing Type 1 from Type 2 DM

Q: Is there a gold standard test for diagnosis of type 1 DM?

A: Yes, the stimulated c-peptide.

Often, the main utility of this test is to satisfy insurance company requirements for provision of insulin pumps.

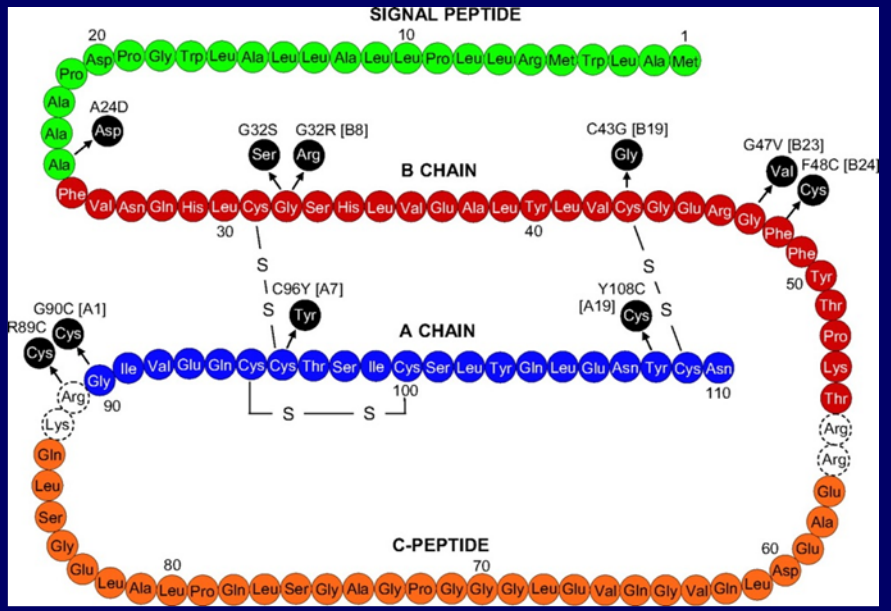
But it is seldom performed correctly!!

Distinguishing Type 1 from Type 2 DM

Performing the stimulated c-peptide challenge correctly:

1. Why c-peptide?

Connecting peptide (c-peptide) links the A and B chains of insulin in its precursor form, proinsulin. Cleavage of c-peptide activates insulin. No synthetic insulin contains the c-peptide fragment. Its presence confirms the presence of non-synthetic insulin of pancreatic origin.



Distinguishing Type 1 from Type 2 DM

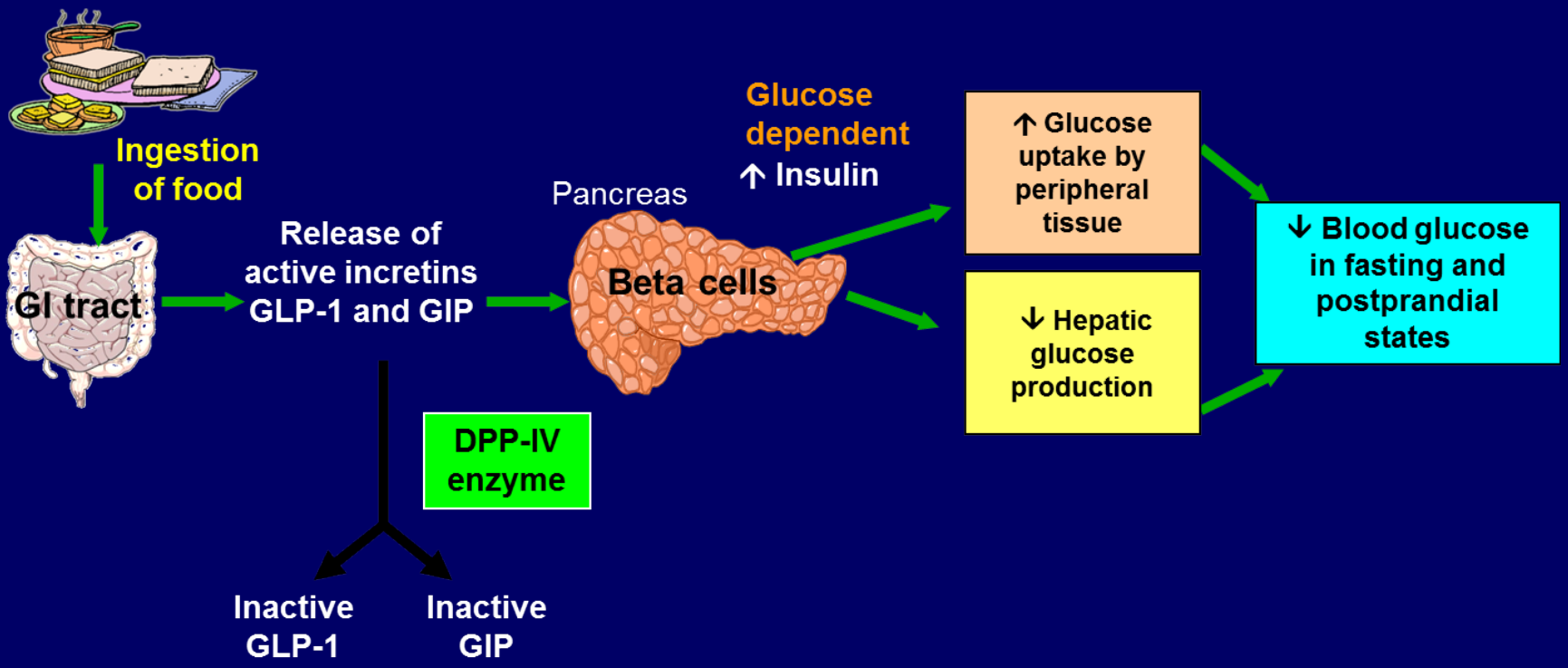
Performing the stimulated c-peptide challenge correctly:

2. How should c-peptide be maximally stimulated in order to reliably indicate endogenous insulin secretory capacity?

Condition	Reason
Insulin therapy must be withheld	Insulin suppresses its own secretion by feedback
Glucose must be elevated above postprandial levels (>150mg/dl)	Elevated glucose promotes maximum insulin secretion
Patient must be fed	Activates the entero-insular axis

Jones AG and Hattersley AT. Diabet Med 30:803–817, 2013.

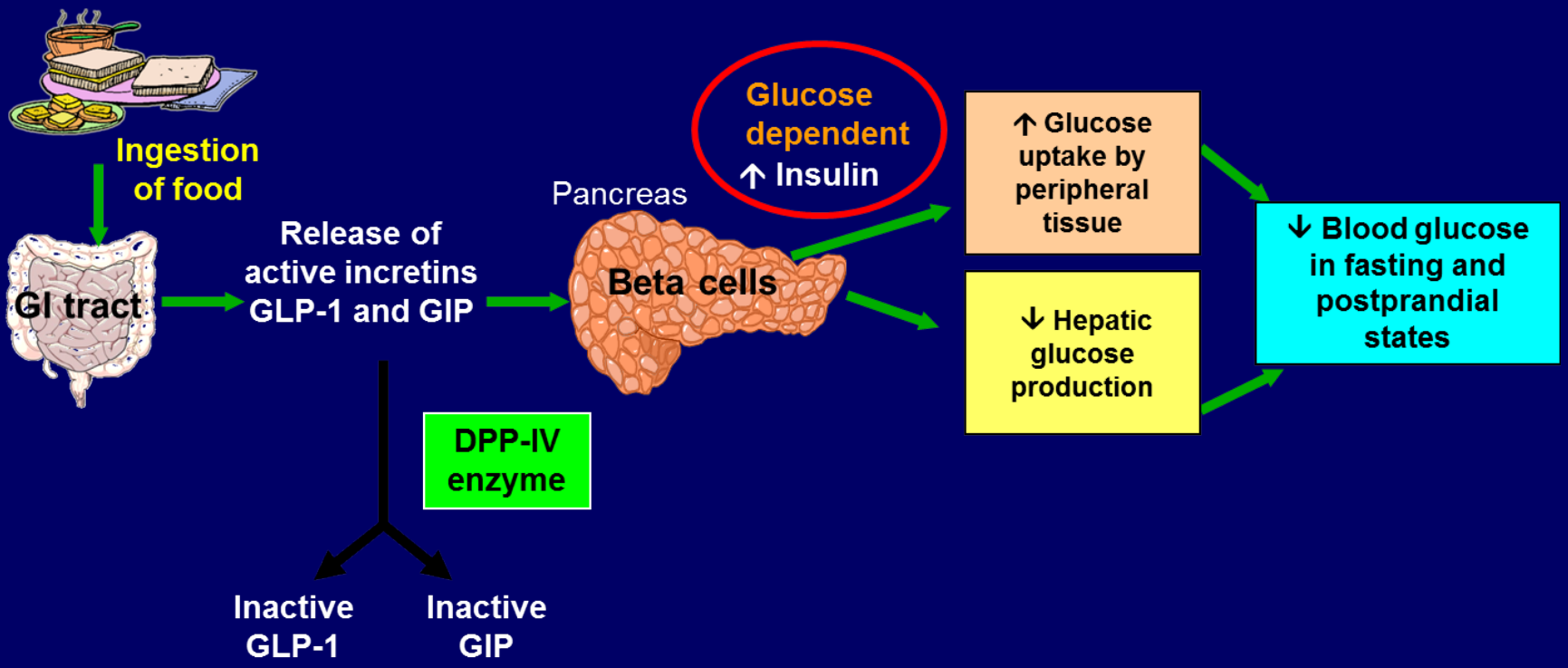
The Entero-Insular Axis



- Incretin hormones GLP-1 and GIP are released by the intestine throughout the day, and their levels ↑ in response to a meal.

GLP-1=glucagon-like peptide-1; GIP=glucose-dependent insulinotropic polypeptide.

The Entero-Insular Axis



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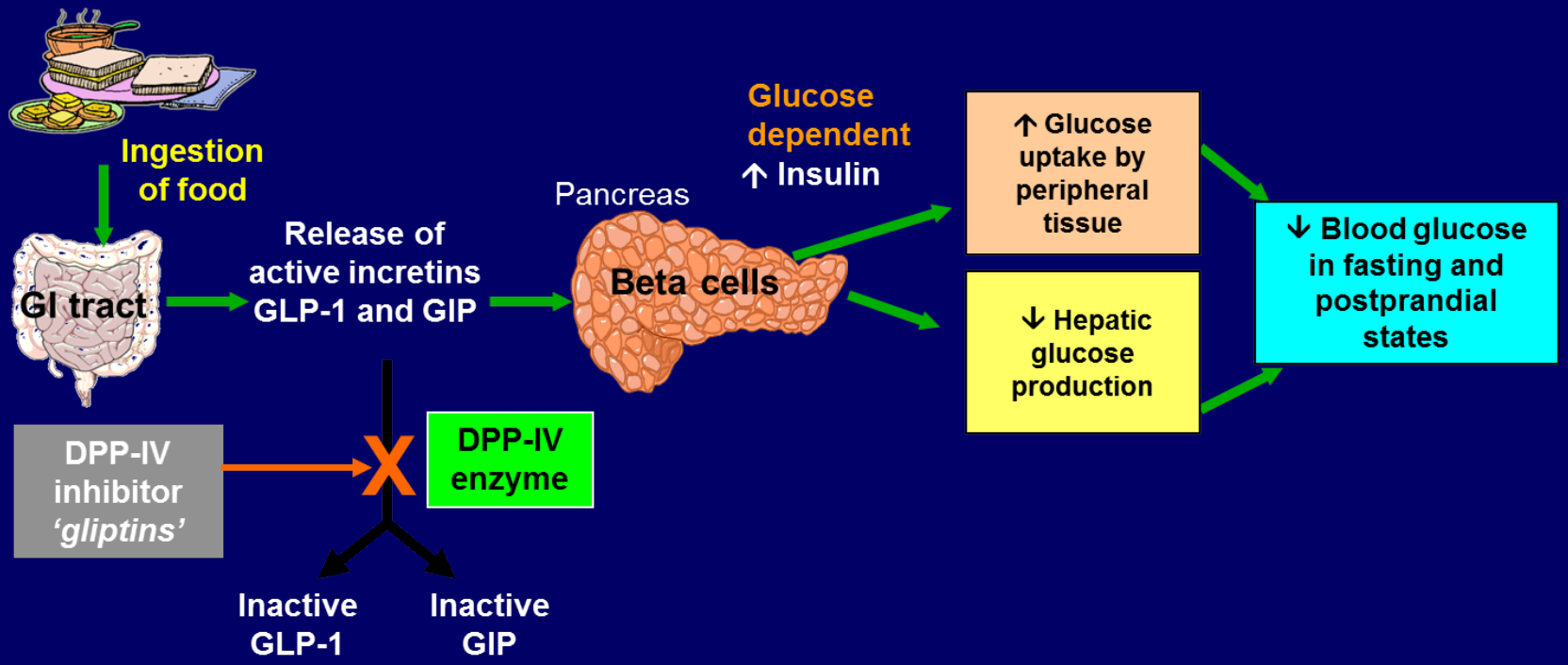
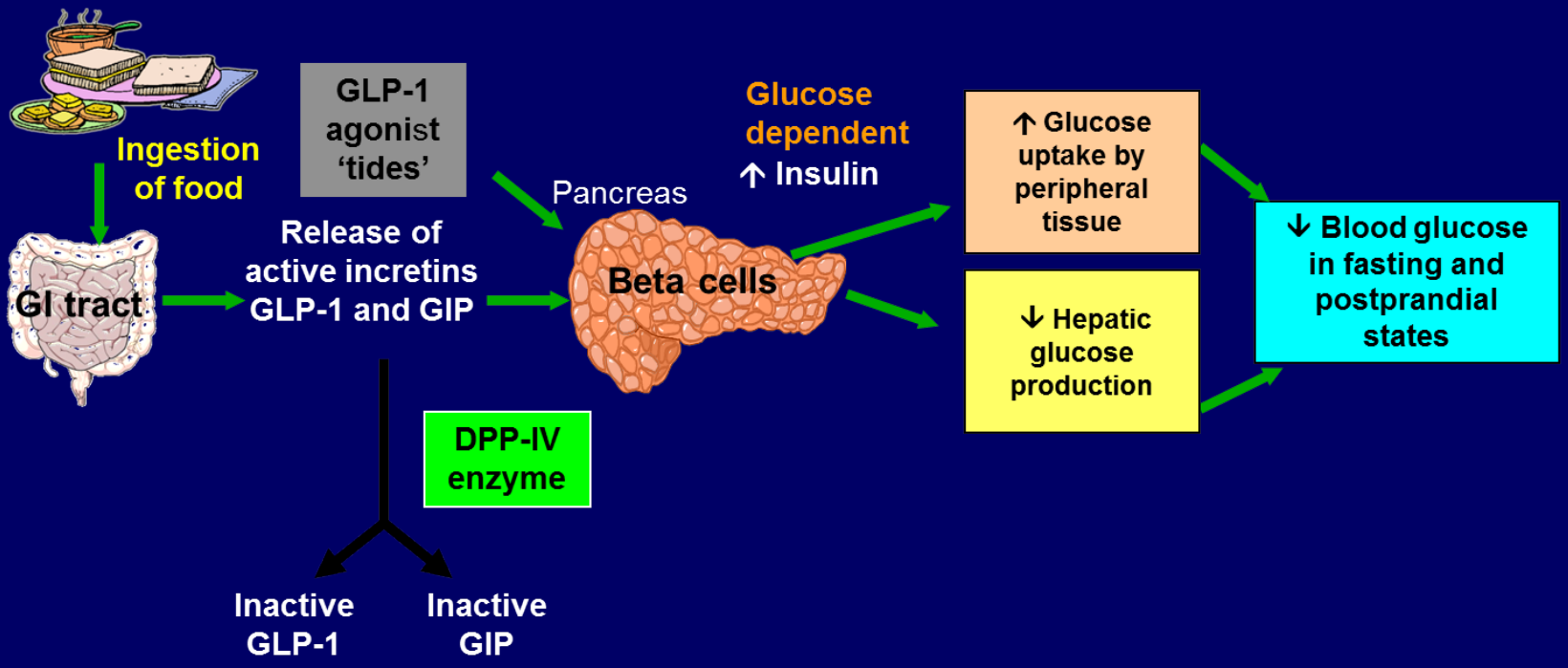
The Entero-Insular Axis (cont.)



DPP-IV inhibitors: sitagliptin, linagliptin, saxagliptin

GLP-1=glucagon-like peptide-1; GIP=glucose-dependent insulinotropic polypeptide.

The Entero-Insular Axis



GLP-1 agonists: exenatide, liraglutide, exenatide extended release.

GLP-1=glucagon-like peptide-1; GIP=glucose-dependent insulinotropic polypeptide.

Distinguishing Type 1 from Type 2 DM

Performing the stimulated c-peptide challenge correctly:

1. Withhold long-acting insulin the previous evening and on the morning of the test
2. Usual short-acting insulin dose with evening meal the night before the test
3. Patient eats breakfast and presents to Clinic one hour later
4. Capillary glucose is tested. When reading is above 150 mg/dl, patient is sent to Laboratory, where glucose and c-peptide are drawn.

Value of <0.6 nmol/L indicates Type 1 DM

Jones AG and Hattersley AT. Diabet Med 30:803–817, 2013.

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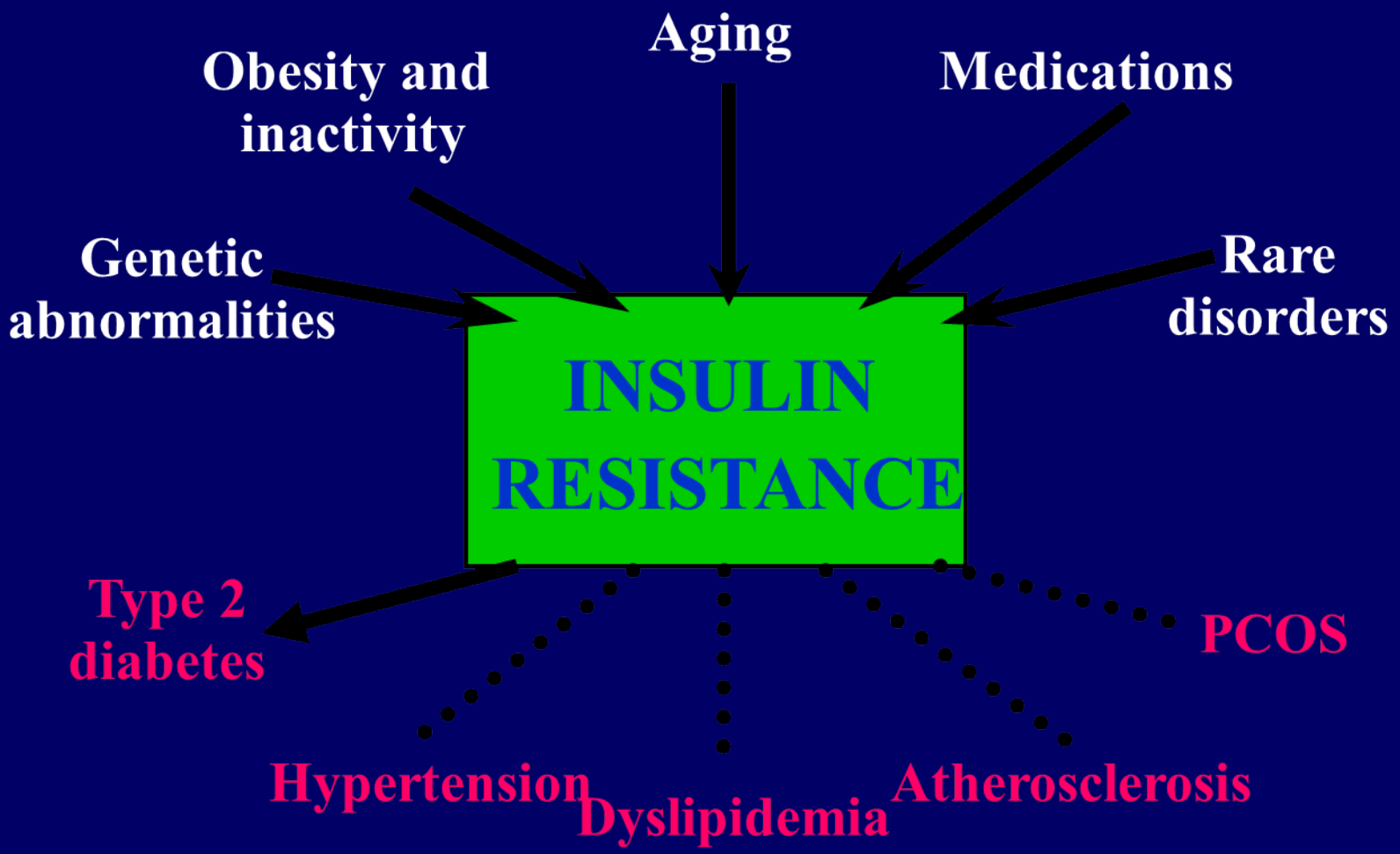
Insulin Resistance: An Underlying Cause of Type 2 Diabetes



Clinically Useful Parameters to Identify Insulin Resistance

Parameter	Sensitivity	Specificity
Acanthosis nigricans, tags, angiomas	High	
Impaired fasting glucose	10%	97%
Impaired Glucose Tolerance	26%	95%
High Fasting Insulin	66%	83%
High Insulin 2 hours post 75g Glucose	71%	86%
Fasting Triglyceride >130 mg/dl	High	High
Low HDL	High	High
Triglyceride: HDL Ratio >3	High	High
BMI > 25 kg/m2	60%	
Waist circumference >ATP III cutoff	68%	

Clinically Useful Parameters to Identify Insulin Resistance in Patients with Type 1 DM

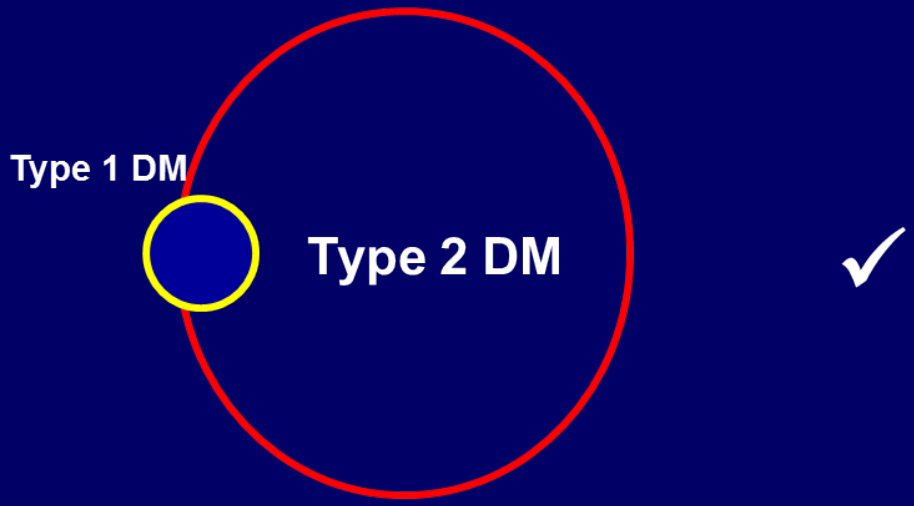
Parameter	Sensitivity	Specificity
Acanthosis nigricans, tags, angiomas	High	
~~Impaired fasting glucose~~	~~10%~~	~~97%~~
~~Impaired Glucose Tolerance~~	~~26%~~	~~95%~~
~~High Fasting Insulin~~	~~66%~~	~~83%~~
~~High Insulin 2 hours post 75g Glucose~~	~~71%~~	~~86%~~
Fasting Triglyceride >130 mg/dl	High	High
Low HDL	High	High
Triglyceride: HDL Ratio >3	High	High
BMI > 25 kg/m2	60%	
Waist circumference >ATP III cutoff	68%	

Coexistence of Insulin Resistance with Type 1 DM – "Superimposing Type 2"

Having Type 1 DM **precludes** expression of the genetic and environmental risk factors of the insulin resistance of type 2 DM

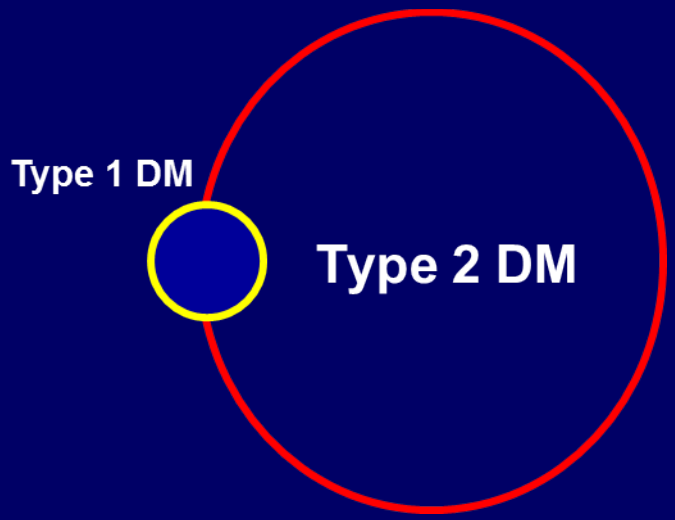
OR ?

Having Type 1 DM **allows** expression of the genetic and environmental risk factors of the insulin resistance of type 2 DM



Coexistence of Insulin Resistance with Type 1 DM – "Superimposing Type 2"

- Therefore, it is important to consider that many AI/AN patients with Type 1 DM can develop the metabolic features of Type 2 DM, which should be treated. Insulin sensitization can therefore be an important component of treatment of Type 1 AI/AN patients, especially as they age.



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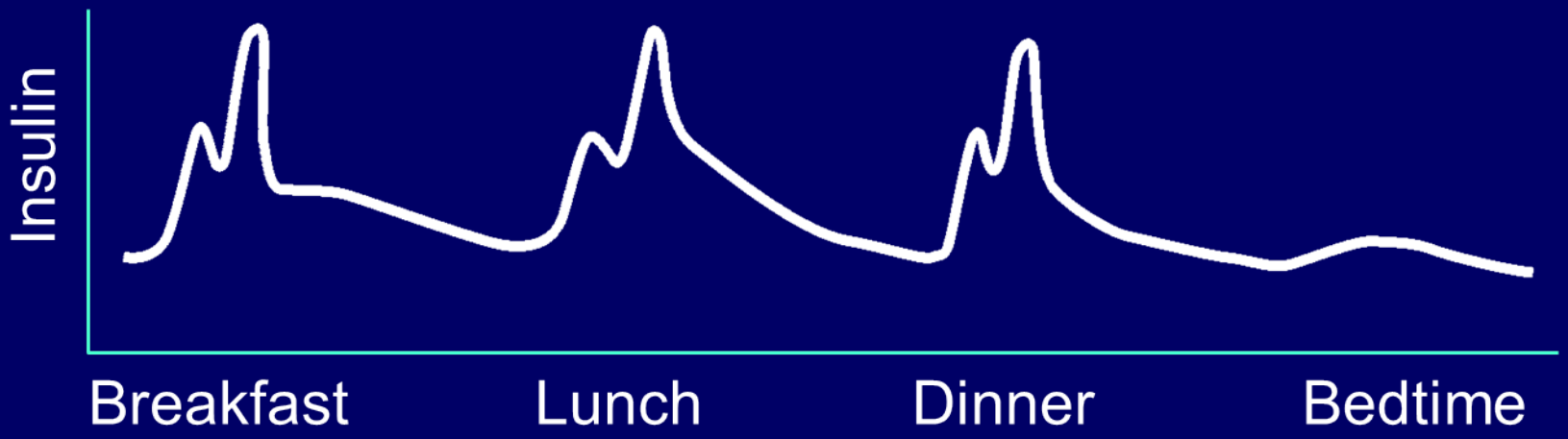
Principles of Insulin Therapy

1. The simplest regimen that achieves glycemic control should be employed:
2. Initiation and adjustment of insulin should be based on appropriate available glucose monitoring data;
3. Sliding-scale insulin alone is ***NEVER*** a suitable prescription and should not be permitted on quick orders;
4. The insulin that is administered now is dosed based on historical data of glucose at a later time point;

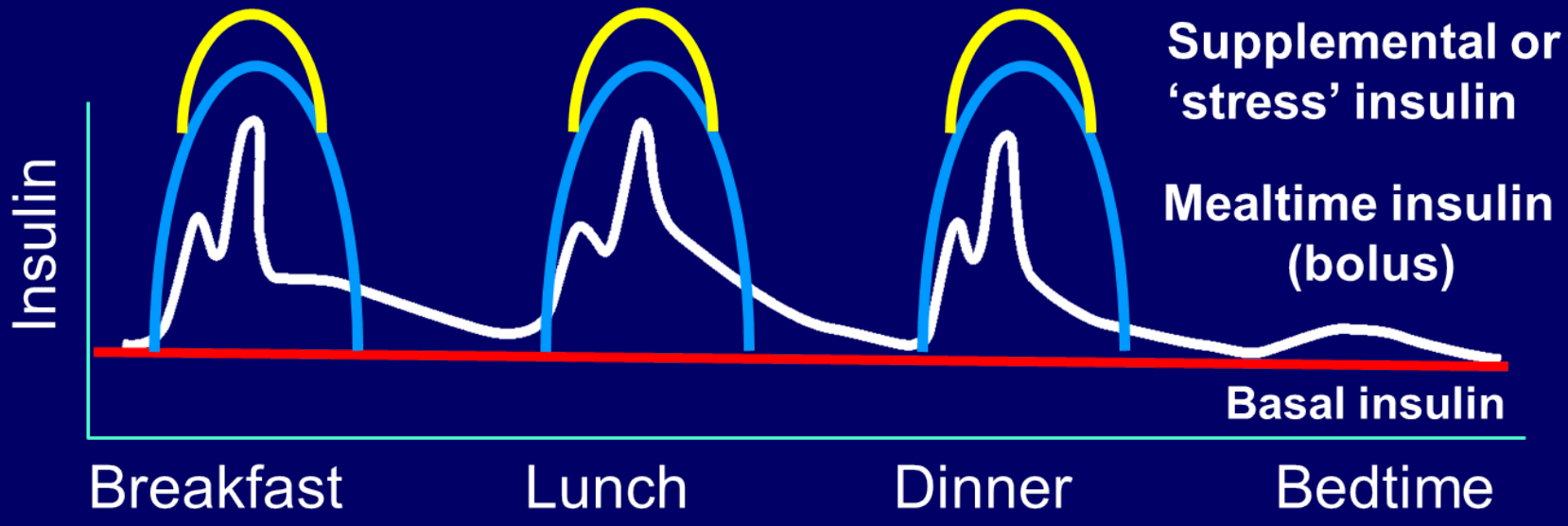
Use of ‘Sliding-Scale’ Insulin Alone Is Strongly Discouraged

- Evidence does not support this technique without basal insulin
- Hazards of sliding-scale insulin use exceed the advantages of its convenience
- Leads to rapid changes in BG levels resulting in exacerbation of both hyperglycemia and hypoglycemia
- Possible iatrogenic diabetic ketoacidosis in patients with T1DM

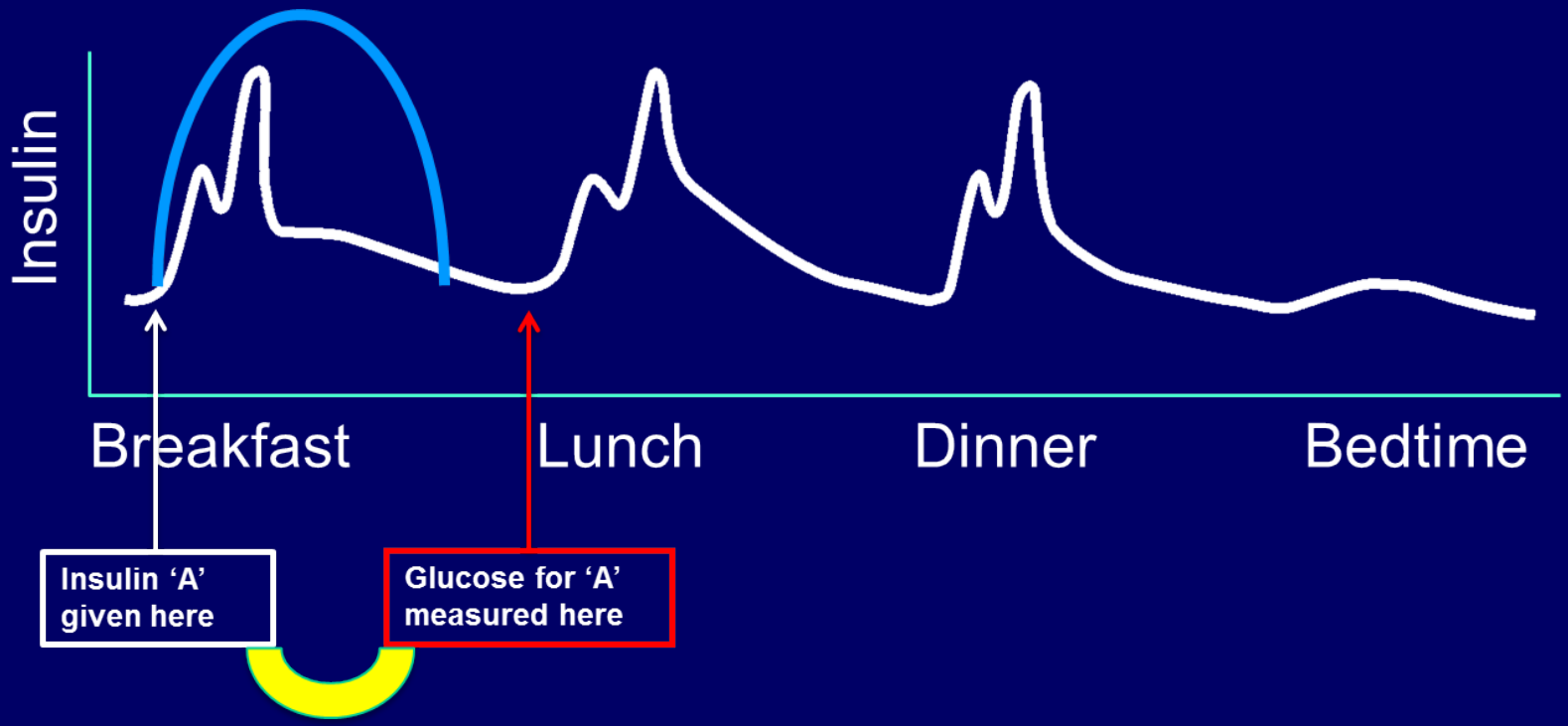
Normal Secretory Pattern of Insulin



Maintaining Physiologic Insulin Delivery: Basal-Bolus



Dosing Short-Acting Insulin



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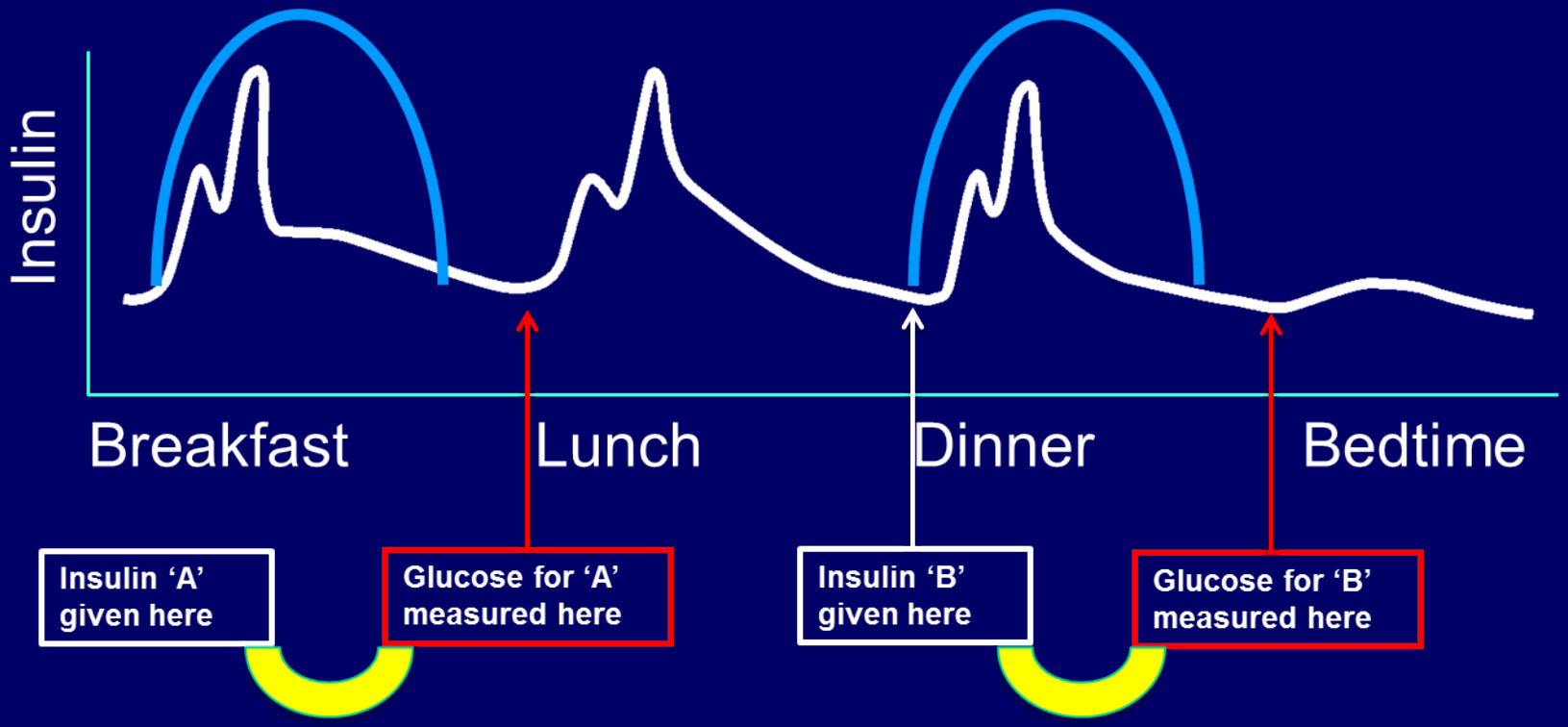

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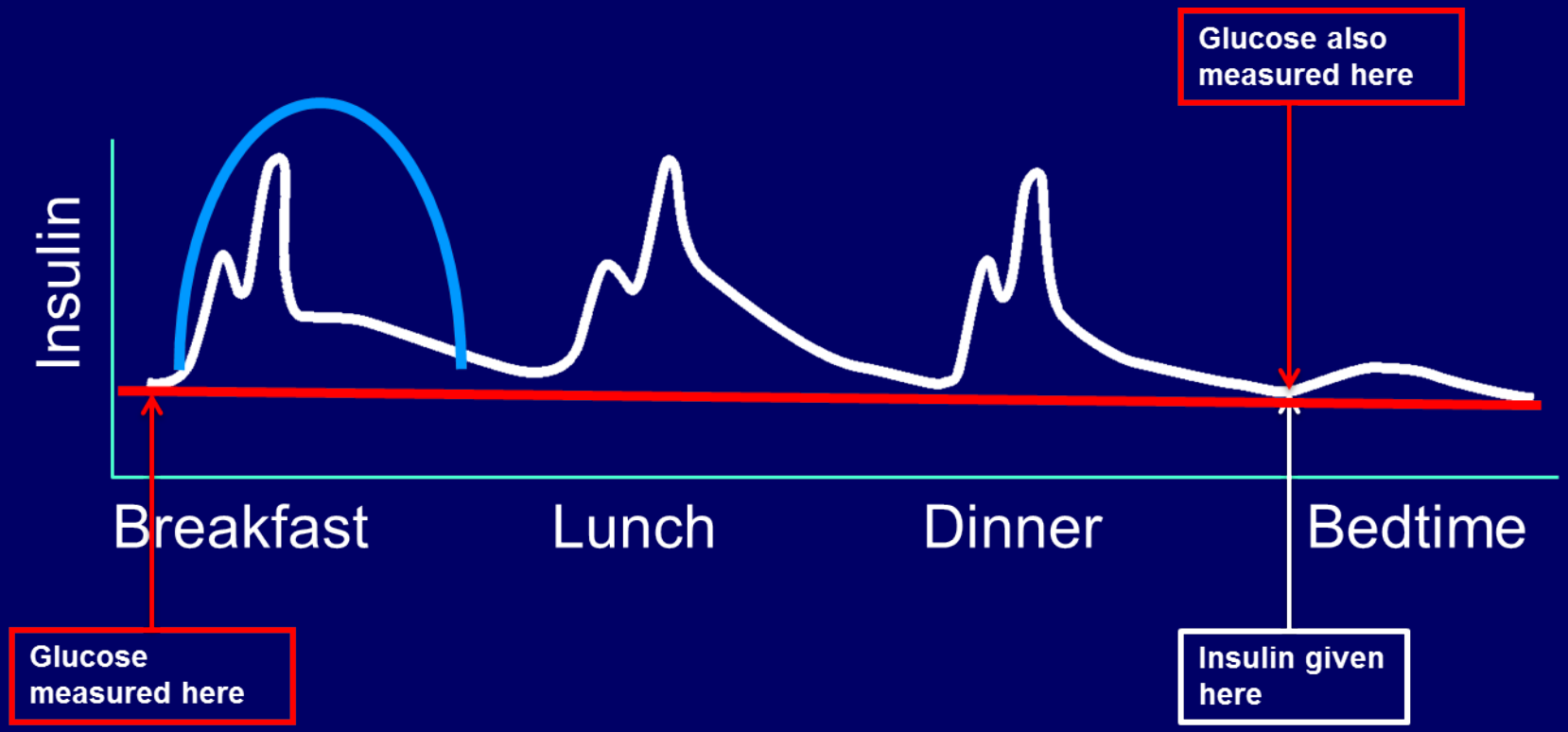


Insulin

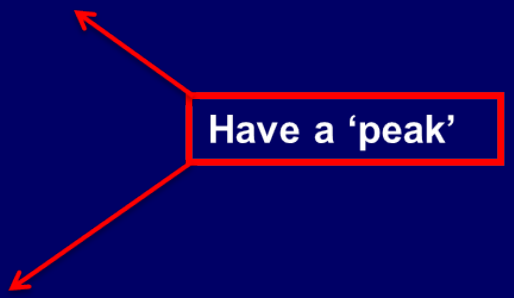
Options for Basal Insulin (controlling BG in fasting state)

Analogs

- Detemir
- Glargine

Human

- NPH



NPH and Detemir are only once a day insulin in low dosage, usually 30 units or less.

Options for Nutritional Insulin (controlling BG when there is caloric intake)

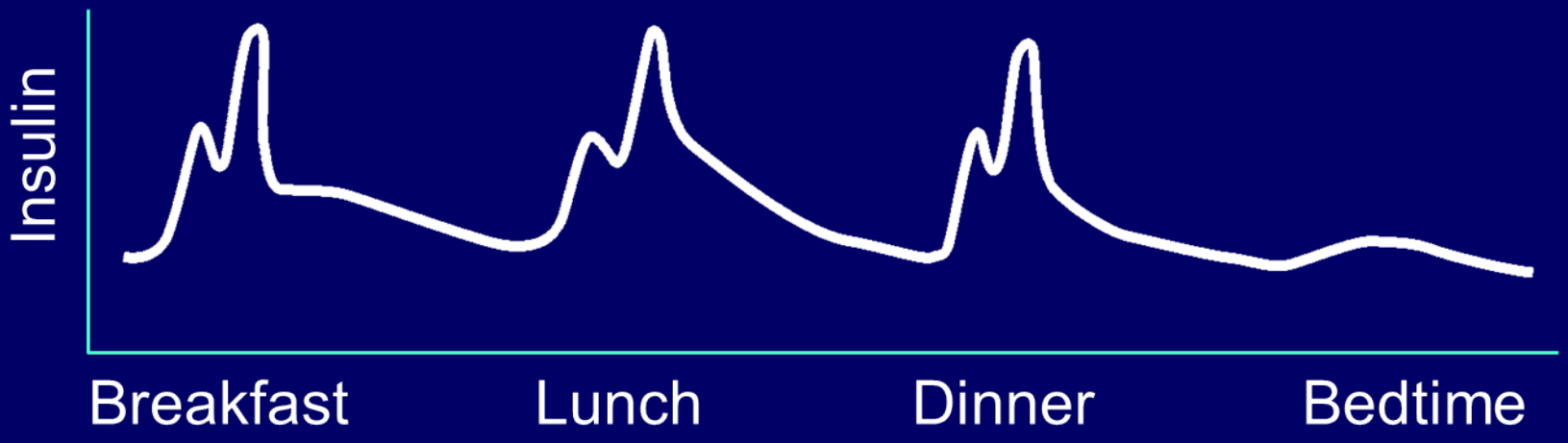
Analogs

- Aspart
- Glulisine
- Lispro

Human

- Regular

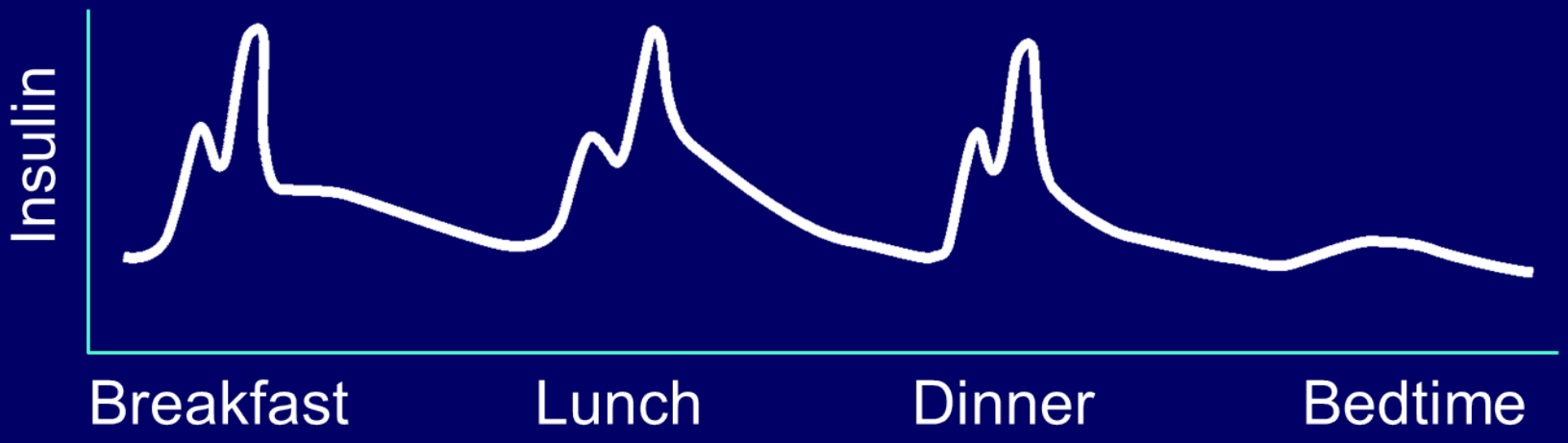
Adjustment of Insulin According to Glucose Readings



164 **248** **151** **272**

Glargine: 35 units; Aspart: 10 - 10 - 10 - 0

Normal Secretory Pattern of Insulin



147 **210** **146** **98** **234**

Glargine: 38 units; Aspart: 12 - 10 - 14 - 0

Additional Considerations in Management of Type 1 DM

1. In patients with coexistent features of insulin resistance, consider the benefits of using insulin sensitizers – pioglitazone sensitizes up to 35 percent, metformin 15-20 percent and effects are additive.
2. Insulin dosing should not be determined based on post-prandial readings alone. The pre-prandial glucose is the dose-determining value for safety reasons.
3. Supplemental dosing of short-acting insulin postprandially is strongly discouraged, most especially in Type 1 DM – it is a form of “stacking” with risk of late hypoglycemia.

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One Recommended Change You Can Make in Your Practice

Four to Choose From:

1. If performing the stimulated c-peptide challenge for diagnosis of type 1 DM, be sure to hold insulin, feed patient and verify glucose above 150 mg/dl in order to get a valid result.
2. Consider the potential benefits of insulin sensitizer use in type 1 DM patients with clinical and laboratory evidence of concomitant insulin resistance.
3. Avoid sliding-scales in ambulatory patients, ensure that there are no quick-orders for sliding-scale insulin in your Pharmacy menu. Dose both short-acting and long-acting insulins proactively against their desired action point.
4. Stacking is for chairs and pancakes, but not for insulin.

The End

Questions or Comments?