An Approach to Diabetes

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Diabetes and Metabolism

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Featuring……

- Definition
- Diagnosis
- Metabolic syndrome concept
- Classification
- Case scenarios

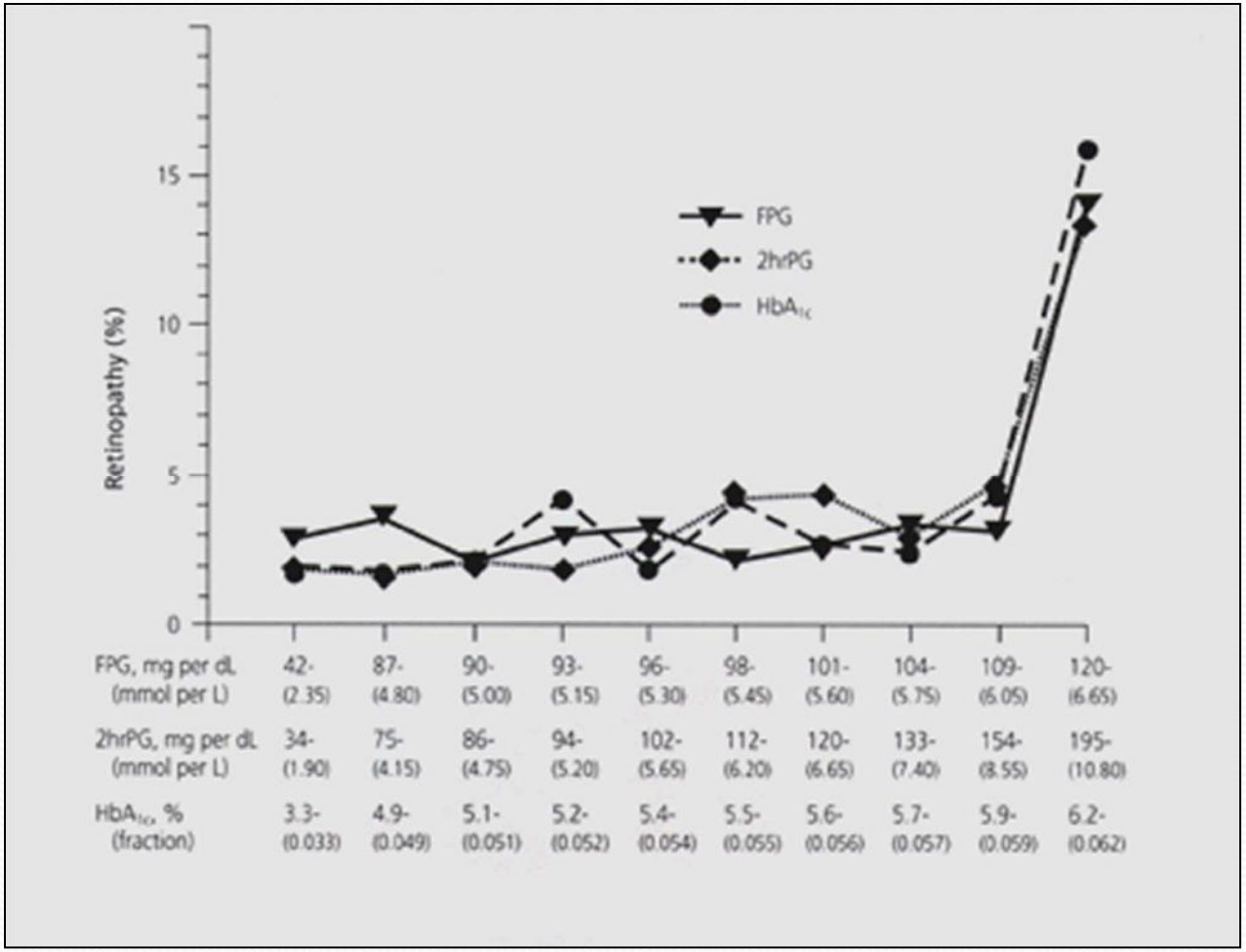
Definition

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both.

Diagnosis and Classification of Diabetes Mellitus
American Diabetes Association
Diabetes Care 28: 2005

Prevalence of retinopathy by deciles of the distribution of FPG, 2hrPPG and HbA_{1C}

The cut-off level for FPG has been defined, based on the sharp increase in the micro vascular complications when the plasma glucose crosses this level



National Health And Nutritional Epidemiologic Survey (NHANES III)

Criteria for diagnosis

- **Fasting ≥ 126 mg% on one occasion**

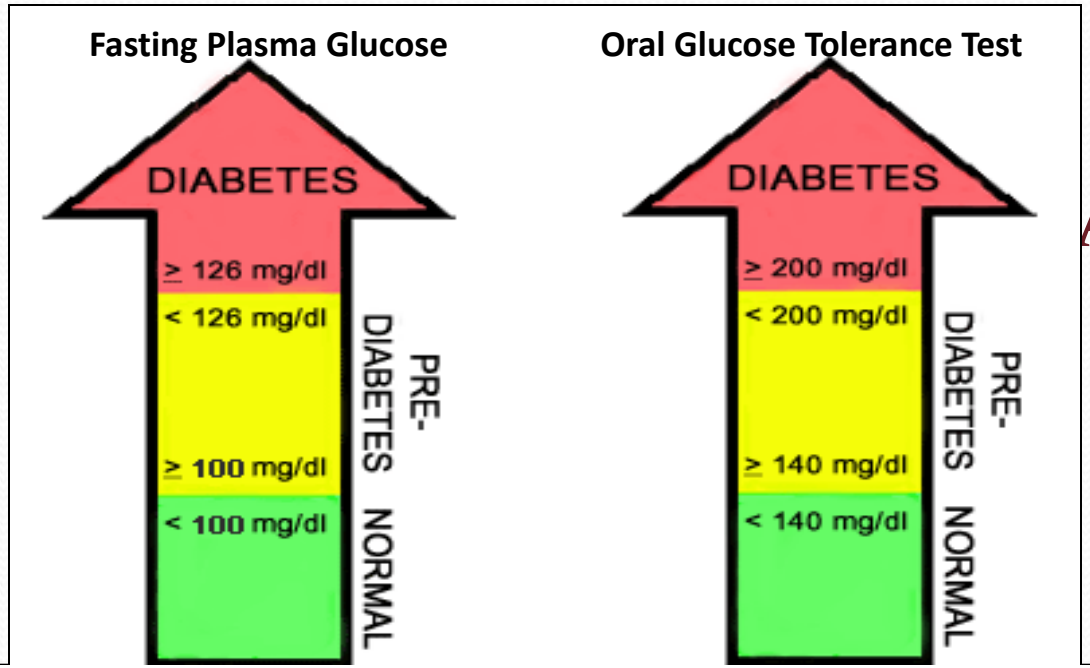
OR

- **Postprandial ≥ 200 mg% on one occasion with symptoms or Check a second time if with out symptoms**
- **OR**

HbA1c >6.5%

Additions…

- Impaired fasting Glycaemia (IFG) 100 - 125 mg%
- Impaired Glucose Tolerance (IGT) 140 – 199 mg%
- Hba1C 6.0-6.5%



ADA criteria)

Advantages of A1C Testing Compared With FPG or 2HPG for the Diagnosis of Diabetes

Standardized and aligned to the DCCT/UKPDS

Better index of overall glycemic exposure and risk for long-term complications

Substantially less biologic variability

Substantially less pre-analytic instability

No need for fasting or timed samples

Relatively unaffected by acute perturbations in glucose levels

Disadvantages of A1C Testing Compared With FPG or 2HPG for the Diagnosis of Diabetes

Lack of Accuracy and Standardization of HbA1c in India

Expensive

What do the terms

Impaired fasting Glycaemia

AND

Impaired glucose tolerance imply?

It means

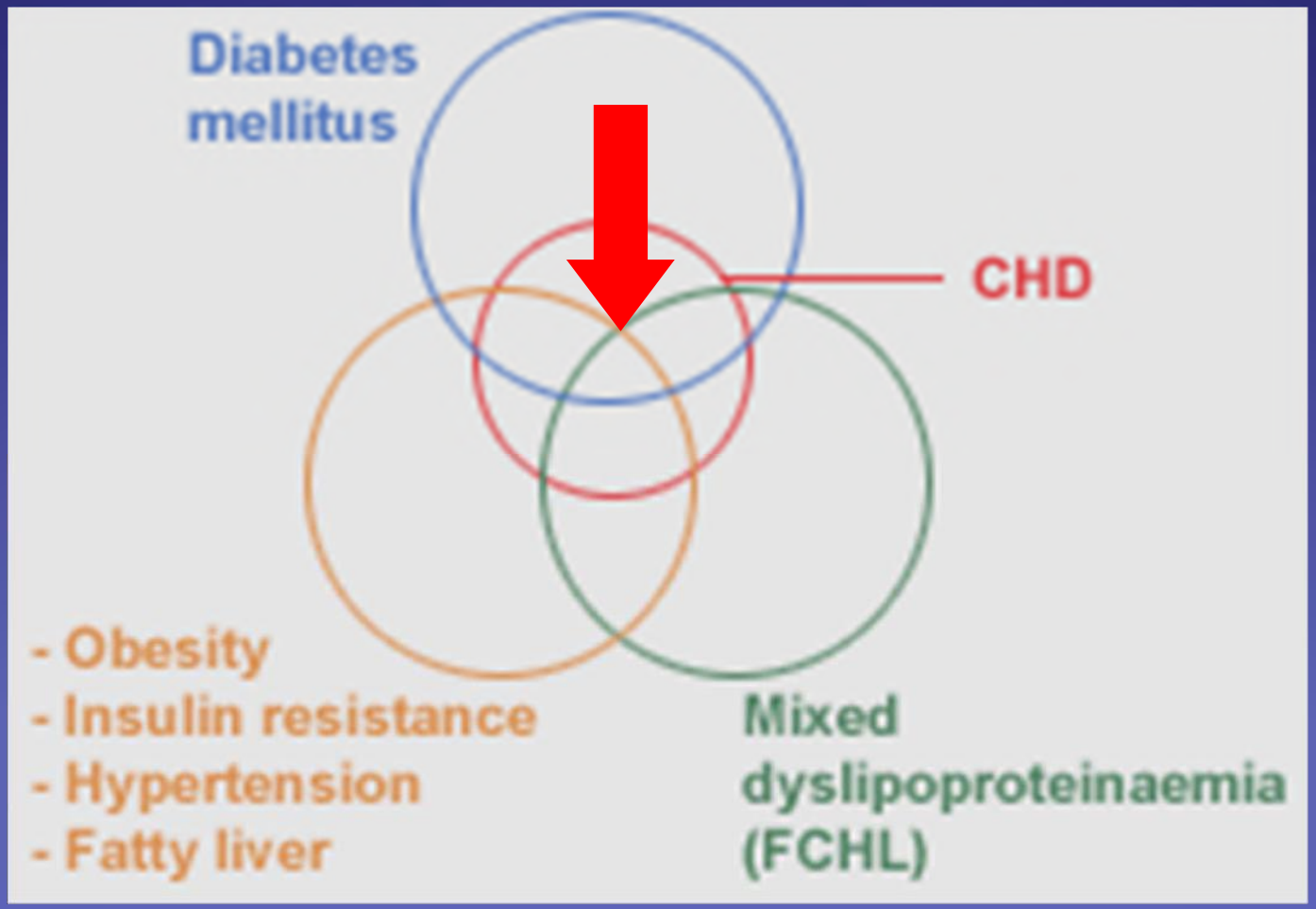
- Increased risk for Cardiovascular /Cerebrovascular disease
- A predictor for subsequent diabetes mellitus
- Diabetic range glucose values unmasked with stress

Vellore Rural Data

- Fasting Plasma Glucose checked in 1995
- Oral Glucose Tolerance Test done in 2006

FPG	.....Relative risk of developing DM
>90mg/dl	1.7
>100mg/dl	3.2
>110mg/dl	6.0

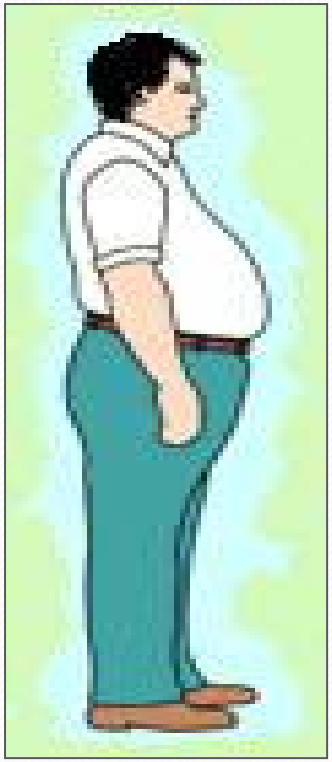
The Concept of the Metabolic Syndrome



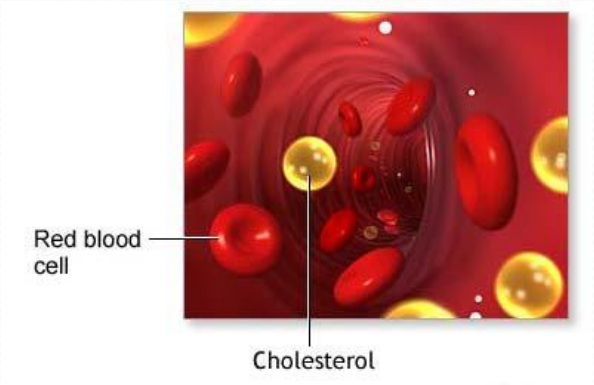
What is the metabolic syndrome ?

(Or Syndrome X or Insulin Resistance Syndrome)

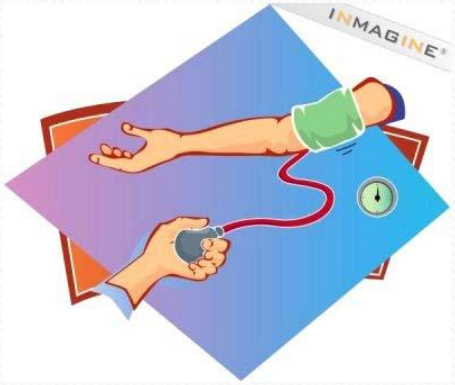
It describes a cluster of CVD risk factors and metabolic alterations associated with excess body fat.



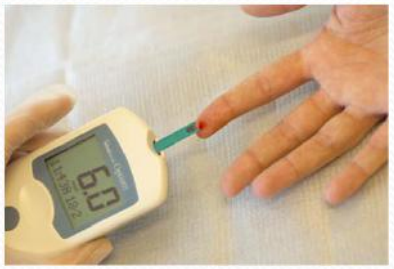
Abdominal obesity



Dyslipidaemia



Hypertension



Glucose Intolerance / Diabetes

ATP III Operational Definition

Occurrence of any 3 of the following abnormalities:

- ↑ Fasting Serum TGL >150 mg/dL
- ↑ Blood pressure (> 130/85 mm Hg)
- Serum Serum HDL Cholesterol
  - ♂ < 40 mg/dL
  - ♀ < 50mg/dL
- ↑ waist circumference
  - ♂ > 102 cm
  - ♀ > 88 cm
- Impaired fasting glucose (≥100 mg/dL)

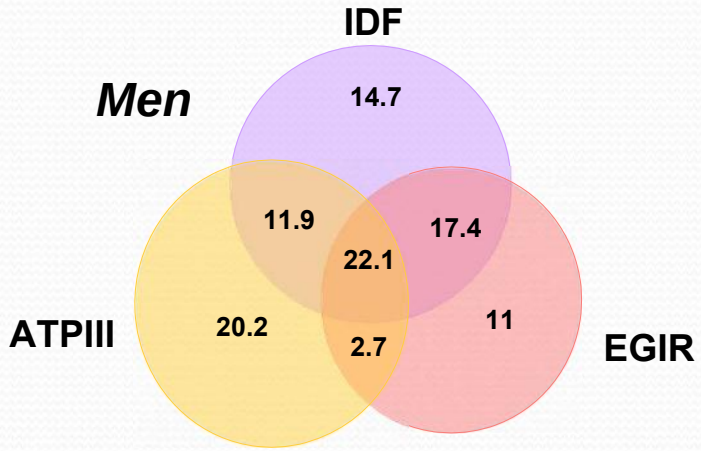
WHO Definition

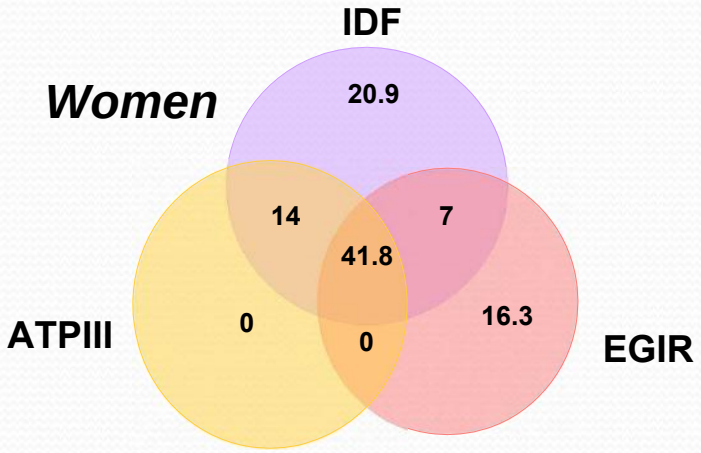
IGT / IFG/T2DM + any of the two below

- ↑ waist: hip ratio
  - 🚹 > 0.9
  - 🚺 > 0.85
- Elevated Blood Pressure > 140/90 mm Hg
- Elevated Triglycerides > 150mg/dl
- Low HDL cholesterol
- Microalbuminuria

Prevalence of the Metabolic Syndrome

	EGIR %	ATPIII %	IDF %
Women (n=289)	6	7	8
Men (n=279)	13	18	19





Revised IDF Criteria for the Metabolic syndrome

Measure Criteria for Clinical Diagnosis of the Metabolic Syndrome	Categorical cut points
Elevated waist circumference	Population-and country-specific definitions M<88cm F<80cm
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator)	>150 mg/dL
Reduced HDL cholesterol (drug treatment for reduced HDL cholesterol is an alternate indicator)	<40 mg/dL for males and <50 mg/dL for females
Elevated blood pressure (drug treatment for elevated blood pressure is an alternate indicator)	Systolic >130 mm Hg and/or diastolic >85 mm Hg
Elevated fasting glucose (drug treatment for elevated glucose is an alternate indicator)	>100 mg/dL

BMI vs WHR in relation to CHD risk

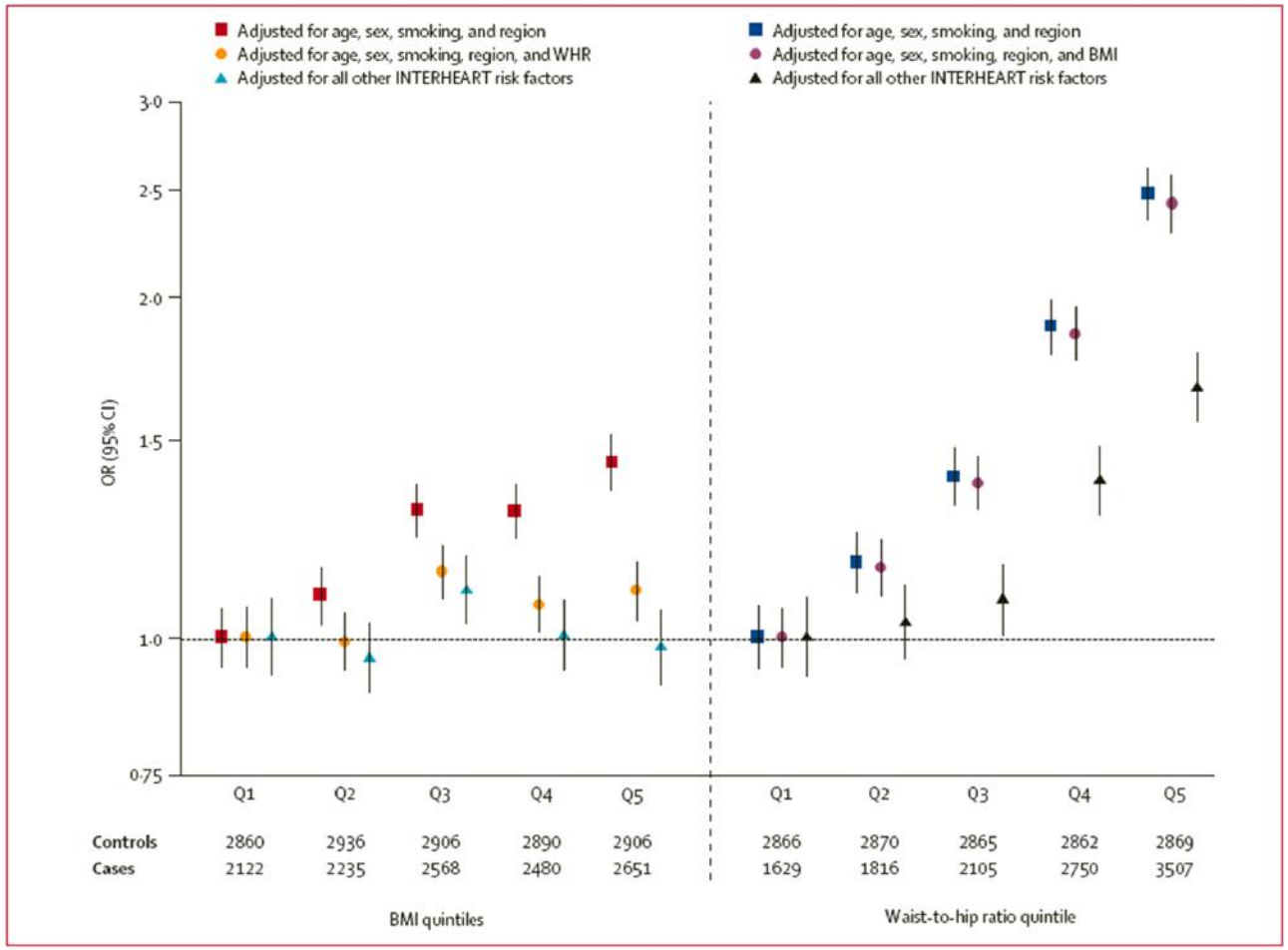
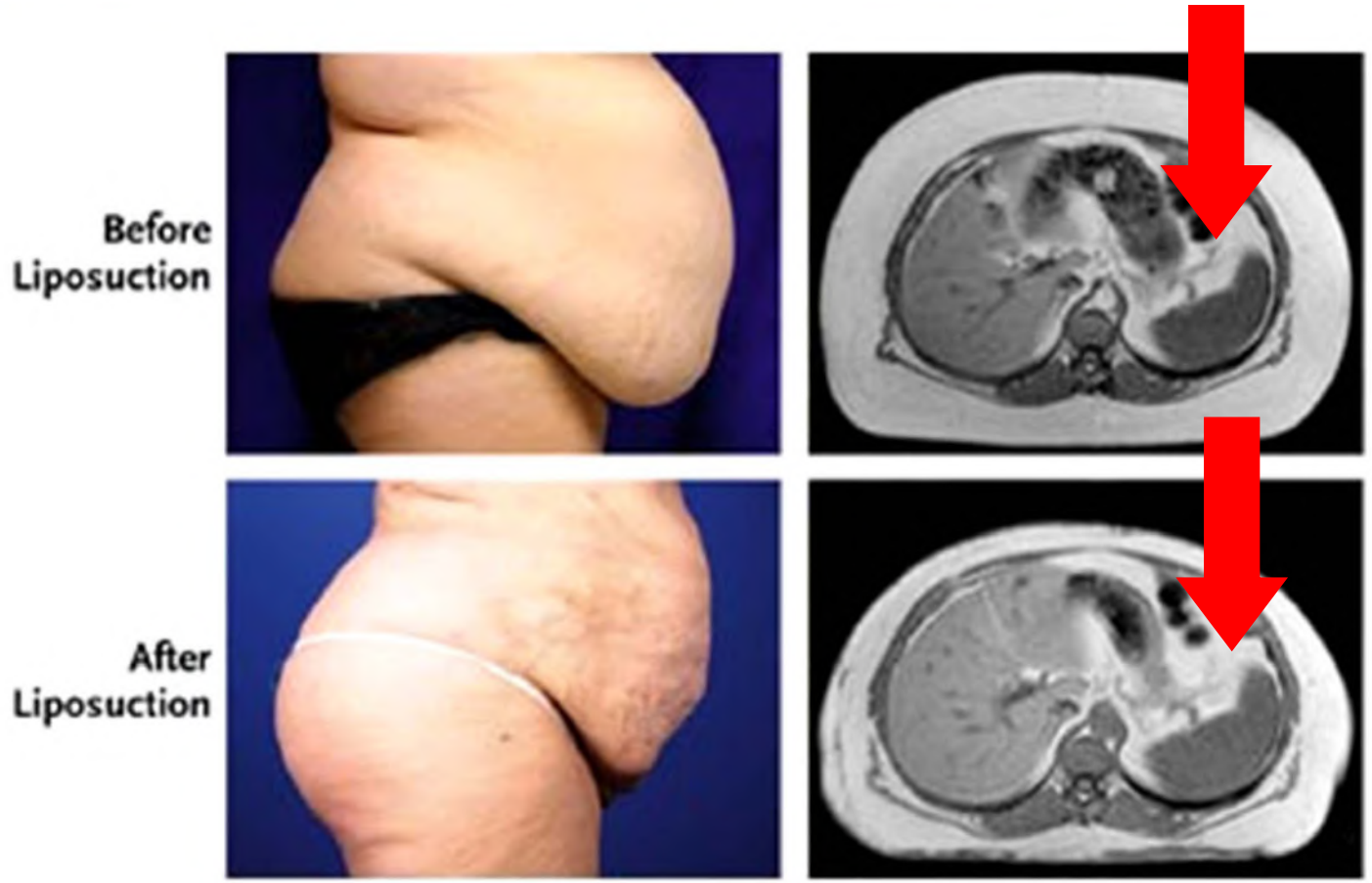


Figure 3: Association of BMI and waist-to-hip ratio with myocardial infarction risk

Yusuf S et al. *Lancet* 2005;366:1640-9



Klein S et al. *NEJM* 2004;350:2549-2557

Classification

- Type 1 Diabetes/LADA
- Type 2 Diabetes
- Other Specific Types
- Gestational Diabetes

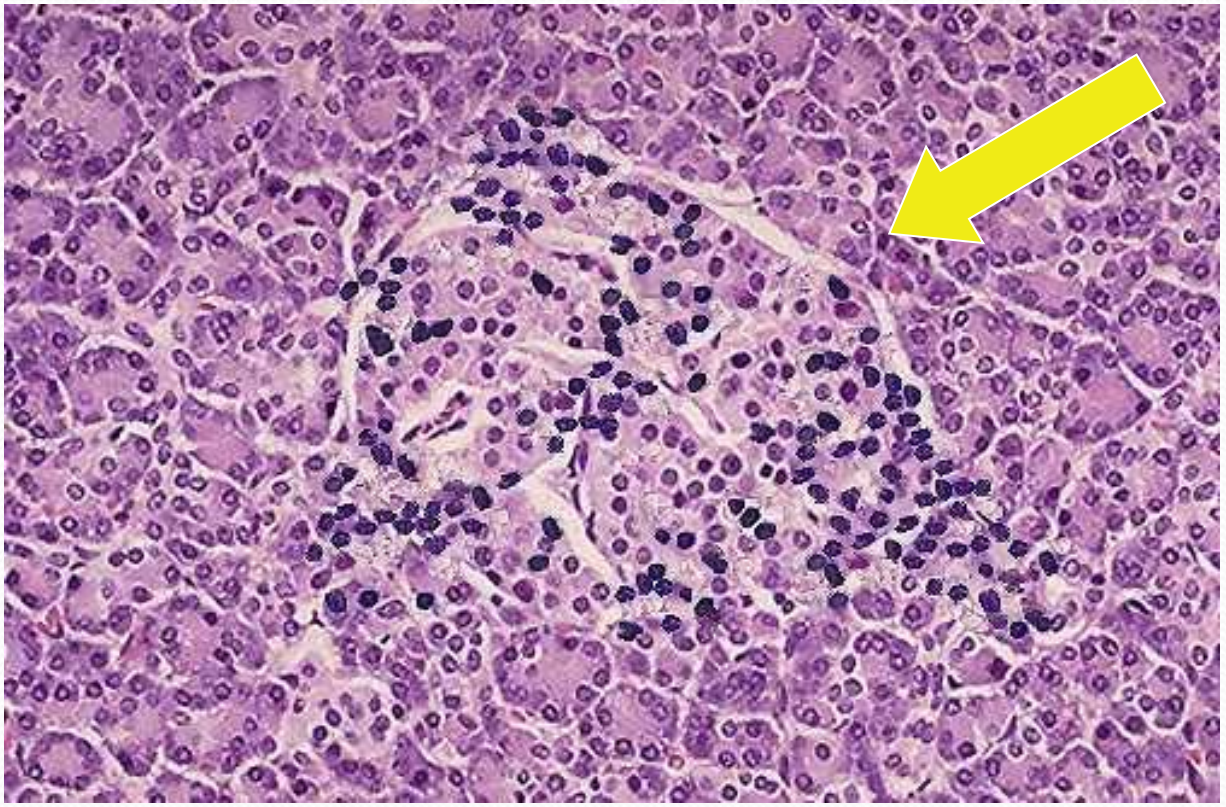
Type 1 Diabetes

ß-cell destruction, leading to absolute insulin deficiency

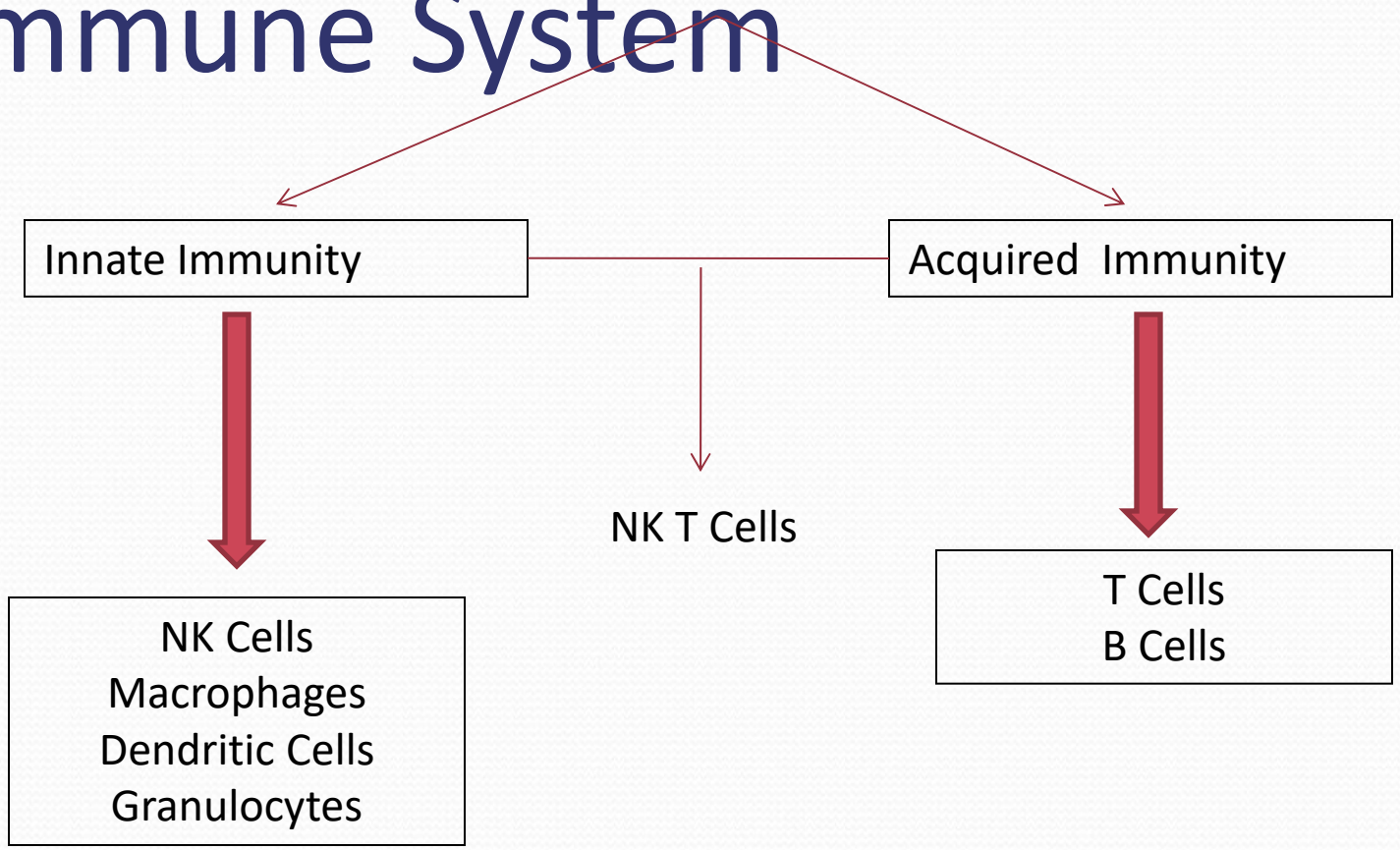
- **Immune-mediated diabetes (common)**
- **Idiopathic diabetes.**

Type 1 Diabetes

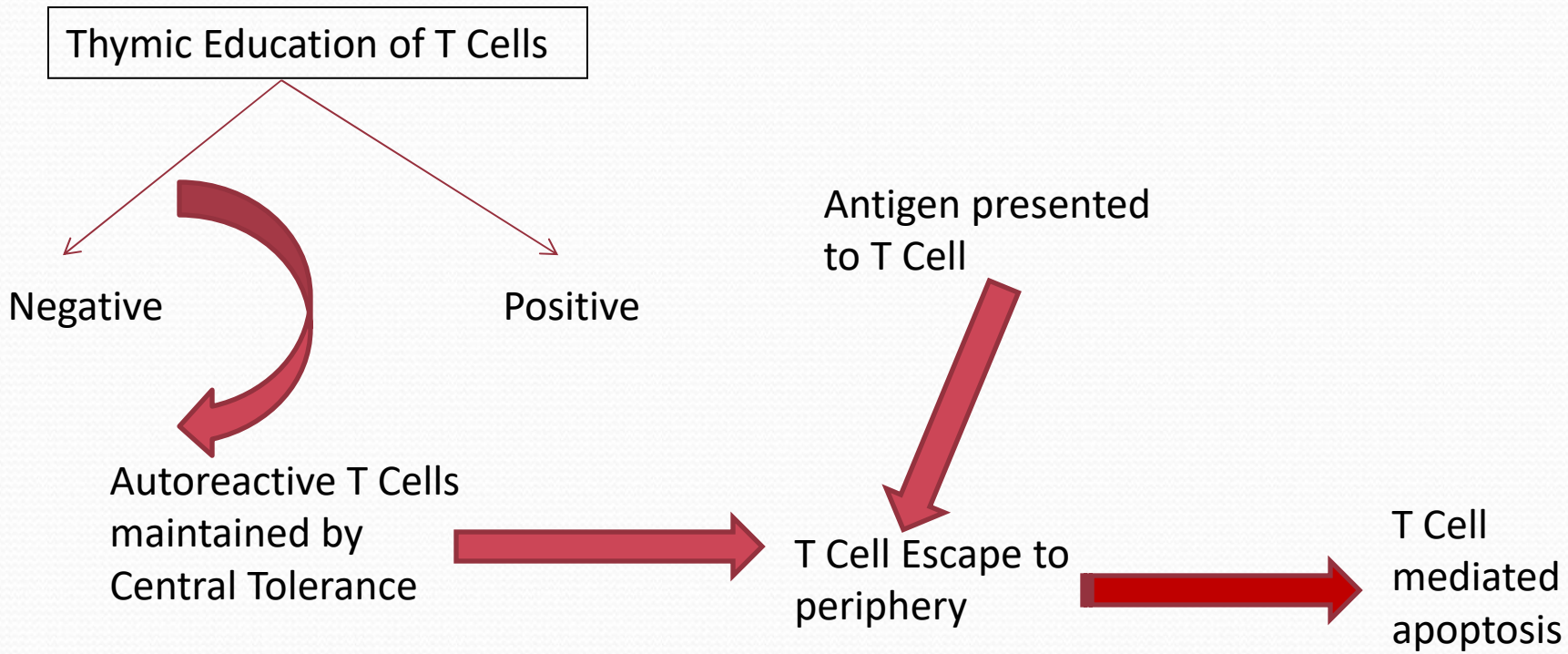
Insulitis



Immune System



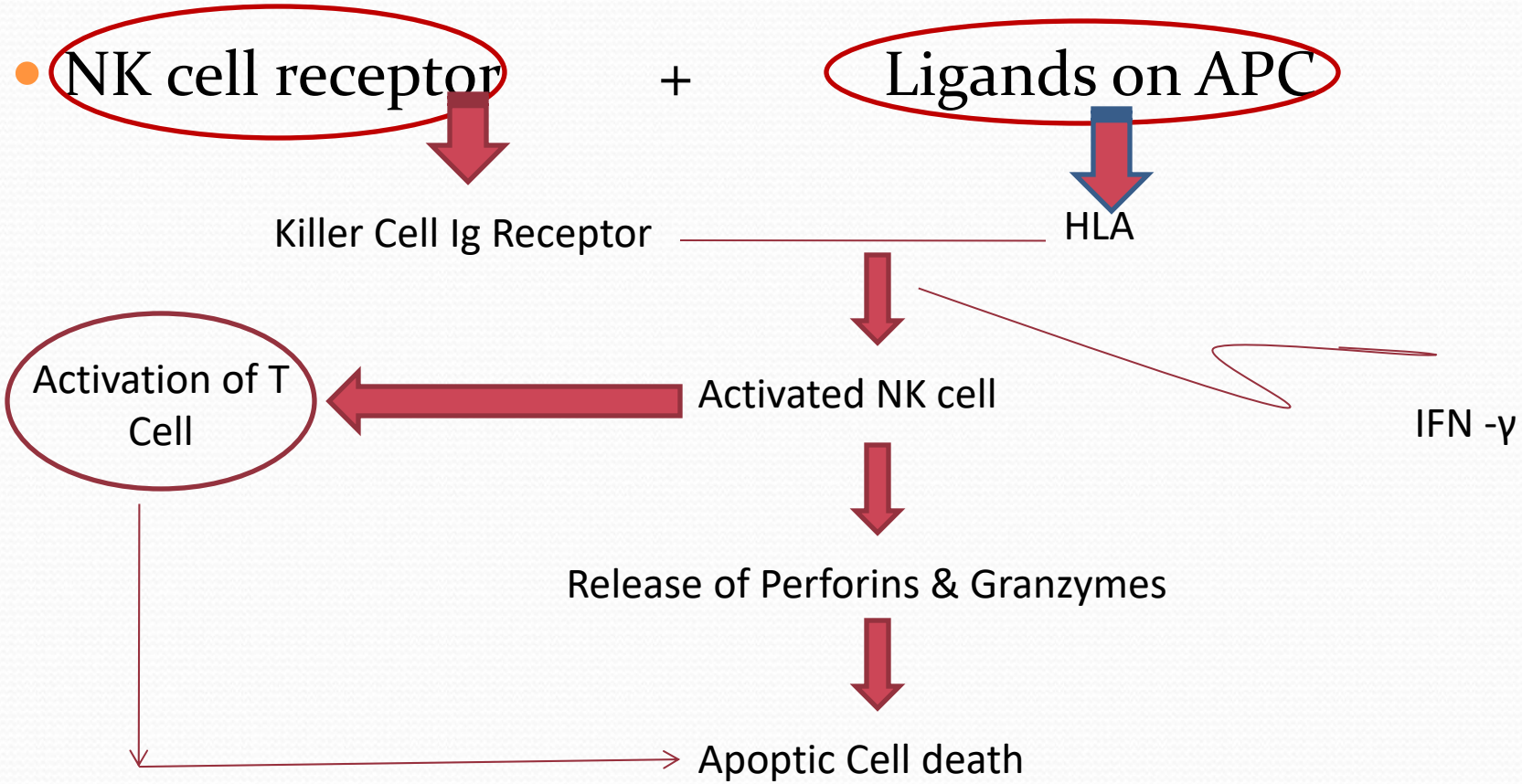
Autoimmune destruction



NK Cells

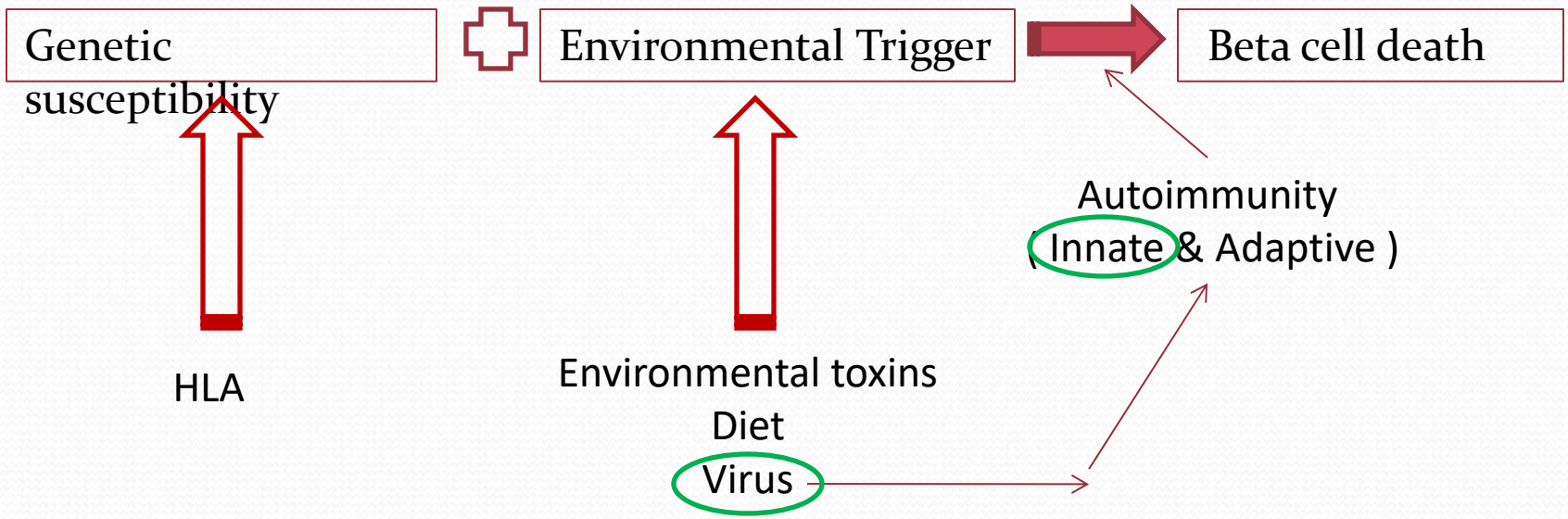
- LGL in peripheral blood – role in tumor immune surveillance and viral infection
- Main role in Innate immunity
- Cytolytic activity - by producing cytokines & ADCC
- Activation markers – CD16, CD 56, CD57, CD94
- Inhibitory markers – CD 158a, CD94
- Effector function mediated by receptor –ligand interaction

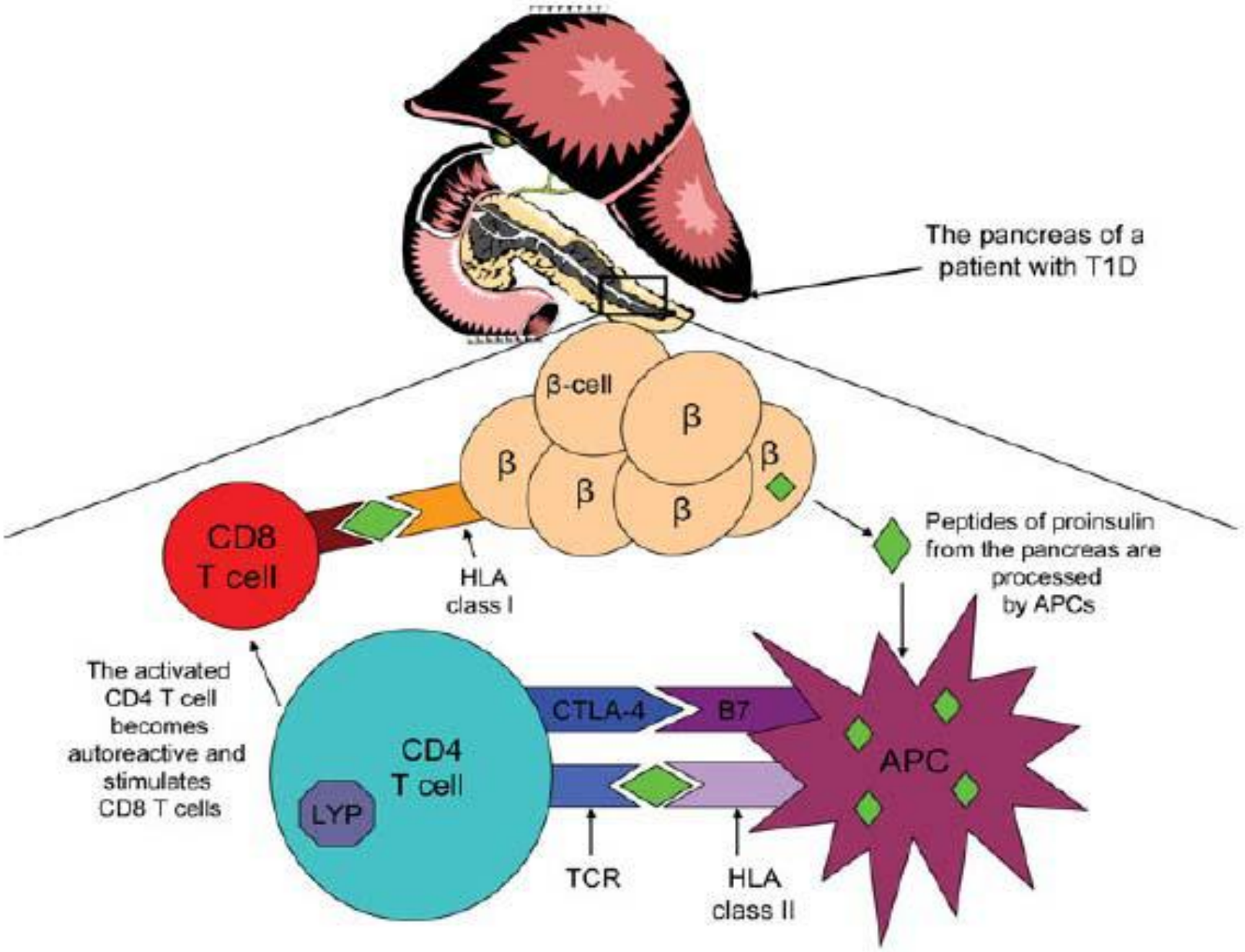
To elicit an autoimune response ……..

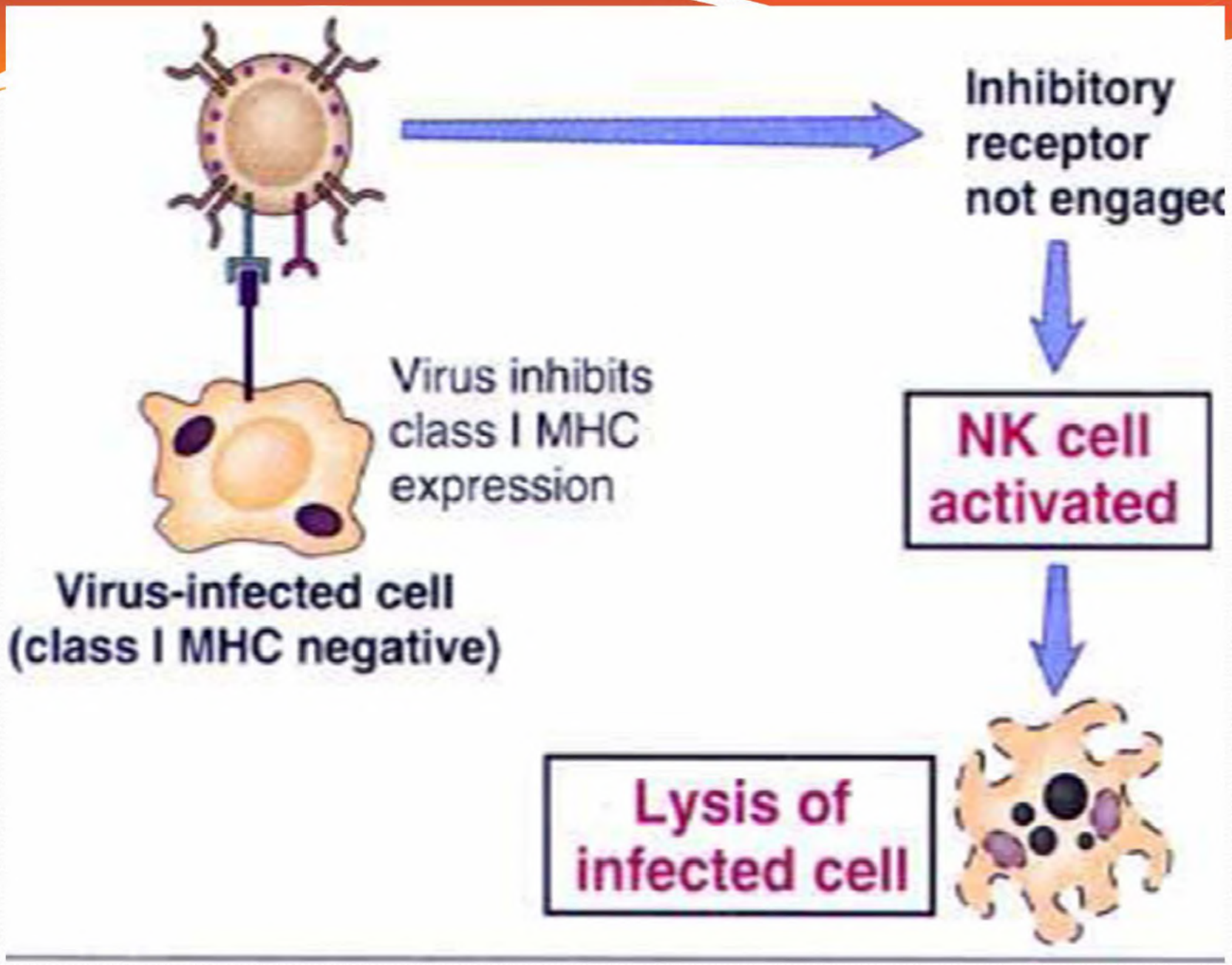


Pancreatic β-cell assault – Is it Innate or acquired ?

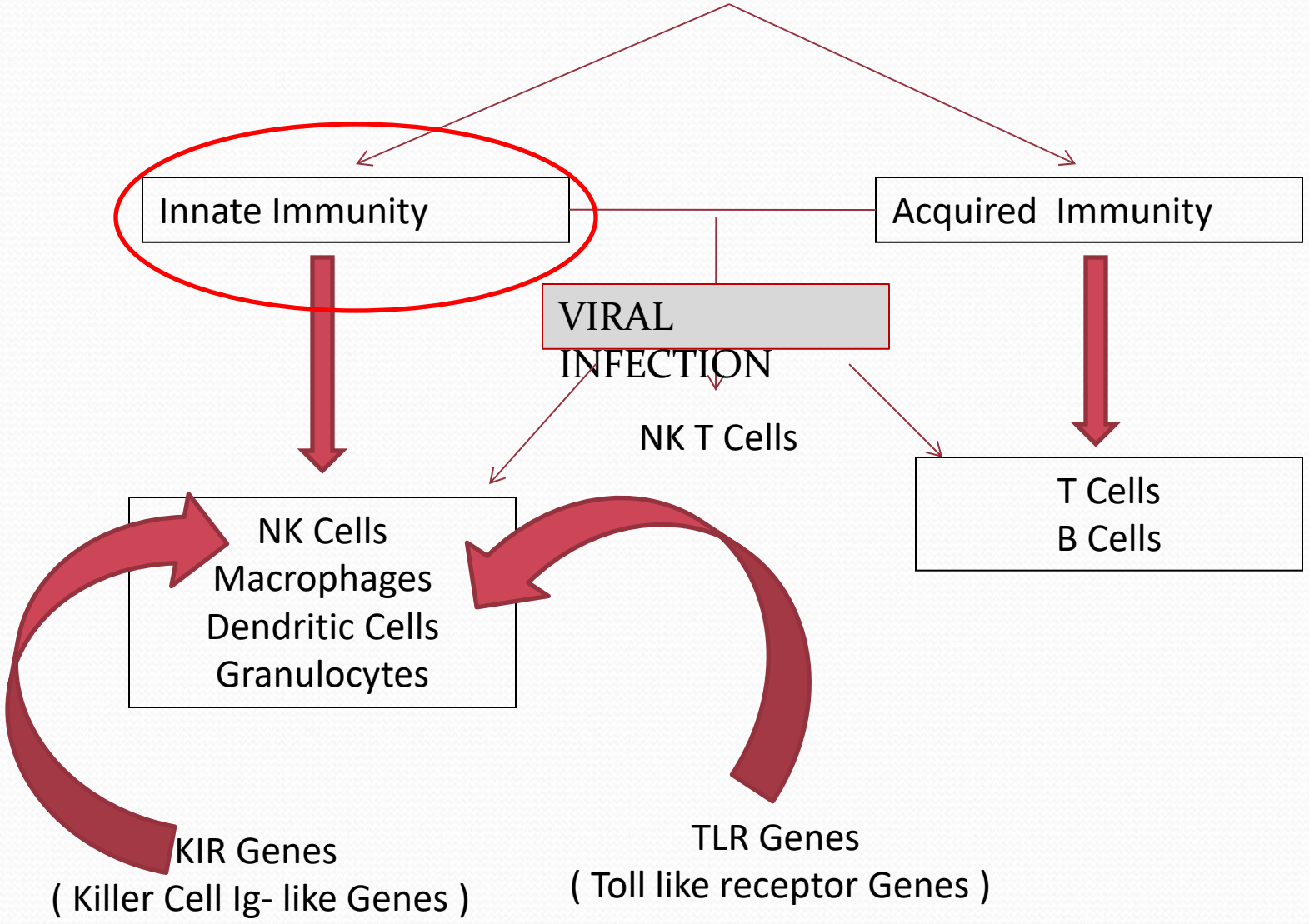
Exact mechanism of trigger for Pancreatic β-cell destruction – NOT KNOWN



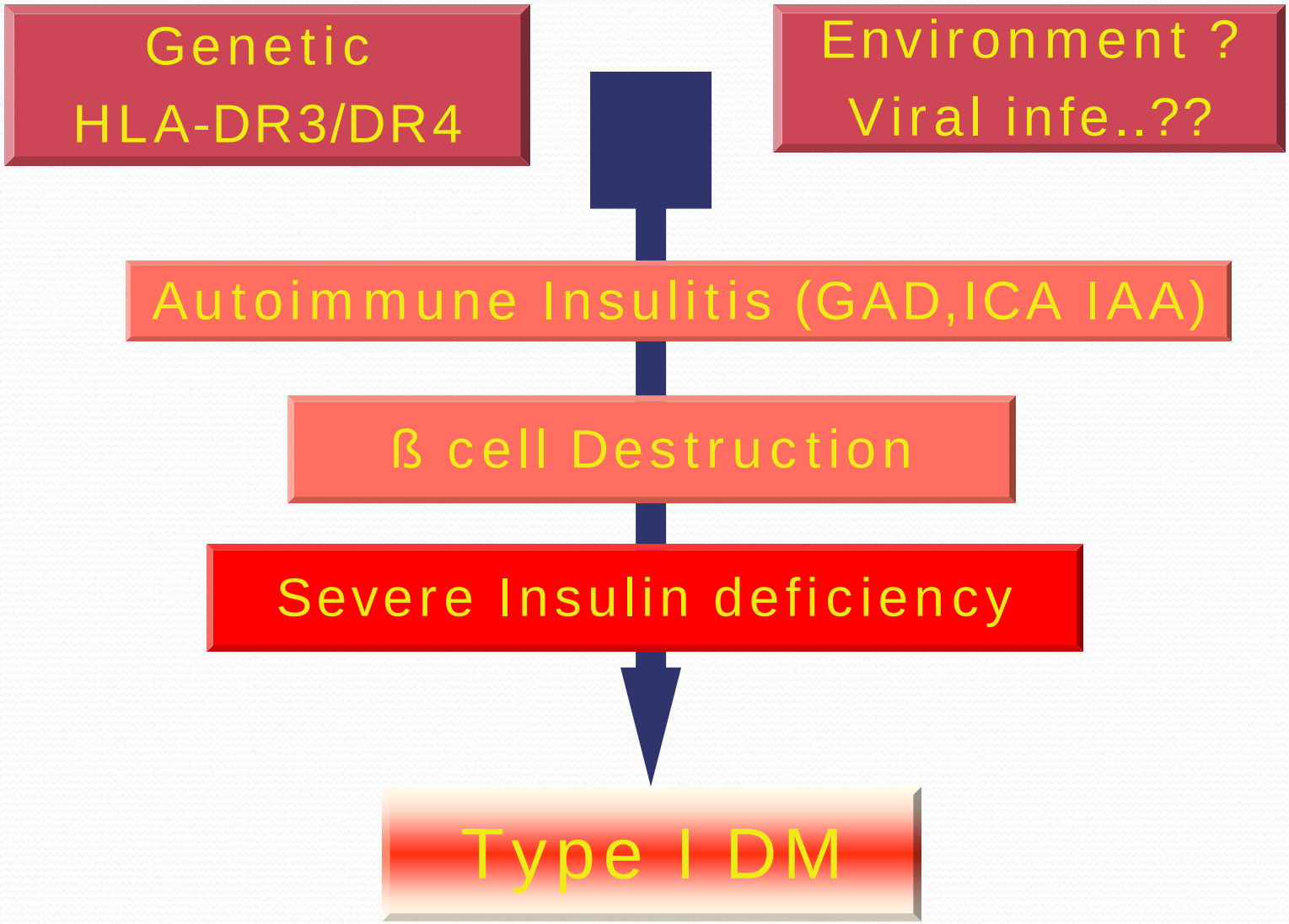

The pancreas of a patient with T1D
β-cell
β
β
β
β
β
CD8 T cell
HLA class I
Peptides of proinsulin from the pancreas are processed by APCs
The activated CD4 T cell becomes autoreactive and stimulates CD8 T cells
CD4 T cell
LYP
CTLA-4
B7
APC
TCR
HLA class II


Inhibitory receptor not engaged
Virus inhibits class I MHC expression
NK cell activated
Virus-infected cell (class I MHC negative)
Lysis of infected cell

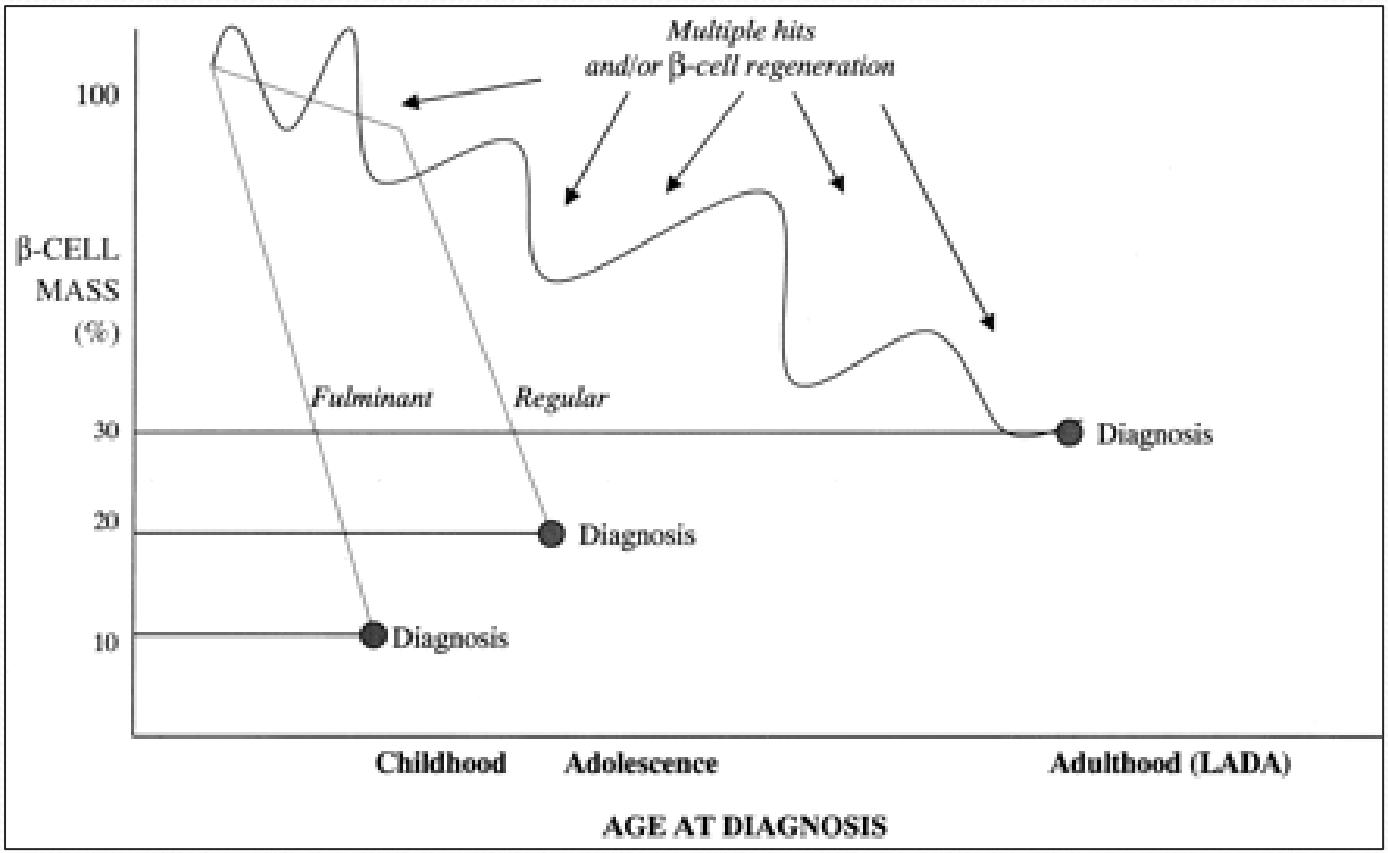
Genes that alter : Immune System



Pathogenesis of Type I DM



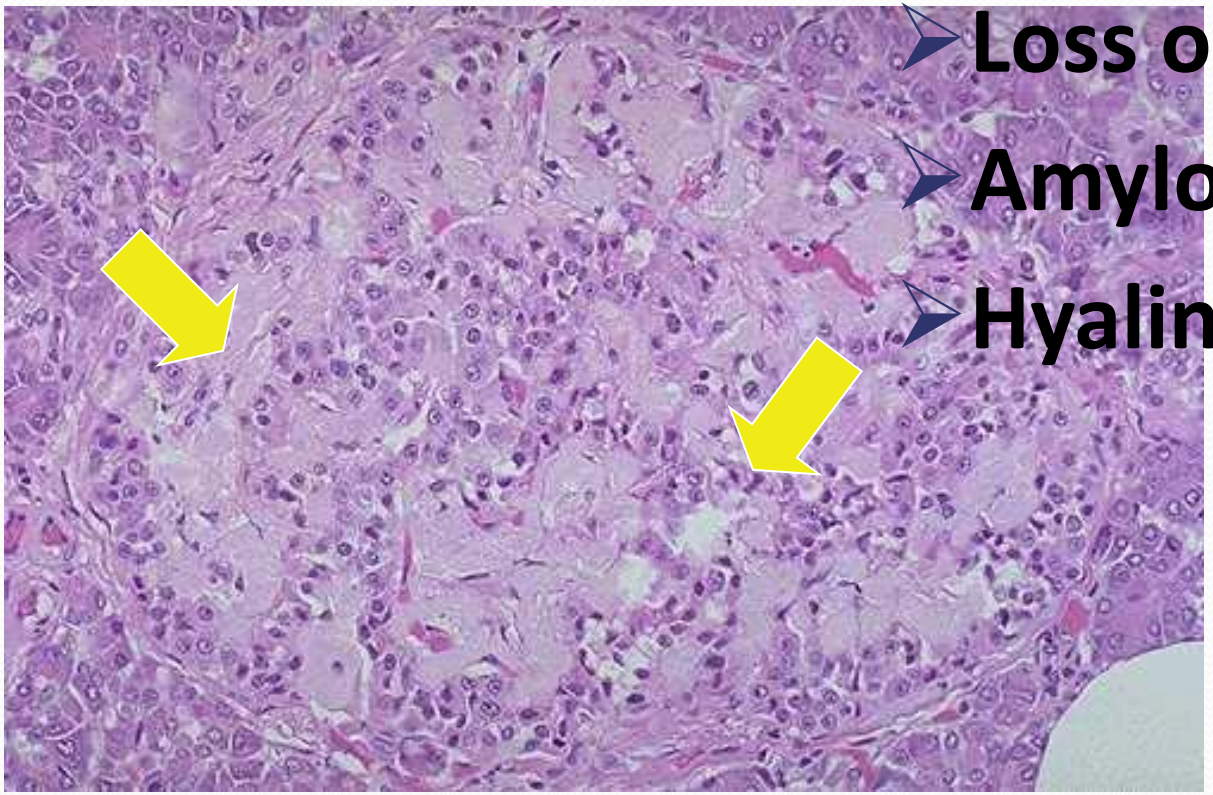
LADA
(Latent Autoimmune Diabetes of the Adult)



Type 2 Diabetes

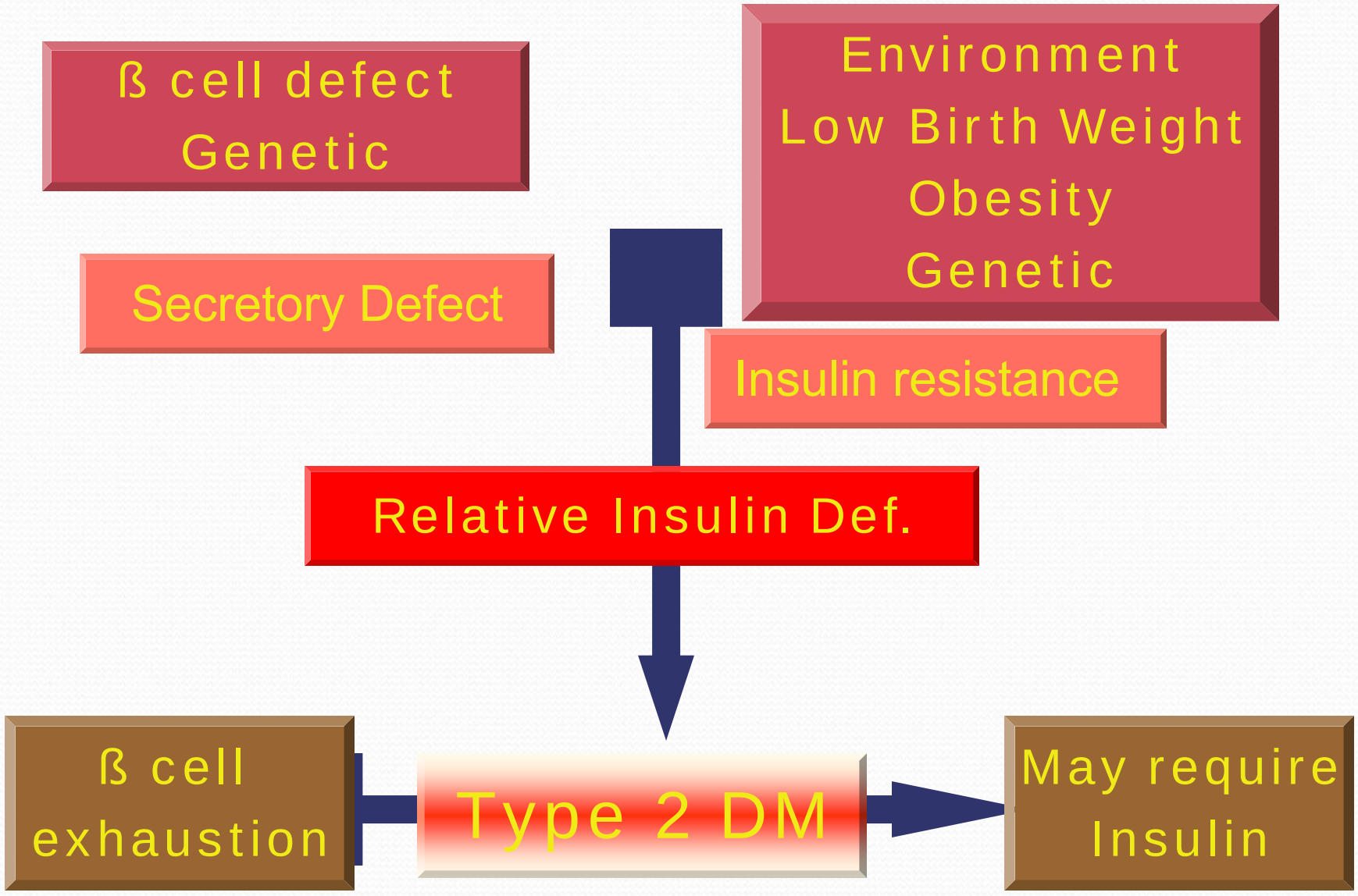
May range from predominantly insulin resistance to predominantly an insulin secretory defect.

Type 2 Diabetes



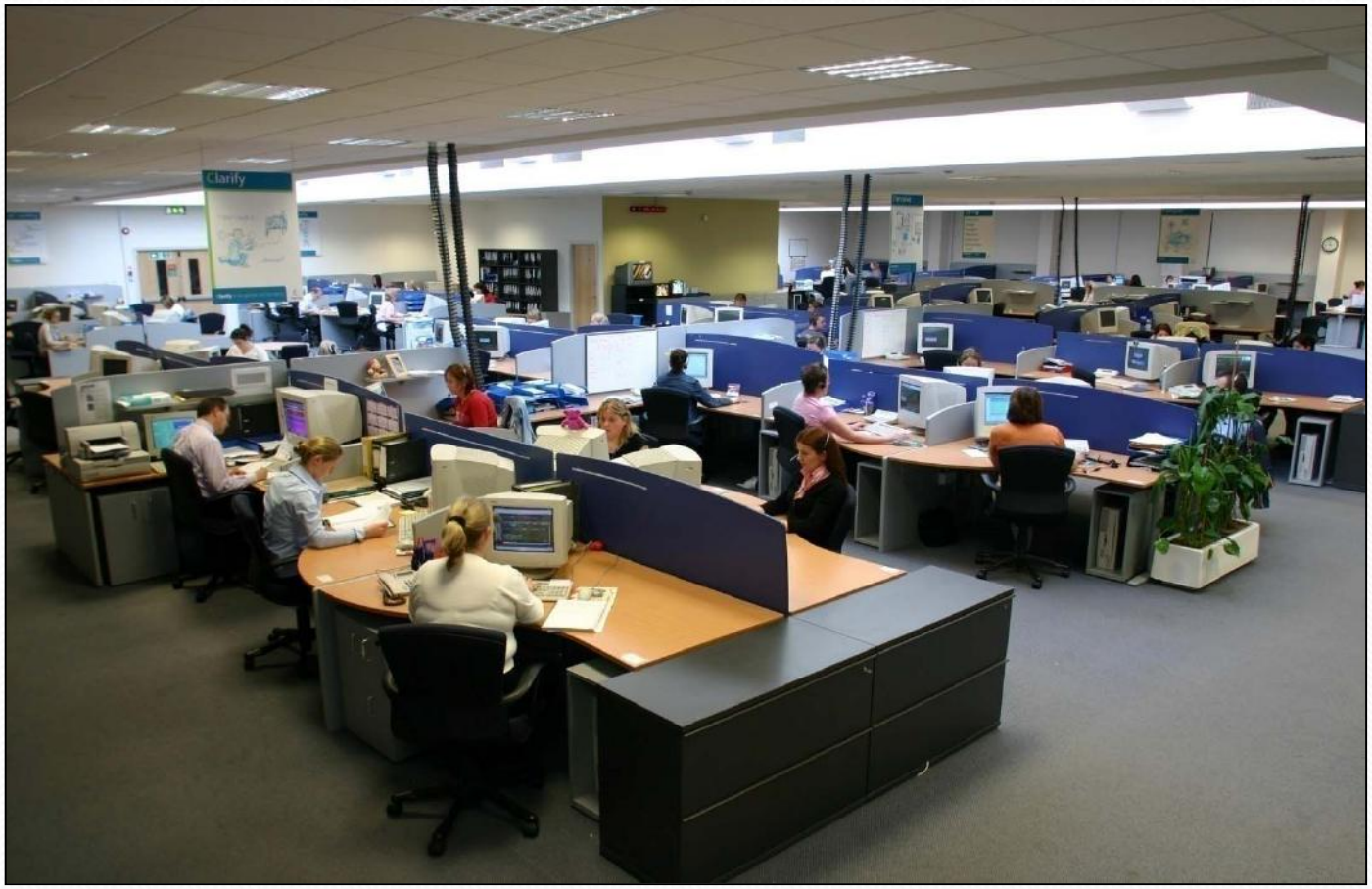
- Loss of ß cells
- Amyloid deposits
- Hyalinization

Pathogenesis of Type 2 DM



Physical Activity on the decline……

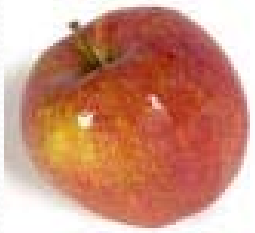
Physical Activity on the decline……

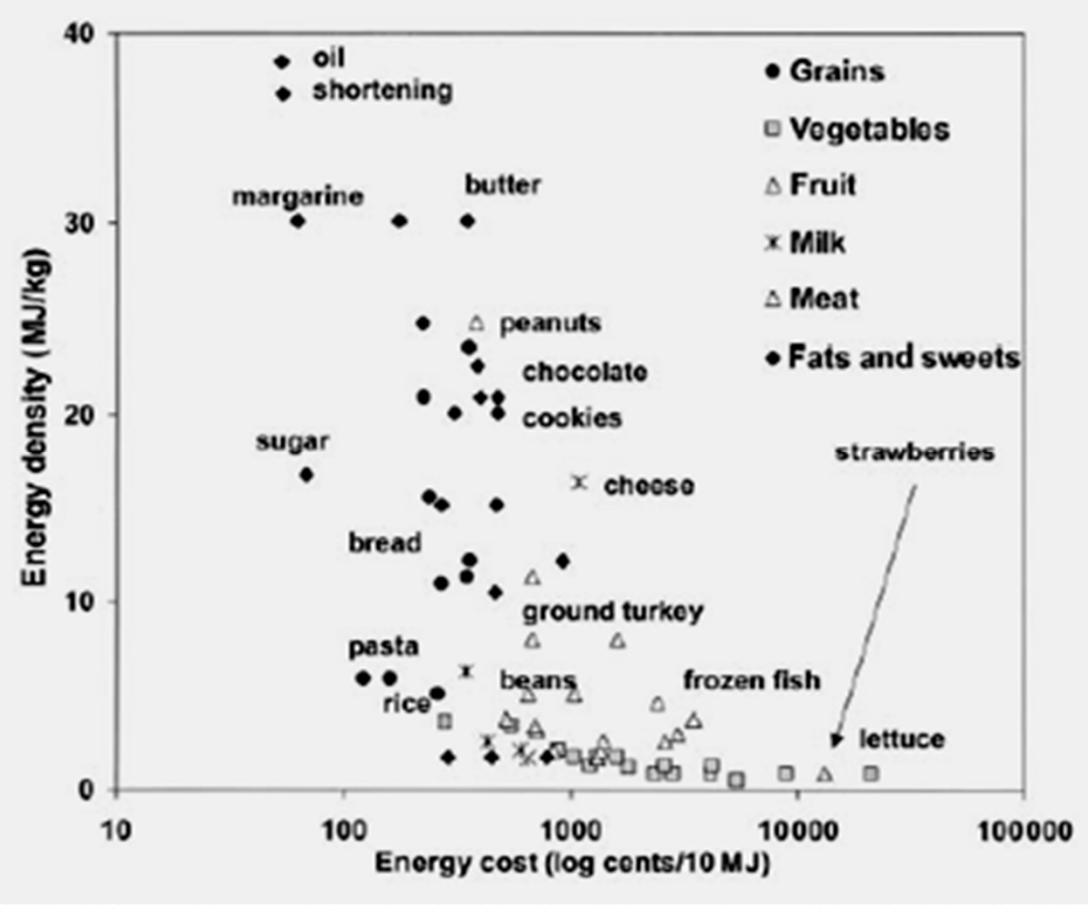


The economic driving factors……

> Rs. 70/- per kg

Rs. 90/- per kg



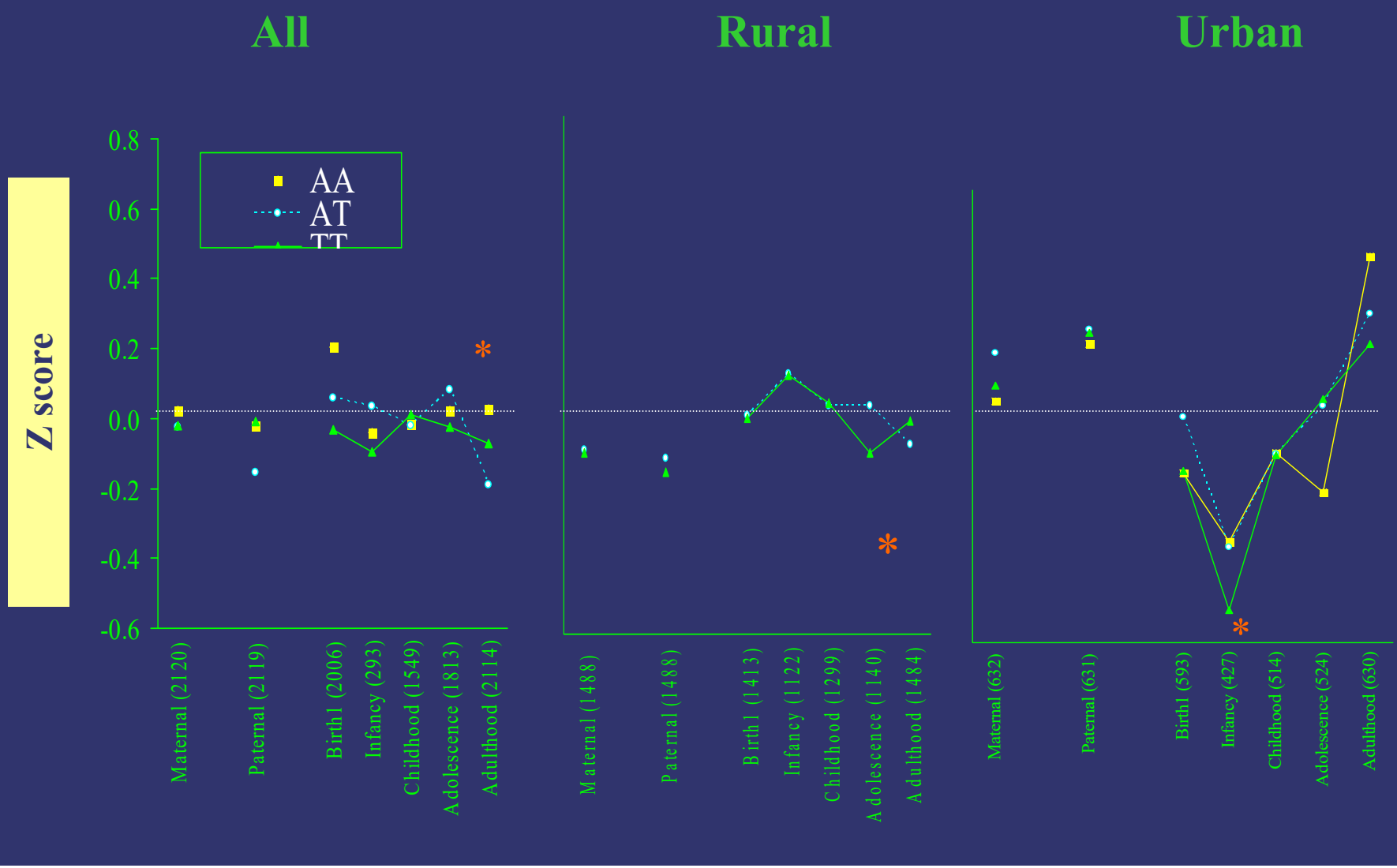


…Consumer Price Index shifts favour unhealthy products

Adam Drewnowski and SE Specter. Poverty, obesity, and diet costs. Am J Clin Nutr 2004;79:6 –16

Mean Body Mass Index
([1] Ponderal Index) of subjects by FTO genotypes according to place of birth

* significant difference in mean BMI Z score by FTO types ($p<0.05$). SD score for the whole cohort is set at 0.



Other Specific Types

A. Genetic defects in Beta Cell function / Insulin secretion

B. Genetic defects in Insulin Action

C. Diseases of the Exocrine Pancreas

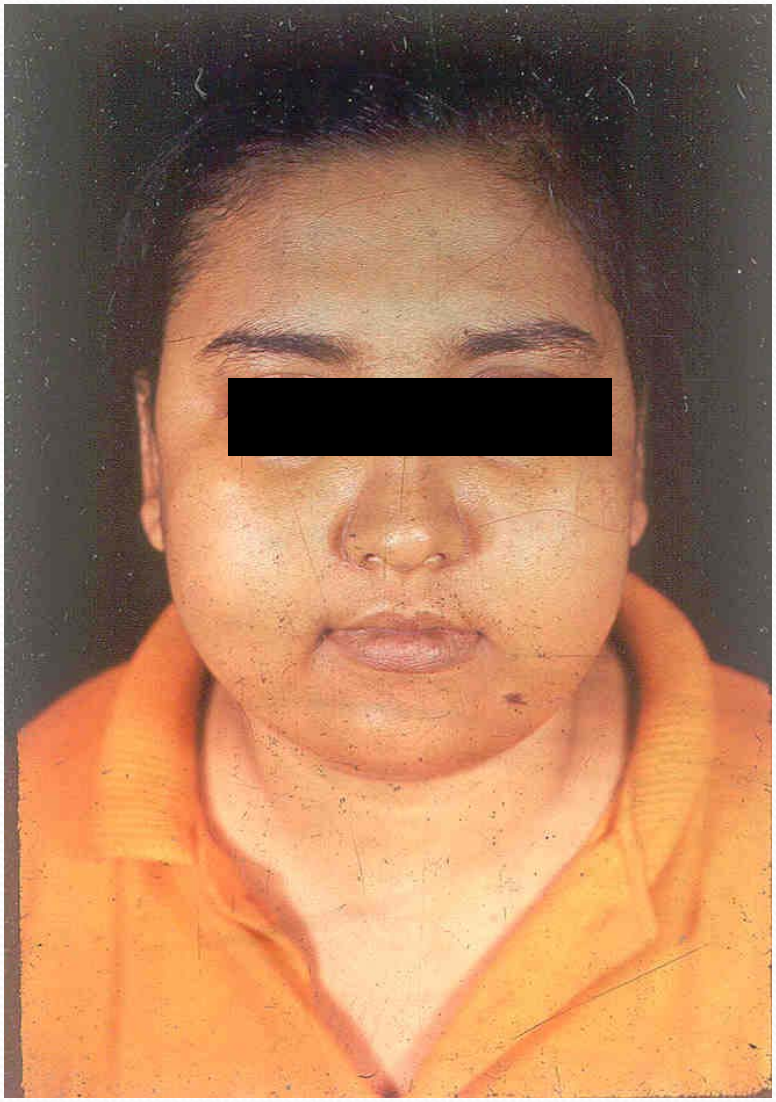
D. Endocrinopathies

E. Drug or Chemical Induced

F. Infections

G. Uncommon Immune forms

H. Genetic Syndromes with Diabetes



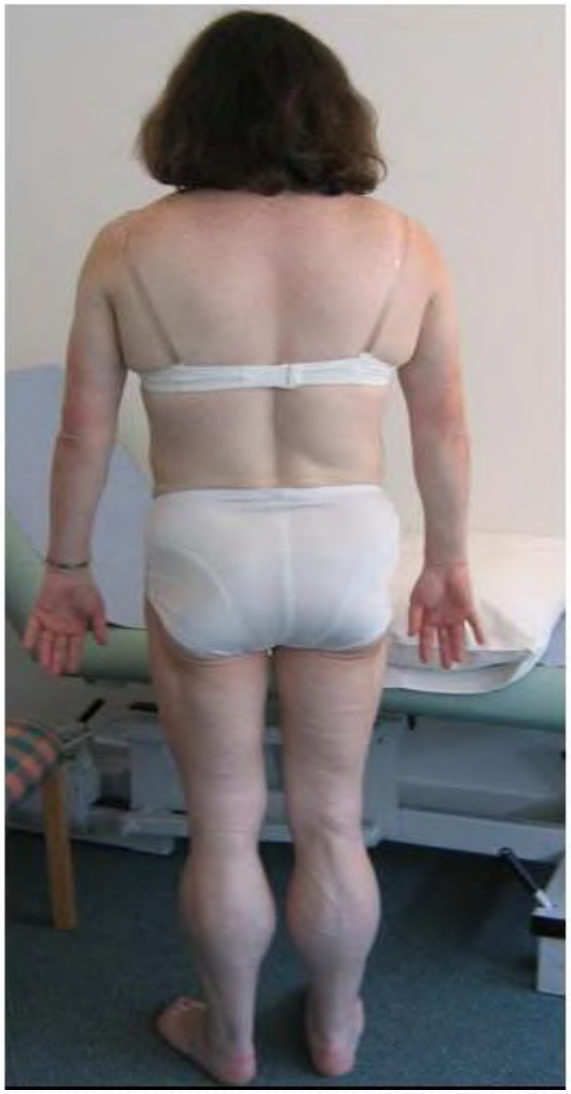
Genetic defects of insulin secretion

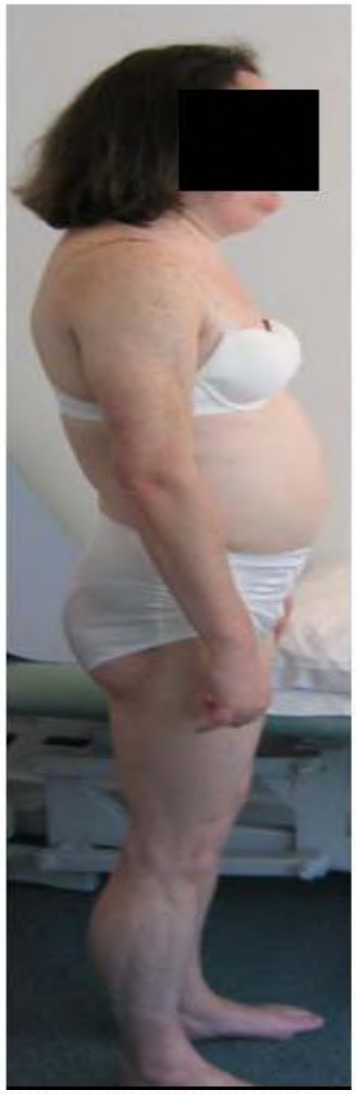
Maturity Onset Diabetes of the Young (MODY)

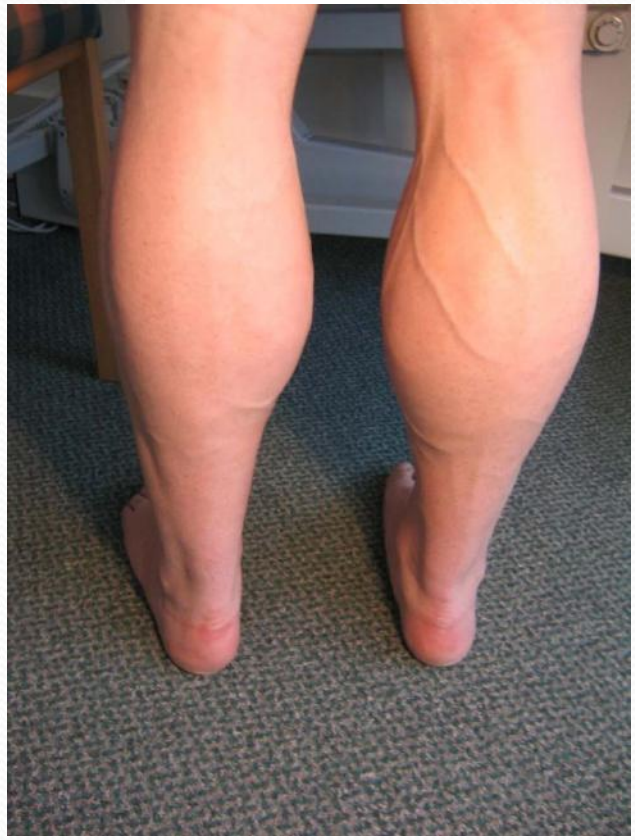
- Six genetic loci on different chromosomes have been identified to date.
- Glucokinase related MODY(MODY 2) is common….but in India….HNF-4 alfa.
- Usually Nonketotic /Nonobese
- Often in sucessive generations

Genetic defects in insulin action

1. Type A insulin resistance
2. Leprechaunism
3. Rabson-Mendenhall syndrome
4. Lipoatrophic diabetes
5. Others

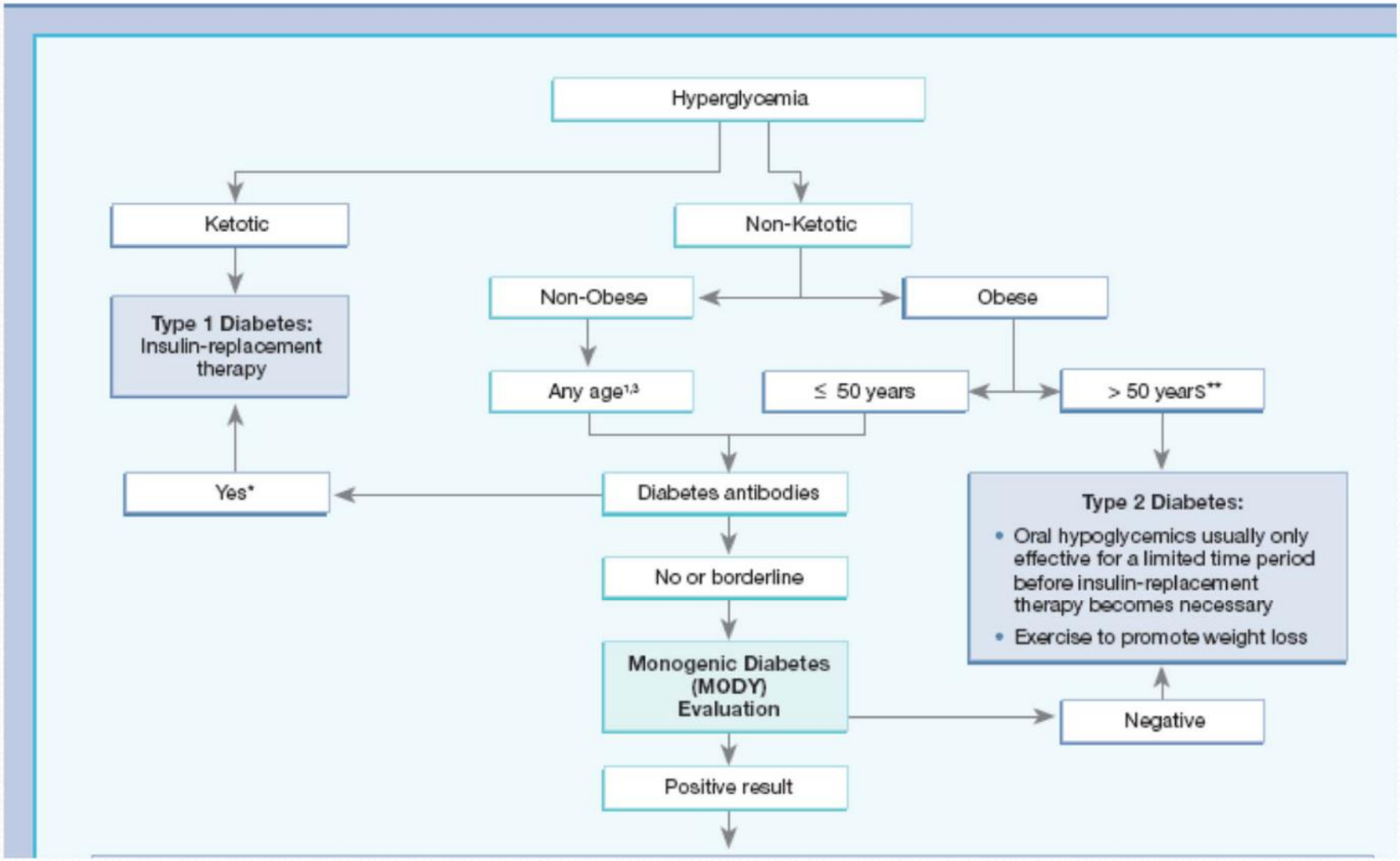






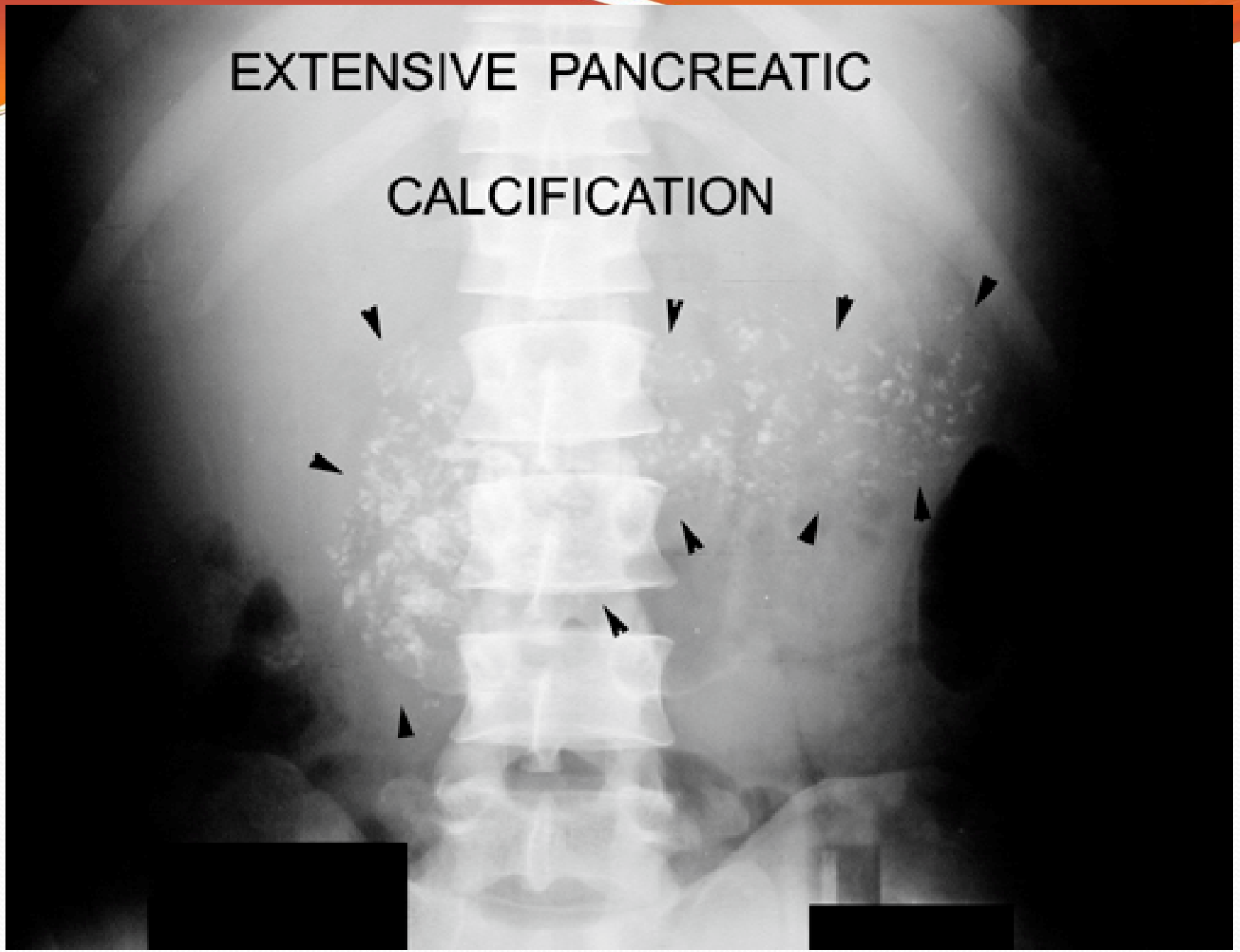
Adapted from F Karpe

Figure 1: An approach to diagnosing MODY



Diseases of the pancreas

- Acquired causes include Pancreatitis, Trauma, infection, pancreatectomy, and pancreatic carcinoma.
- Fibrocalculous pancreatopathy
- Cystic fibrosis and Hemochromatosis


EXTENSIVE PANCREATIC
CALCIFICATION

Fibrocalculous pancreatic diabetes

The classical triad of clinical presentation in tropical chronic pancreatitis:

- Abdominal pain.
- Maldigestion leading to steatorrhoea.
- Diabetes (fibrocalculous pancreatic diabetes).

Drug induced diabetes

- Drugs and hormones can impair insulin sensitivity and reduce insulin action.
- glucocorticoids, phenytoin, thiazides & interferons
- Intravenous pentamidine can permanently destroy pancreatic ß-cells.

Clinical Scenarios

CASE 1

- 36 year old Mr.R who had his blood glucose levels checked since he had a family history of diabetes
- BMI : 31 kg/m^2
- His fasting plasma glucose(FPG) was 118 mg%, 2hr PPBG was 155 mg%.

DIAGNOSIS ?

Case 2

- 20 year old gentleman was diagnosed to have diabetes on a pre-employment check up.

  He was born of non consanguineous marriage and his mother and his maternal grand father were having diabetes
- His BMI was 21 kg/m^2 · BP =120/80mm Hg.

Probable Type ?

Case 3

39 yr old Mr. Al was diagnosed to have diabetes..

- Polyuria and weight loss in previous 4 months. No recurrent abdominal pain/steatorrhea
- BMI: 20 kg/m^2. Urine ketones:negative.
- Glycemic control for first one year achieved with OHAs. Required insulin thereafter.
- GAD antibodies were positive
- Type of diabetes-

Case 4

- 20 year old lady was diagnosed to have diabetes mellitus.
- Menstrual irregularity+
- BMI =31 kg/m^2
- Proximal muscle weakness+, Purplish abdominal striae+
- Further work up-

Summarizing……

- Diabetes Mellitus should be looked at as a whole with the metabolic syndrome.
- Impaired fasting Glycaemia and glucose tolerance should be given due importance
- In the young the clinical features should be taken into account to determine the cause of diabetes.

Thank you