SPECIFIC TYPES OF DM (SECONDARY DM)

MODY & LADA

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Four main types of Diabetes

1. Type 1 DM
2. Type 2 DM (IR > ID or ID > IR)
3. Specific types (Secondary diabetes-the underlying defect or disease process identified) (Diabetes plus or Syndromic DM)
4. Gestational DM

(85-90% T2DM, 10-15% others)

Specific (secondary) types of diabetes (ADA)

1. Genetic defects of β-cell function (insulin secretion)
2. Genetic defects of insulin action (Receptoropathies)
3. Diseases of exocrine pancreas
4. Endocrinopathies
5. Drug-induced or chemical-induced
6. Infections
7. Uncommon forms of immune-mediated diabetes
8. Other genetic syndromes sometimes associated with diabetes

M O D Y

Maturity-**O**nset **D**iabetes of the **Y**oung

- In 1928, first noticed by Cammidge
- In 1975, first reported as MODY by Tattersall & Fajans (“Father of MODY”)

MODY DEFINITION: New

- DM due to a primary genetic disorder of the pancreatic β-cell (with mutations in autosomal dominant genes affecting insulin secretion and not insulin resistance

- MODY is not a single entity but represents genetic, metabolic, and clinical heterogeneity

Diagnostic criteria for MODY (Positive)

1.Onset of diabetes - before age 25 yrs

2.Not insulin-dependence - Absence of insulin treatment for at least 2 yrs after diagnosis

3. Autosomal-dominant inheritance. i.e. vertical transmission of diabetes through at least two (ideally three) generations with a similar phenotype in cousins or second cousins

4.β-cell dysfunction : insulin levels inappropriately low for the degree of hyperglycemia

Diagnostic criteria for MODY (Negative)

- No obesity or metabolic syndrome
- No acanthosis nigricans
- No autoantibodies

Prevalence

1. 1 % younger diabetic (<25 yrs)
2. 1-2 % of all patients of NIDDM in most white European populations
3. In France, 13% of Caucasian NIDDM families
4. 4.8 % of patients with T2DM (Mohan et al, Chennai)
5. About 60-70% of MODY mutations known in Scandinavia, France and UK.

Triggering factors

- Infection
- Puberty
- Pregnancy (3% GDM)
- Obesity
- Drugs

All increase IR

Different subtypes of MODY

MODY type	Gene locus	Gene name	Prevalence	Diabetes
MODY 1	20q	HNF4A	2-5%	Severe
MODY 2	7p	GCK	**7-41%**	Mild
MODY 3	12q	HNF1A	**Up to 70%**	Severe
MODY 4	13q	PDX-1 (IPF)	<1%	Moderate
MODY 5	17q	HNF1B	2%	Severe
MODY 6	2q32 IDDM7	NEUROD1/Beta-cell E-box transactivator 2 (BETA2)	<1%	Severe

HNF-Hepatocyte Nuclear Factor GCK-Glucokinase
NEUROD1-Neurogenic differentiation 1 gene IPF-insulin promoter factor

Type of MODY	Molecular basis
MODY2	Reduced phosphorylation of glucose results in a defect in sensitivity of beta cells to glucose and a defect in the storage of glucose as glycogen in the liver.
MODY1, MODY3, MODY5	Abnormal regulation of gene transcription in beta cells causes a defect in the metabolic signaling of insulin secretion, beta cell mass, or both.
MODY4,MODY 6	Abnormal transcriptional regulation of beta cell development and function.

Non genetic Investigations

	MODY	Type 1	Type 2
Autoantibodies (ICA, IA2 or GAD)	Not present	>95%	unusual
C peptide	Usually detectable (0.1-1 nmol/l)	not measurable (<0.33nmol/l)	detectable may be high (>1nmol/l)
Lipids	normal (HDL ↑,TG ↓ MODY3)	normal	HDL low TG high

Biochemical/Clinical Clues:MODY

- In an OGTT, the increment [(2 h glucose) − (fasting glucose)] is small (<3 mmol/l)
- FPG > PPPG (F 140 mg%, PP 136 mg%)
- Any child with DM when good glycemic control is achieved with a low insulin dose over a prolonged period (e.g., less than 0.5 u/kg/day)

MODY vs. T1DM

Clinical Features	MODY	T1DM
Family history	AD	2-7%
Auto antibodies	**Negative**	**Positive**
C peptide reserve (nmol/l)	0.1-0.7	< 0.33
BMI	Normal/low	Low
Symptoms	Minimum	Maximum
Hyperglycemia	Mild to moderate	Severe
Doses of insulin	< 0.5 U/kg/d	> 0.5 U/kg/d
Onset	From birth or later	> 6 months of age
Extra-pancreatic features	May be present	Absent
Presentation	Insidious	Acute

Characteristics	MODY	EARLY ONSET T2DM
Inheritance	Monogenic, autosomal dominant	Polygenic
Age at onset	Childhood, adolescence, or young adulthood (usually < 25 yrs)	Early Adulthood (usually 25-40) Occasionally adolescence (if obese)
Pedigree	Usually multigenerational	Rarely multigenerational
Penetrance	80-95 %	Variable (possibly 10-40%)
Body habitus	Non obese	Usually obese
Metabolic Synd	Absent	Usually present
Acanthosis Nigricans,PCOS	Absent	May be present
Glucose rise in OGTT	Small increment(< 3.5 mmol/L)	Large increment
% of parents abnormal	50%	> 90%
% of siblings abnormal	50%	68%

Glucokinase mutation (MODY 2)

- Persistent Fasting hyperglycaemia (5.5–8.0 mmol/l)
- In OGTT the increment (2hr glucose – fasting glucose) is small (typically <3.5 mmol/l)
- Often asymptomatic
- Parents may/may not have mild T2DM
- HbA_{1c} levels rarely > 7.5%
- Microvascular complications rare
- 3% of GDM
- May coexist with T2DM/T1DM
- Reduced BW
- Not obese (usually)
- Glucokinase activator class of drugs might be useful

Confirmation:

Molecular-genetic testing- Too expensive and labor-intensive

Gene mutation screening methods

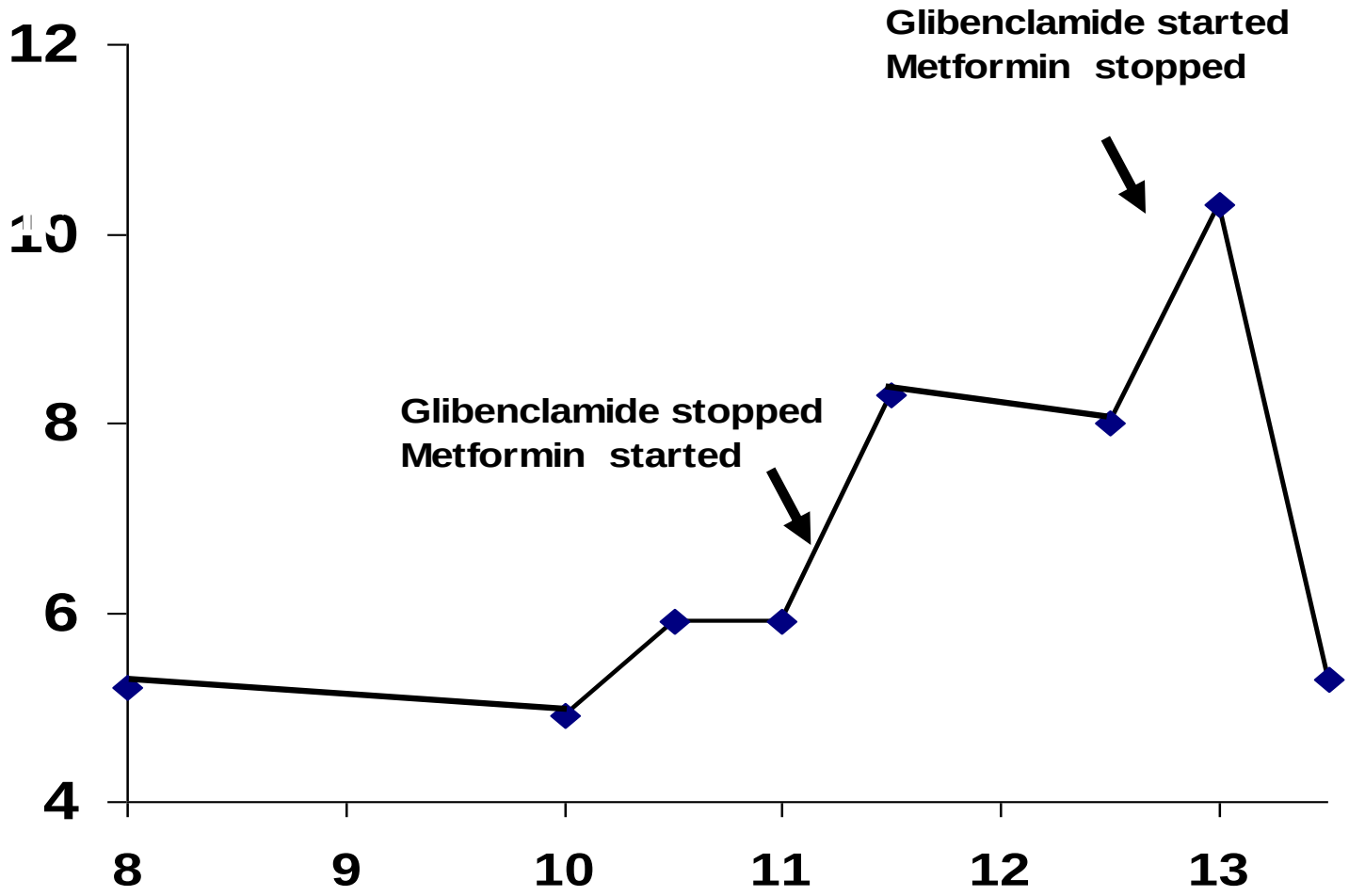
✓ Direct sequencing (gold standard)
✓ Fluorescent Single Strand Conformation Polymorphism (SSCP)

✓ Denaturing High-Performance Liquid Chromatography (DHPLC) –cheapest and fastest method.

Treatment of MODY

- 1/3 –Diet control
- 1/3-OHA (SU)
- 1/3-Insulin
- Mostly diet only in MODY-2
- DPP-IV Inhibitors
- Glinides

HNF1α: very sensitive to sulphonylureas



(Pearson et al Diab Med 2000)

Genetic Screening for MODY

1. Diagnostic implications
   - Clinically MODY patients
   - GDM patients
   - Differentiation from T1DM
2. Prognostic Implications
   - Children of MODY patients
   - LBW babies born to GDM mothers
   - Helps family counselling
   - Predicts likely clinical course
3. Therapeutic Implications
   - (? T1DM)
   - To switch a person from insulin injections to SUs without loss of glycemic control.

To Summarize……

- **MODY**
  - Early onset diabetes
  - Not ketosis prone
  - Autosomal dominant inheritance
- **GK Mutations MODY 2**
  - Lifelong, stable, mild fasting hyperglycemia, requires no other additional treatment than diet
- **TF Mutations MODY**
  - Born with normoglycemia → progressive hyperglycemia
  - Requires OHA or Insulin
  - May develop micro vascular complications
  - Extra-pancreatic features

LADA

Definition of LADA

Latent
Autoimmune
Diabetes in (of)
Adults

A form of autoimmune diabetes that resembles T1DM,but has a later onset and slower progression toward an absolute insulin requirement

LADA: Type 1.5 diabetes?

- Many genetic, immune, and metabolic features of T1DM
- Some clinical, anthropometric, and metabolic traits with T2DM

- Most recently, the eponym ADA (autoimmune diabetes in adults) has been suggested to replace the term LADA

HISTORY

- In 1986, Groop et al. - latent type 1 diabetes
- In 1993, Tuomi et al. and Zimmet et al.- LADA

Prevalence

- Roughly 10-30% of T2DM
- 10% of T2DM patients in UKPDS
- Significant prevalence in India

DIAGNOSTIC Δ :The Immunology of Diabetes Society

1. ≥ 30 years of age at diabetes onset
2. Positive for at least one of the four antibodies (ICAs and autoantibodies to GAD65*, IA-2, and insulin)
3. Insulin independence for at least 6 months after diagnosis

Clinical Types

LADA-type 1 :Multiple antibodies or high titers of GADAb. More resembles T1DM

LADA-type 2 :Single antibody positivity in low titers. More resembles T2DM

Extra Features

1. Eventually becomes truly insulin - dependent (6 months-12yrs)
2. F > M
3. Clinical or subclinical autoimmune endocrinopathies (thyroid and adrenal)
4. Obesity +/_

Pathogenesis

- ✓ Genetic predisposition (higher rates of HLA DR3 & DR4)
- ✓ Environmental triggers such as viruses, cow milk proteins, chemical toxins (N-nitroso compounds),vit D deficiency, wheat gluten, drugs
- ✓ Slow autoimmune destruction of β-cells
- ✓ Gradual development of glucose intolerance

Why autoimmune process is slow

1. Genetic factors
2. Age at onset of insult
3. Environmental factors
4. Metabolic factors
   - Glucotoxicity
   - Lipotoxicity.

IR in LADA

- Significantly present
- Features of IRS absent
- Secondary to ↑glucose & FFA

Diagnosis

- GAD 65 antibodies (first step)
- IA2 / ICA512 antibodies
- IAA (insulin autoantibodies)
- ZnT8 antibodies
- C-peptide assay (basal & stimulated)

Screening for LADA

- In a country like India with limited resources, should we screen all T2DM patients for LADA?
- “NO”
- Follow **Clinical clues or Clinical Risk Score**

Clinical clues for LADA

- Age ≥ 30 yrs
- Non obese or lean built
- No features of metabolic syndrome
- Poor response to OHA
- Presence of other autoimmune diseases

(e.g.Hashimoto, celiac or Addison's disease)

- No family H/O DM
- Relatives with T1DM
- Wt loss

LADA: Clinical Risk Score

1) Age of diabetes onset < 50 years

2) Acute symptoms (polydipsia and/or polyuria and/or unintentional weight loss before diagnosis)

3) BMI <25 kg/m2

4) Personal history of autoimmune disease

5) FH of autoimmune disease (thyroid , celiac, Addison's , vitiligo ,rheumatoid arthritis , pernicious anemia and hepatitis)

Clinical risk score ≥ 2 at diagnosis has 90% sensitivity and 71% specificity for detecting LADA & a negative predictive value for a LADA clinical risk score ≤1 of 99%.

(Diabetes Care, May 1, 2006; 29(5): 970 - 975.)

FEATURES	T1 DM	LADA	T 2 DM
Age at onset	Young/adult	Adult	Adult
HLA susceptibility	Yes (strong)	Yes	No
Autoantibodies	Yes (strong)	Yes (by definition)	No
Ketosis	Present	Absent	Absent
BMI	Normal	Normal/High	High
Insulin secretion	Absent/low	Present (but declines)	Present
Met.Syndrome	Infrequent	Variable	Frequent
IR	Absent/ infrequent	Variable	Present
Initial therapy	Insulin	Insulin/OHA	LSO/OHA

MANAGEMENT OF LADA

- Obtaining good metabolic control
- Protecting residual β-cell mass and function

METABOLIC CONTROL IN LADA

- Diet
- Obese LADA patients - restriction in calories intake and increased levels of physical activity.
- SU – Caution or Never
- Metformin
- Glitazones: Better choice*
- Insulin – most appropriate (ß-cell rest and reduction in antigen exposure associated with insulin output)
- Incretin mimetics/enhancers
- AGIs

(* Diabetes Res Clin Pract. 2009 Jan;83(1):54-60)

SU Caution in LADA!

- Exhaustion or desensitization of β-cells
- Acceleration of oxidative stress and apoptosis
- Stimulation of insulin release might be associated with increased autoantigen expression, which might accentuate the ongoing autoimmune process
- Expedite the progression toward β-cells depletion and the necessity of insulin initiation

Early initiation of insulin treatment

1. Anti inflammatory effects & slowing down of the autoimmune destruction
2. Less β-cell stimulation → β-cell rest
3. Long term β-cell protection
4. Tolerance induction or “bystander” suppression of autoreactive T-cells through the local release of regulatory cytokines
5. Better outcome in terms of metabolic control, insulin secretion, and autoimmune responses against pancreatic β-cells

STRATEGIES FOR PREVENTING ß-CELL DESTRUCTION IN LADA

- Nicotinamide
- Tolerance induction plan using alum-formulated recombinant human form of GAD65 vaccination(Diamyd)
- Peptide analog of heat shock protein 60 (DiaPep 277)
- Early insulin intervention
- Anti-CD3 monoclonal antibodies
- Vitamin D
- Insulin sensitizers

To conclude…..

MODY & LADA

is one area

in which clinical

observations have led,

&

will continue to lead to Scientific advances!!!

***Wait and Watch*……**