Autoimmune Hypoglycemia

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Introduction

- **Hypoglycemia**
  - Plasma Glucose under 70 mg/dl
  - Glucose levels <55 mg/dL (3.0 mmol/L) with symptoms that are relieved promptly after the glucose level is raised

- Hypoglycemia by ***Whipple's triad***:

  (1) symptoms consistent with hypoglycemia

  (2) a low plasma glucose concentration measured with a precise method

  (3) relief of those symptoms after the plasma glucose level is raised

Introduction

- **Hypoglycemia incidence**
  - In DCCT, 10-30% of type 1 diabetics per year and of those,10% require 3rd party Intervention
  - In the UKPDS,30-35%of type 2 diabetics on Insulin require 3rd party Intervention

- **Classification of hypoglycemia**
  - Fasting hypoglycemia
  - Postprandial(reactive) hypoglycemia

Introduction

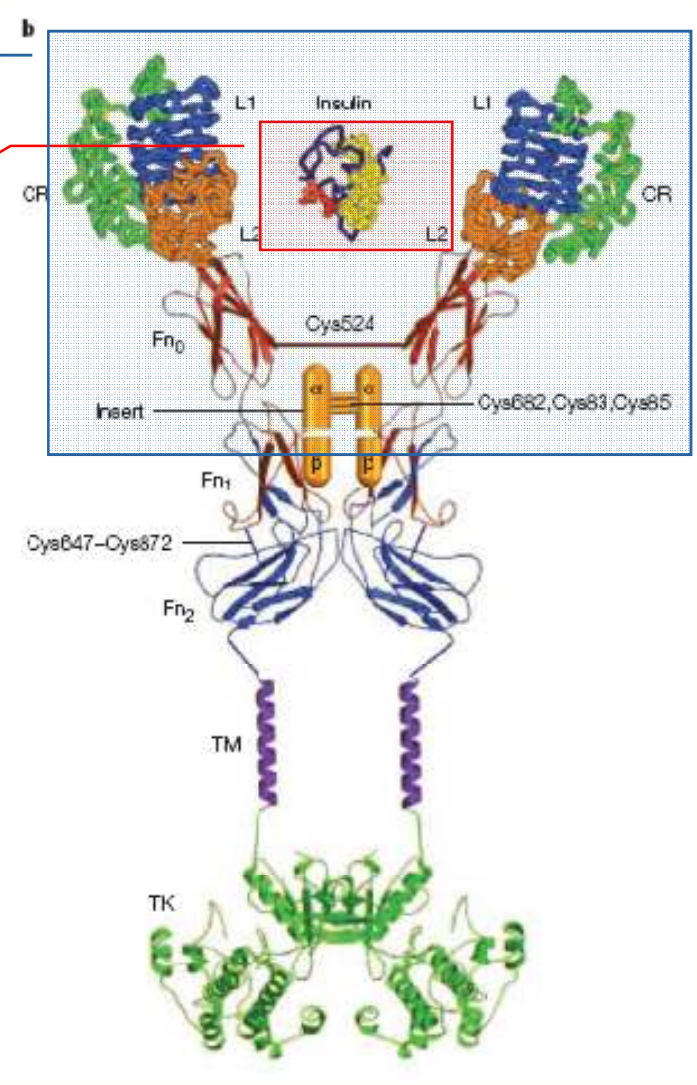
Table 339-1 Causes of Hypoglycemia
Fasting (Postabsorptive) Hypoglycemia
Drugs
Especially insulin, sulfonylureas, ethanol
Sometimes quinine, pentamidine
Rarely salicylates, sulfonamides, others
Critical illnesses
Hepatic, renal, or cardiac failure
Sepsis
Inanition
Hormone deficiencies
Cortisol, growth hormone, or both
Glucagon and epinephrine (in insulin-deficient diabetes)
Non-β-cell tumors
Endogenous hyperinsulinism
Insulinoma
Other β cell disorders
Insulin secretagogue (sulfonylurea, other)
Autoimmune (autoantibodies to insulin or the insulin receptor)

Table 339-1 Causes of Hypoglycemia
Fasting (Postabsorptive) Hypoglycemia
Ectopic insulin secretion
Disorders of infancy or childhood
Transient intolerance of fasting
Congenital hyperinsulinism
Inherited enzyme deficiencies
Reactive (Postprandial) Hypoglycemia
Alimentary (postgastrectomy)
Noninsulinoma pancreatogenous hypoglycemia syndrome
In the absence of prior surgery
Following Roux-en-Y-gastric bypass
Other causes of endogenous hyperinsulinism
Hereditary fructose intolerance, galactosemia
Idiopathic

Introduction

Autoimmune causes

- Insulin autoimmune syndrome (IAS)
  - Insulin autoantibody (IAA)
- Type B insulin resistance
  - Insulin receptor antibody (IR-A)



Insulin Autoimmune Syndrome

Insulin Autoimmune Syndrome

- First observation of IA and hypoglycemia
  - A 34-year-old T1D woman with intermittent episodes of severe hypoglycemia
  - The patient's serum contained IA with high insulin binding capacity and a slow rate of dissociation of insulin-antibody complexes
  - It was postulated that insulin was "stored" at high levels in the serum bound to IA, and that the slow rate of dissociation of insulin from the IA complex resulted in intermittent hypoglycemia

HARWOOD R. N Engl J Med. 1960

Insulin Autoimmune Syndrome

- In 1970, Hirata described a patient

  with severe hypoglycemia with presence of IA
  - Hirata suggested the term *autoimmune insulin syndrome* to describe a syndrome of
    - hypoglycemia
    - elevated insulin levels
    - high levels of IA without previous exposure to exogenous insulin

Hirata Y, J Soc Diabetes Cos. 1970

- Over 300 cases of IA-associated hypoglycemia have been reported since 1970, with 80% of cases reported in Japan

Insulin Autoimmune Syndrome

- ***Clinical Presentation in 197 Asian***
  - postprandial hypoglycemia
  - old-aged(>60), no sex predilection
  - concomittent autoimmune disorder (thyroiditis)
  - sulfhydryl group drug use (44%) : (methimazole, 50%)

Uchigata, Ann Med Interne. 1999

- ***Clinical Presentation in 58 Non-Asian***
  - postprandial(42%), fasting(31%), both(24%) hypoglycemia
  - middle-aged(>40), no sex predilection
  - concomittent rheumatologic or hematologic disorder
  - variable drug

Lupsa BC, Medicine. 2009

Insulin Autoimmune Syndrome

- ***Laboratory Findings in 197 Asian***
  - Insulin levels - usually > 100 mU/L (upto 100,000 mU/L)
  - C-peptide - not suppressed
  - Elevated IAA - polyclonal IgGs with variable kappa and lambda light chains and two classes of insulin-binding sites: high affinity/low capacity and low affinity/high capacity
- ***Laboratory Findings in 58 Non-Asian***
  - Insulin levels - usually > 100 mU/L (over upper limit)
  - C-peptide - markedly elevated
  - Elevated IAA - monoclonal IgGs (8/12 data collected)

Insulin Autoimmune Syndrome

- ***Pathogenesis of Hypoglycemia***

  (1) "buffering" effect and release at inappropriate timing

  (2) cross-linking of insulin-insulin receptor complexes by IA resulting in the potentiation or prolongation of insulin action

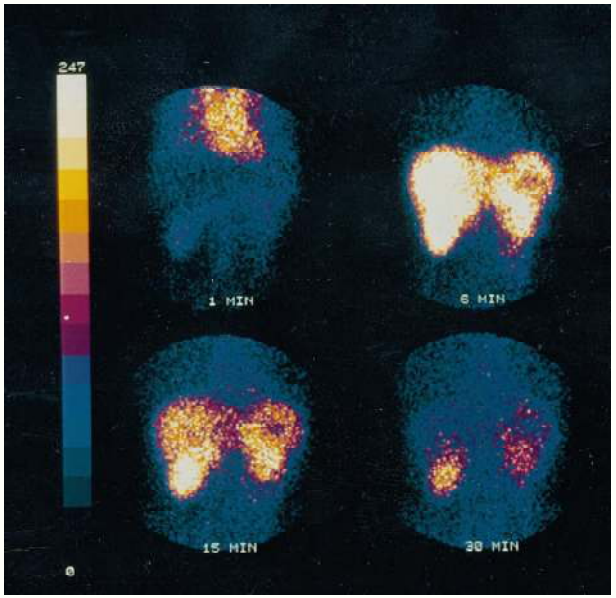
  (3) development of anti-idiotypic antibodies to the IA that are capable of directly activating insulin receptors

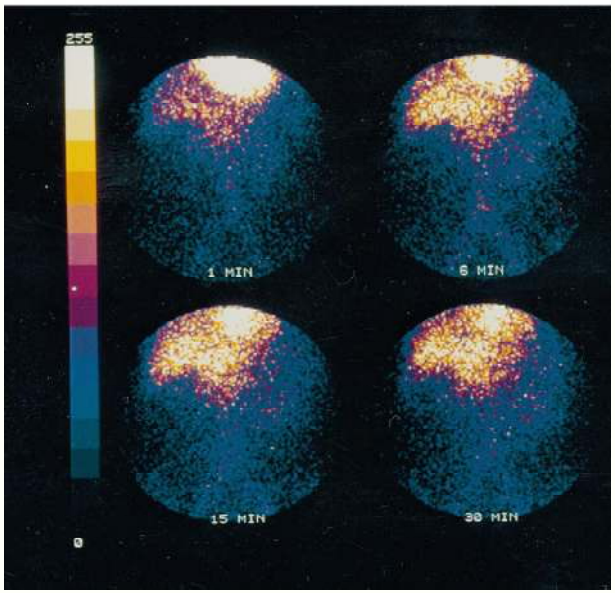
  (4) direct stimulation of insulin secretion by IA

Insulin Autoimmune Syndrome

- IV injection of ^{123} I-labeled insulin, the patient demonstrated persistent labeled insulin activity in the blood and the absence of liver or kidney uptake of labeled hormone
- Following treatment with prednisone and plasmapheresis, IA levels decreased, and an increased clearance of ^{123} I-labeled insulin from the blood pool

Dozio, JCEM. 1998



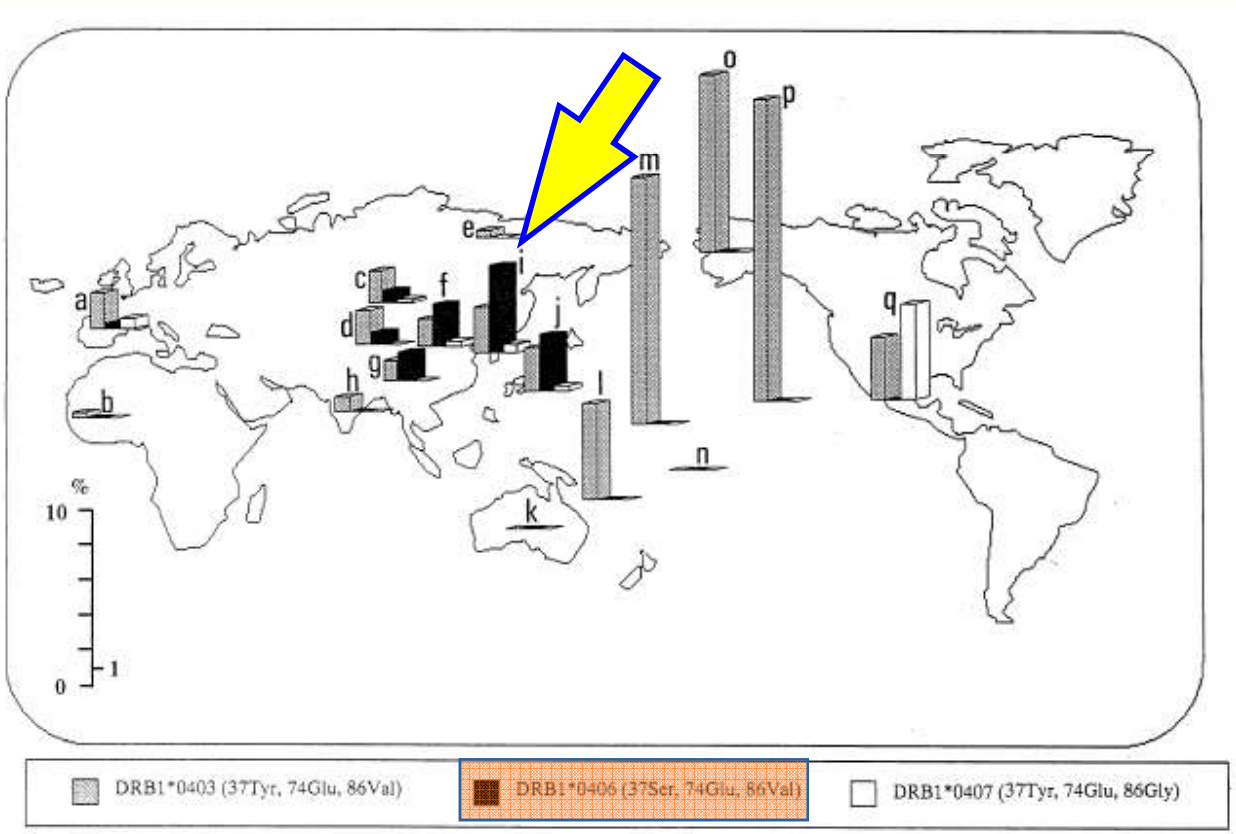


Insulin Autoimmune Syndrome

- ***Origin of Insulin Antibodies in Patients with Hypoglycemia***
- Origin of the IAA in this syndrome is unknown
- The development of IAA and hypoglycemia in patients with
  - autoimmune disease
  - history of exposure to sulfhydryl medications
  - strongly associated with specific HLA class II alleles, DRB1*0406, DQA1*0301, and DQB1*0302
  - These alleles are 10 to 30 times more prevalent in Japanese and Koreans in comparison with Caucasians

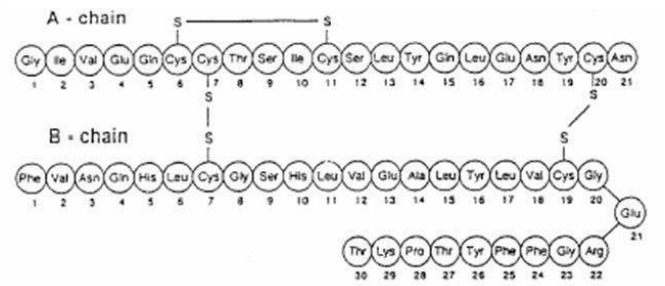
Insulin Autoimmune Syndrome

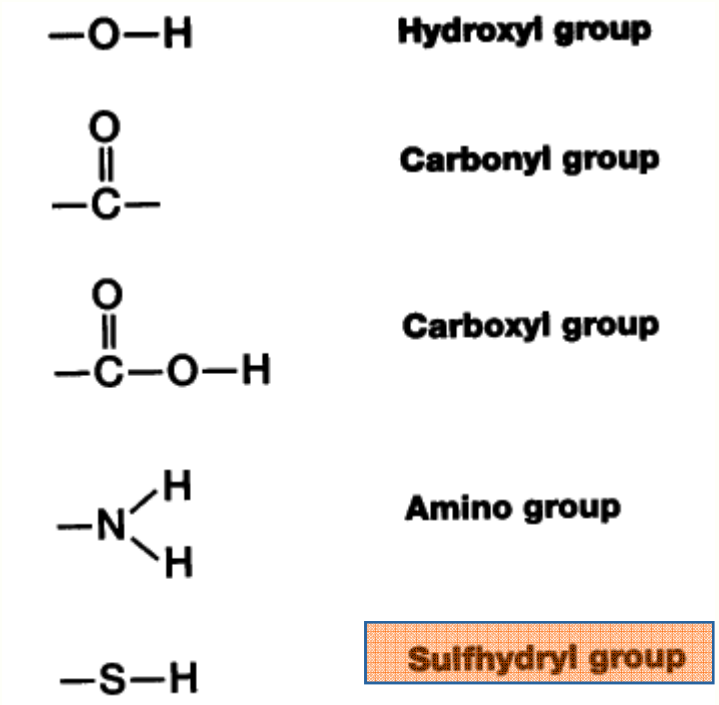
- ***Origin of Insulin Antibodies in Patients with Hypoglycemia***
- This distribution may explain the higher prevalence of the disorder in the Japanese population



Insulin Autoimmune Syndrome

- Numerous drugs related to the development of IA
  - hydralazine, isoniazid, IFN-alpha
- sulfhydryl groups
  (methimazole, tiopronin, glutathione
  captopril, D-penicillamine)





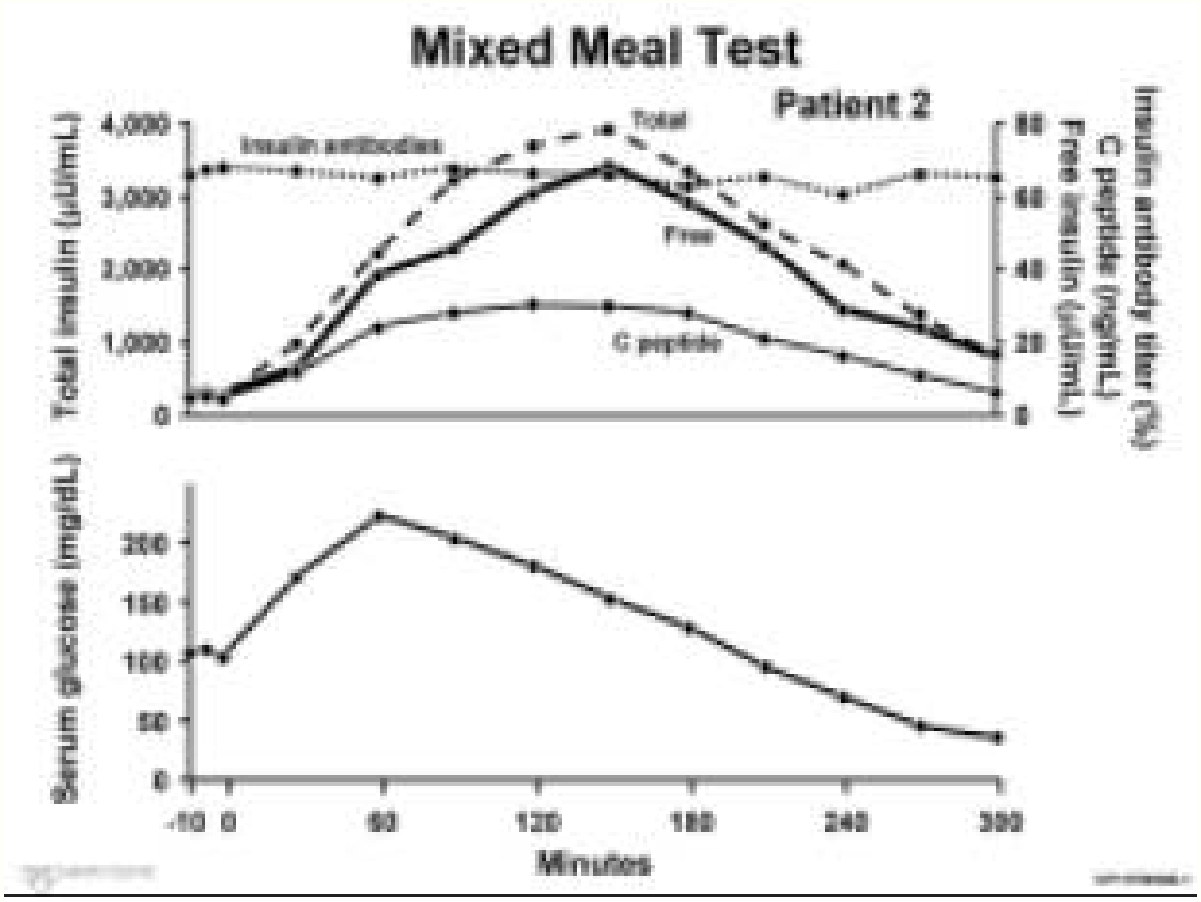
- sulfhydryl groups interact with disulfide bonds in the insulin molecule, making the insulin more immunogenic

Insulin Autoimmune Syndrome

- ***Diagnosis***
  - The presence of **a high insulin level (>100 mU/L)** and an **incompletely suppressed C-peptide** concentration during hypoglycemia
  - Insulinoma - insulin level usually < 100 muU/mL
  - With exogenous insulin injection > 100 muU/mL,
    the C-peptide concentration is very low
  - A history of autoimmune disease, exposure to a sulfhydryl-containing medication
  - Presence of IAA (or IA)

Insulin Autoimmune Syndrome

- Altered insulin kinetics
- prolonged peak and delayed decline of insulin



Insulin Autoimmune Syndrome

- ***Course and Treatment***
  - In Uchigata's review of 197 cases from Japan, 82% of patients experienced spontaneous remissions within 3 to 6 months of diagnosis
  - Most cases of IA and hypoglycemia occur in the setting of autoimmune disease with or without precipitating drugs
  - For these patients, the hypoglycemia is usually transient and resolves spontaneously without permanent sequelae
  - Possible offending medications should be stopped

Insulin Autoimmune Syndrome

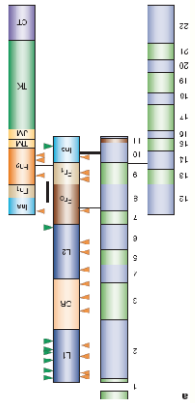
- ***Course and Treatment***
  - In patients with severe or prolonged symptoms and in patients with IA owing to monoclonal gammopathy
    - spontaneous remission would not be expected
    - various therapies have been tried
  - frequent small meals (~6/day)
  - low carbohydrate diet
  - acarbose therapy
  - steroid therapy (prednisolone 30 to 60 mg/day)
  - plasmapheresis

Type B insulin resistance

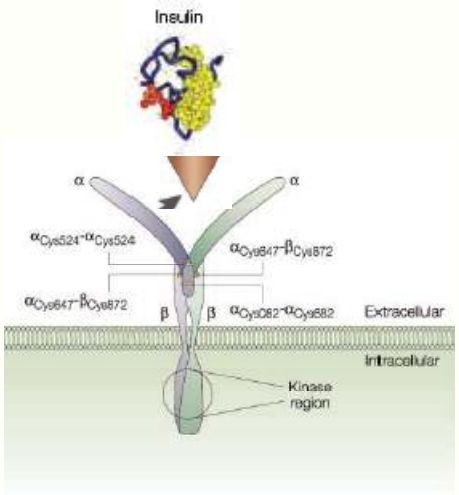
Type B insulin resistance

- In 1975, Flier reported six women with an extreme insulin resistance and acanthosis nigricans

  - In type A insulin resistance :
    a primary defect in the insulin receptor

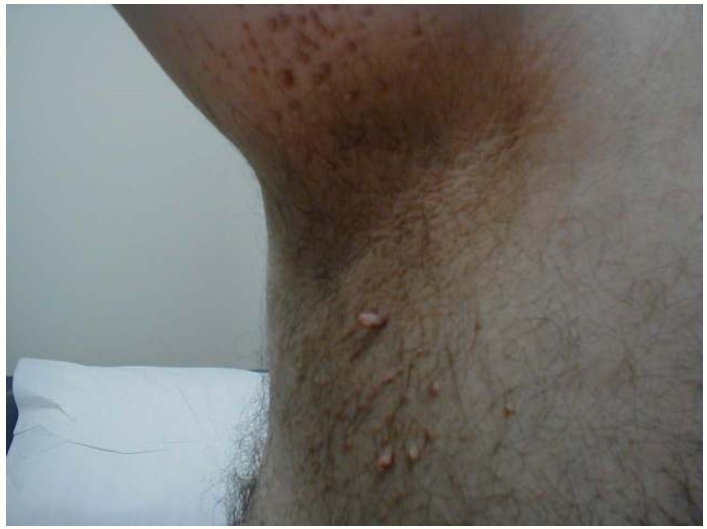


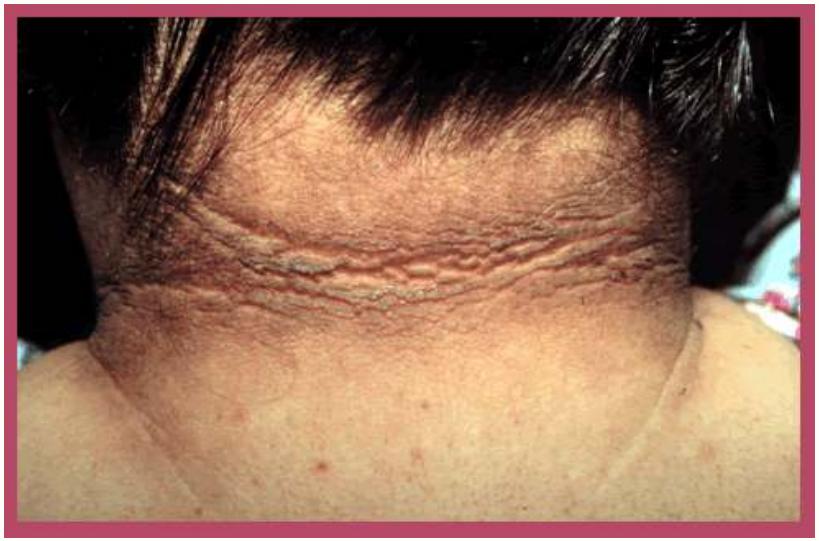
  - In type B insulin resistance :
    insulin receptor antibodies (IR-A)
    present in the circulation inhibited
    insulin binding to the insulin receptor



Type B insulin resistance

- ***Clinical Presentation***
  - Severe insulin resistance with acanthosis nigricans (95%)
  - Either fasting or postprandial hypoglycemia
  - Female predominance
  - History of autoimmune disease, Hodgkin's disease
  - Hypoglycemia at low-titer of IR-A



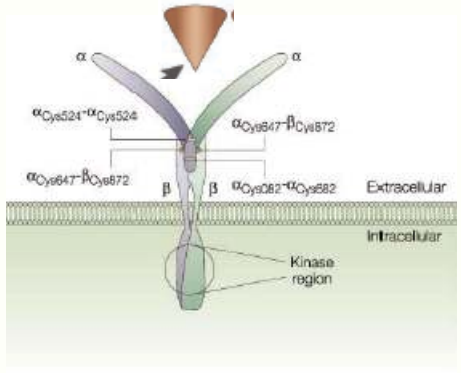


Type B insulin resistance

- ***Laboratory Findings***
  - Hypoglycemia may be severe(15~30 mg/dL)
  - Insulin levels - inappropriately high
  - C-peptide levels - appropriately low during hypoglycemia
  - Low TG, high adiponectin, polyclonal IgG
  - Elevated variable autoantibodies including antinuclear, antithyroid, antimitochondrial, and antiplatelet antibodies - suggestive of subclinical autoimmune disease
- The absence of any of these laboratory findings in a patient with IR-A and hypoglycemia should prompt a search for Hodgkin's disease

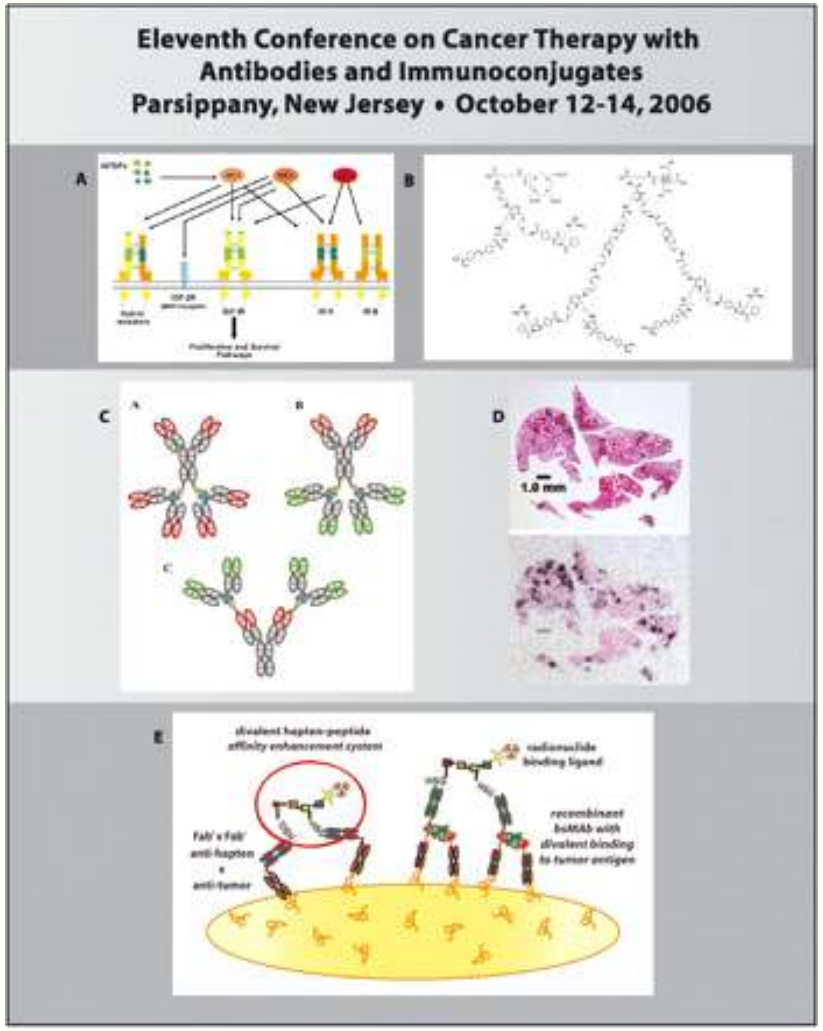
Type B insulin resistance

- ***Pathogenesis of Hypoglycemia***
- IR-A for hyperglycemia
  - insulin antagonist in high titer
  - accelerated receptor degradation
  - receptor downregulation
- IR-A for hypoglycemia
  - insulin agonist in low titer



Type B insulin resistance

- IR-A
  - Polyclonal IgGs, which may be composed of various subpopulation of immunoglobulins with varying agonist or antagonist activity toward the insulin receptor
  - In support of this hypothesis, Sesti and co-workers demonstrated that two IgG subfractions from a patient with IR-A and hypoglycemia differed in their ability to inhibit insulin binding to the two distinct human insulin receptor subtypes



Sesti G, Diabetes. 1992

Type B insulin resistance

- **"Spare receptor hypothesis"**
  - When IR-A titers are relatively low, insulin agonist effects may be near maximal with little effect on insulin receptor degradation rate or receptor number, as only a small fraction of insulin receptors are occupied
  - When IR-A titers are high, binding of IR-A to receptors is near maximal, resulting in receptor downregulation, decreased receptor number, insulin resistance, and hyperglycemia

Type B insulin resistance

- ***Diagnosis***
  - The diagnosis of hypoglycemia owing to IR-A requires the demonstration of IR-A in the serum
  - The immunoprecipitation assay is considered the more sensitive test for detecting IR-A because it will detect IR-A that bind to the receptor at sites other than the insulin-binding site
  - IA are usually negative, although low titers may be present in subjects treated with insulin during a preceding hyperglycemic phase

Type B insulin resistance

- ***Course and Treatment***
  - Hypoglycemia in association with IR-A
    - a high mortality rate owing to progressive autoimmune disease, malignancy, or hypoglycemia
  - Because of this risk and the severity of the hypoglycemia, aggressive therapy is often warranted
  - High-dose steroid therapy (prednisone, 1 mg/kg/d to 120 mg/d) seems to be the most effective therapy
  - Hypoglycemia may respond rapidly to steroid therapy well before any change in IR-A titers is noted

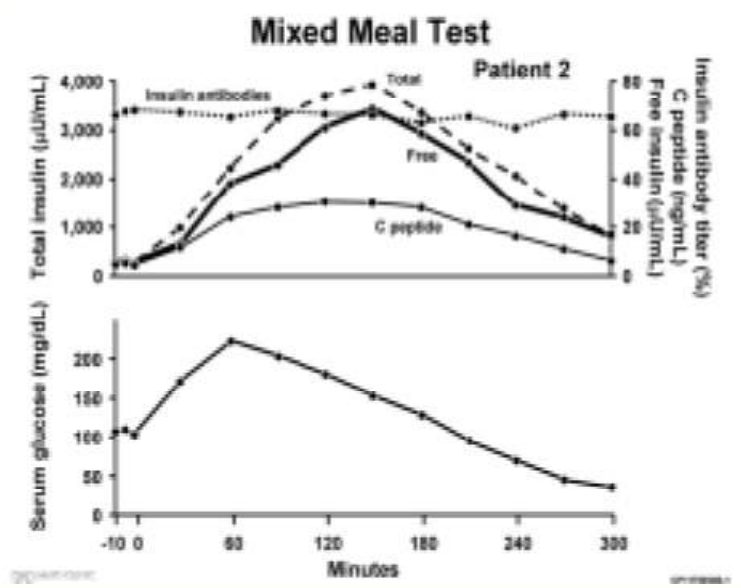
Type B insulin resistance

- ***Course and Treatment***
  - Some patients remain in remission, whereas others may require chronic therapy
  - Plasmapheresis and immunosuppressive therapy with cyclophosphamide have been employed to reduce IR-A titers but with less consistent results
  - Plasmapharesis can dramatically lower IR-A titers; however, the effect is transient, and the impact on clinical parameters may not match the decline in antibody level

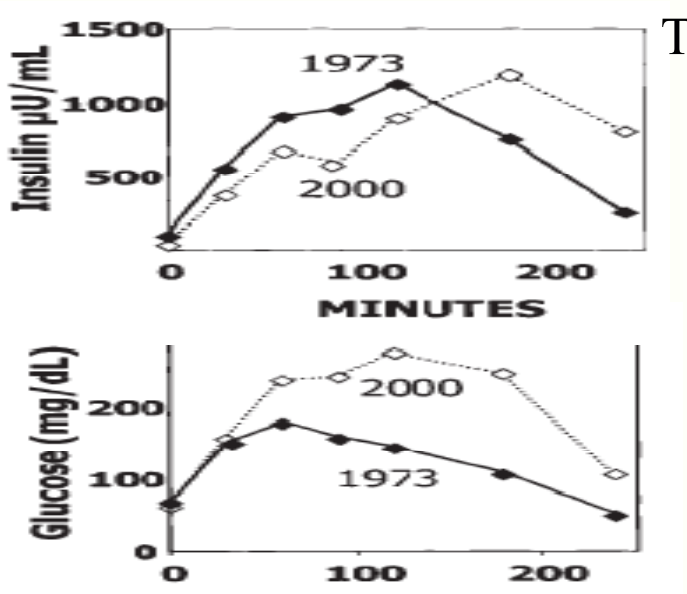
Summary

Feature	Autoimmune Hypoglycemia	Insulinoma
Hypoglycemia	Fasting, reactive, both	Fasting*
48 h fast	Variable	Positive
Insulin	Very high	High
C-peptide	Very high	High
Proinsulin	Very high	High
Anti-insulin or insulin receptor antibodies	Positive	Negative
Sulfonylurea screening	Negative	Negative
Imaging	Negative	Positive
Selective arterial calcium stimulation test	Negative	Positive
Association	Hematologic and rheumatologic diseases, medication induced	MEN type 1

IAS

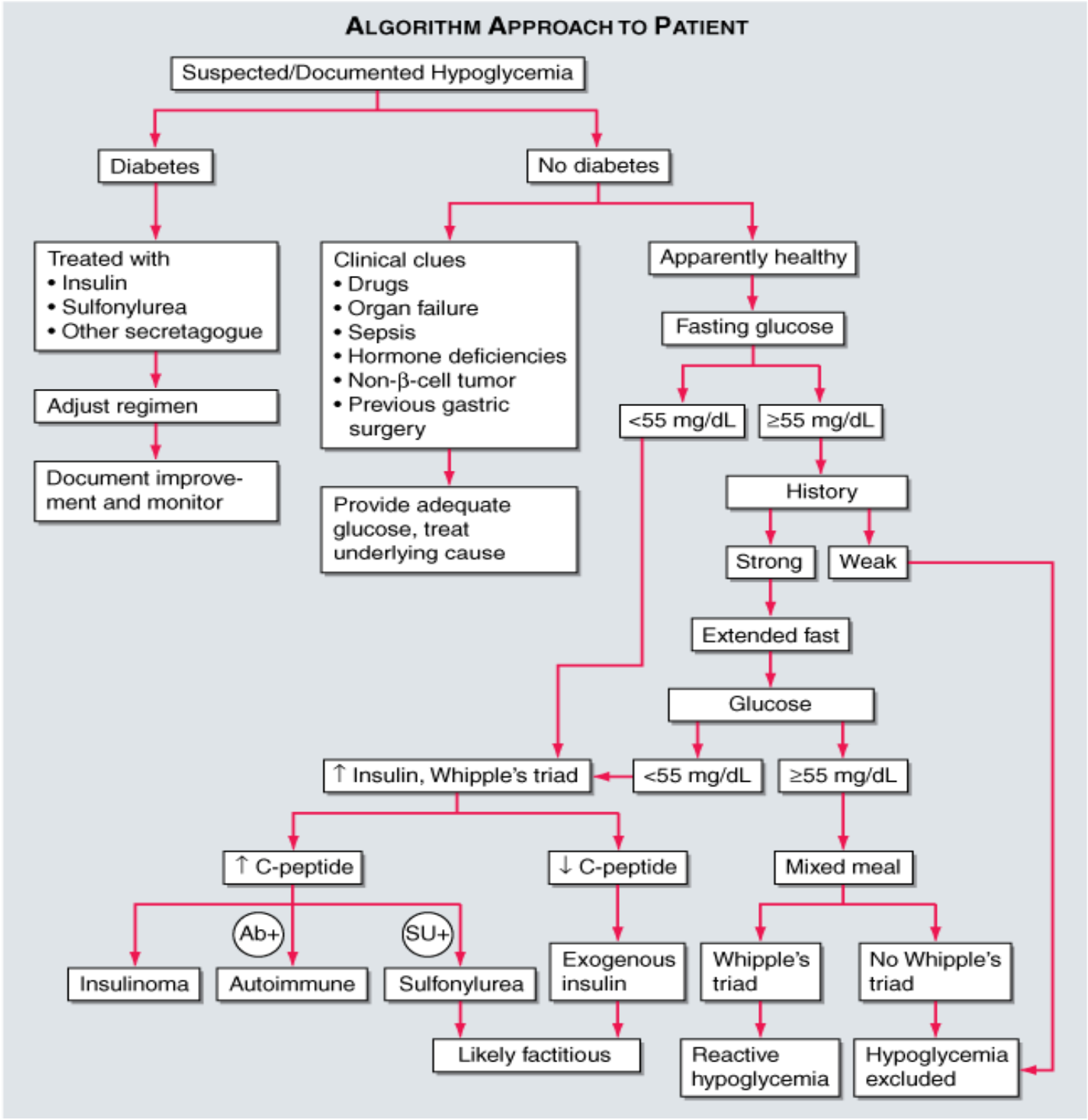


Type B IR



Summary

Feature	Insulin Autoimmune Syndrome	Type B Insulin Resistance
Type of hypoglycemia	Fasting, reactive, both	Fasting; reactive uncommon
Hyperglycemia	Variable	Common
Insulin level	Very high	High
C-peptide level	Very high	High
Proinsulin level	Very high	High
Sex	Men and women	Mostly women
Age (yr)	40–80	40–50
Race	Mostly white	Black
Acanthosis nigricans	Rare	Common
Hyperandrogenism	No	Common
Underlying rheumatologic disease	Yes	Common
Underlying hematologic disease	Yes	Common
Medication induced	Yes	No
Insulin autoantibodies	Universal	Usually no*
Insulin receptor antibodies	Usually no*	Universal
Response to therapy	Usually good	Variable/poor


ALGORITHM APPROACH TO PATIENT
Suspected/Documented Hypoglycemia
Diabetes
No diabetes
Treated with
• Insulin
• Sulfonylurea
• Other secretagogue
Adjust regimen
Document improve-ment and monitor
Clinical clues
• Drugs
• Organ failure
• Sepsis
• Hormone deficiencies
• Non-β-cell tumor
• Previous gastric surgery
Provide adequate glucose, treat underlying cause
Apparently healthy
Fasting glucose
<55 mg/dL
≥55 mg/dL
History
Strong
Weak
Extended fast
Glucose
<55 mg/dL
≥55 mg/dL
↑ Insulin, Whipple's triad
↑ C-peptide
↓ C-peptide
Mixed meal
Ab+
SU+
Insulinoma
Autoimmune
Sulfonylurea
Exogenous insulin
Whipple's triad
No Whipple's triad
Likely factitious
Reactive hypoglycemia
Hypoglycemia excluded

Conclusion

- Autoimmune forms of hypoglycemia are uncommon
- However, they should be considered in any patient with hypoglycemia in the setting of unsuppressed insulin levels
- Although not essential for the diagnosis, the coexistence of a separate autoimmune or hematologic disease should be sought in patients with a diagnosis of autoimmune hypoglycemia

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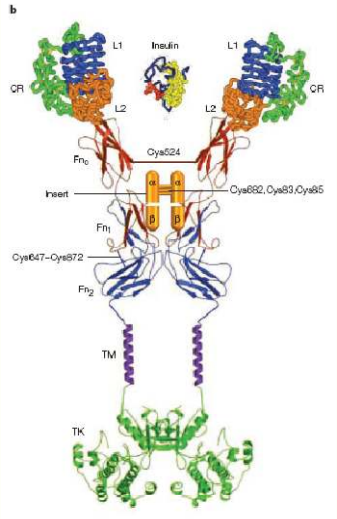
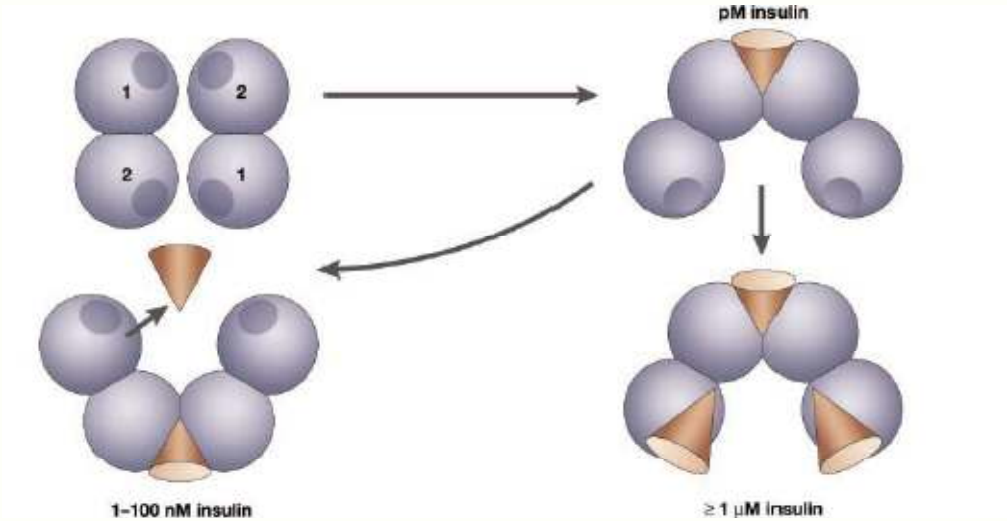
Insulin immunogenecity





- Insulin autoantibodies(IA)
  - 1% to 8% of healthy subjects without diabetes or autoimmune disease
  - 40% of newly diagnosed type 1 diabetic patients
  - 30% of nondiabetic patients with other autoimmune disease
  - 10% of patients receiving alpha-interferon for chronic viral hepatitis

Di Cerbo A, J Endocrinol Invest. 1995

Palmer J, Diabetes Metab Rev. 1987

Di Mario U, Acta Endocrinol. 1990

Wilkin TJ, Endocr Rev. 1990

Insulin Autoimmune Syndrome

- ***Laboratory Findings***
- IA & IAA - undistinguishable in insulin-treated diabetic patients

- IAA usually bind equally well to human, beef, and pork insulins, although cases of IA with binding specificity restricted to human insulin have been reported

Insulinoma

- Pancreatic β-cell tumors that secrete Insulin
- Small,solitary, benign(< 10% malignant)

Inability of insulinoma cells to suppress insulin secretion during low levels of circulating glucose, leading to severe hypoglycemia

Diagnosis and Tumor Localization

- Very high Insulin levels
- spiral CT, arteriography, ultrasonography

Treatment of Choice

- Enucleation
- Recurrence at 10 yrs is 6% and 20 yrs is 10%

Interpretation of values after 72 hour test

Insulin	C Peptide	Proinsulin	Sulfonylurea	Insulin Antibody	Diagnosis
↑	↓	↓	–	–	Exogenous insulin
↑	↑	↑	–	–	Insulinoma, CHI
↑	↑	↑	+	–	Sulfonylurea
↑	↑	↑	–	+	Insulin autoimmune
± ↑	↓	↓	–	–	Insulin receptor autoimmune

Target autoantigens in type 1 diabetes mellitus

Glutamic acid decarboxylase (GAD)
Insulin autoantibody (IAA)
Insulinoma –associated protein 2 (IA-2)
Carboxypeptidase H, PM-1 polar antigen
Islet cell proteins of varying size and unknown function - 37 or 40 kD, 38 kD, 52 kD, 69 kD
Peripherin
Heat shock protein 65
Insulin receptor
Endocrine cell antigens
Cytoskeletal proteins - tubulin, actin, reticulin
Nuclear antigens - single-stranded DNA and RNA

Autoantibody :

GADA (antibody to glutamic acid decarboxylase)--- β-cell destruction early marker

ICA (islet cell autoantibody)—specificity low

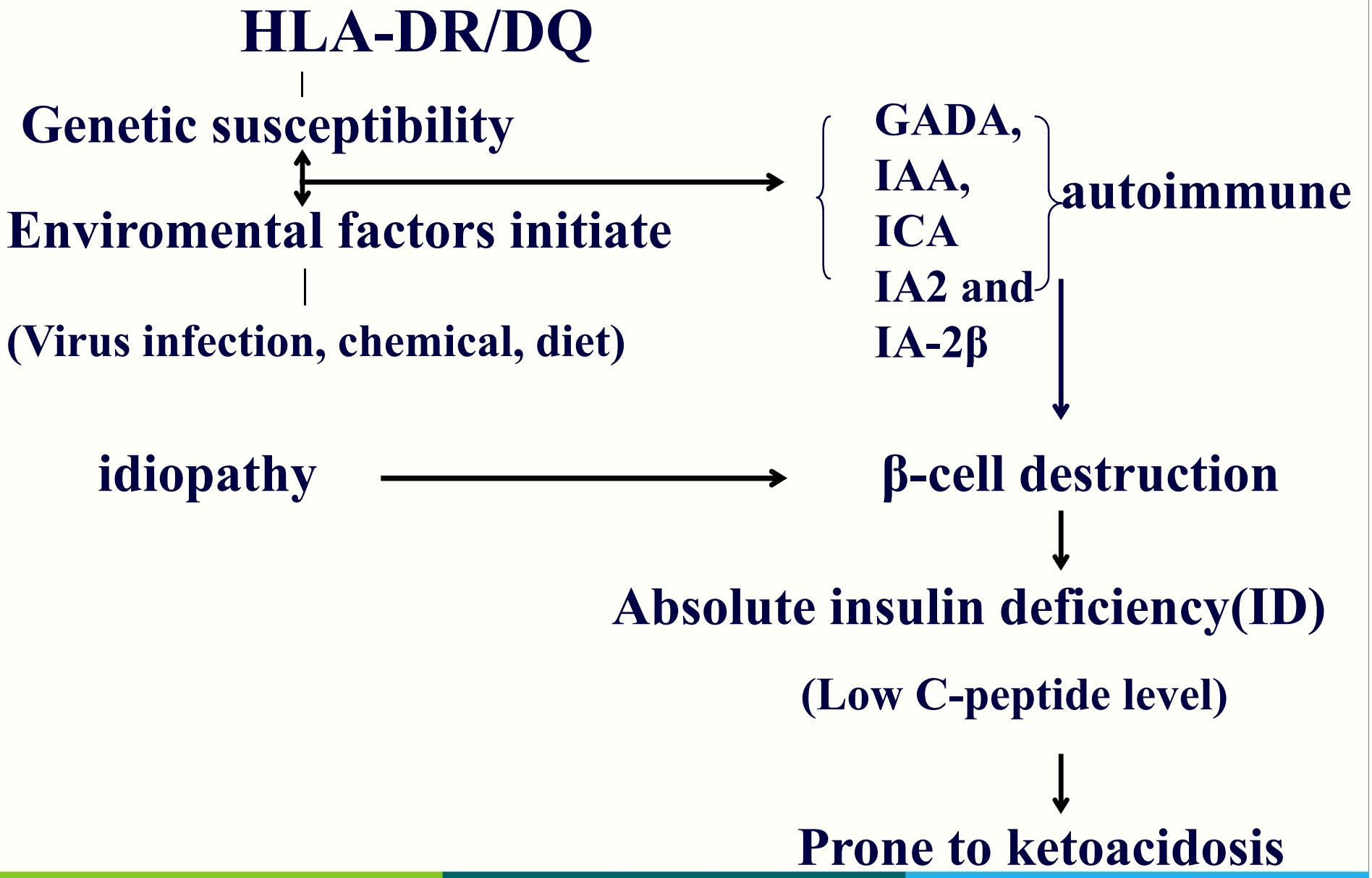
IAA (autoantibody to insulin) —specificity low

IA-2 (autoantibody to tyrosine phosphatases IA-2 andIA-2β)---specificity high

Target autoantigens in type 1 diabetes mellitus

- **Insulin auto antibody (IAA)**
  - The early appearance of anti-insulin antibodies suggests that insulin is an important autoantigen
  - Confirmed at 1993, from studies in NOD mice
- **Glutamic acid decarboxylase (GAD)**
  - found in about 70 percent of patients with type 1 diabetes at the time of diagnosis
- **Insulinoma-associated protein 2 (IA-2)**
  - neuroendocrine protein called insulinoma-associated protein 2, which is a protein tyrosine phosphatase
  - 58 percent of patients with type 1 diabetes at the time of diagnosis
  - usually appear later than IAA and GAD, and are highly associated with expression of multiple anti-islet autoantibodies and progression to diabetes

Type 1 DM Pathogenesis



Introduction

- IA have also been demonstrated with lispro insulin therapy and in women receiving short-term human insulin therapy for gestational diabetes

- IA induced in response to insulin therapy are typically polyclonal IgGs with two classes of binding sites
  - sites with high affinity/low capacity (Ka 10^{7} M^{-1} , b10^{-9} M)
  - sites with low affinity/high capacity (Ka 10^{7} M^{-1} , b10^{-7} M)