

Autoimmune Diabetes: An Emerging Epidemic?

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A. Diabetes Facts

- Diabetes affects 25.8 million Americans (or 8.3% of US population).
- Diabetes affects 215,000 Americans ages 20 and under.
- Diabetes was the 7th leading cause of death in the US during 2007.
- The total direct cost of diabetes care was \$117 billion in the US during 2007.

B. Classifying Diabetes

- Type 1 – autoimmune (most), idiopathic
- Type 2 – insulin resistance, impaired insulin secretion
- Gestational
- Secondary – e.g. medications (prednisone, antiretrovirals), pancreatic disease (cystic fibrosis, hemochromatosis, Wilson's disease, chronic pancreatitis), endocrinopathies (Cushing's, acromegaly), infectious (congenital rubella)
- Genetic (MODY, others) – HNF -1-alpha, HNF-1-beta, HNF-4-alpha, glukokinase, IPF-1, NEUROD1; Wolfram's syndrome
- Latent autoimmune diabetes in adults (LADA)
- Hybrid – features of both Type 1 and Type 2

C. Diabetes Prevalence in US

- Type 2 80%
- Type 1 5-10%
- Other 10-15%
- LADA up to 10% of adults classified as T2DM?

D. Epidemiology of T1DM

1. Worldwide distribution
2. Variable prevalence and annual incidence
 - Lowest = China
 - Highest = Finland, Sardinia
3. Prevalence in US children:
 - highest rate in NHW
 - lowest in API, AI
4. Bimodal age distribution – peaks at 4-6 yo, 10-14 yo
5. No gender difference (unlike most autoimmune disorders)

E. Pathophysiology of Autoimmune Diabetes

1. Genetic predisposition
 - HLA DR4 DQB*032, DR3 DQB*021
2. One or more environmental triggers
 - Viral (Coxsackie B, mumps, enterovirus)?
 - Dietary (ingestion of cow's milk, cereal, infant formula, nitrates; deficiency of Vit D, omega-3 fatty acid)?
 - Immunizations? – no association detected
 - Prenatal (maternal age, diet; birth order; C-section)?
3. Preclinical period
 - Progressive T cell-mediated beta cell destruction
 - May last months to years
 - Difficult to characterize (no non-invasive way to measure beta cell mass in humans)
4. Clinical phase
 - Absolute insulin deficiency --> hyperglycemia, ketoacidosis

F. Hypotheses of T1DM Pathogenesis

- Hygiene hypothesis - decreased exposure to infectious agents early in life leads to disordered immune response (molecular mimicry)
- Accelerator hypothesis - increasing BMI in susceptible persons accelerates beta cell decline.

G. Immunologic Markers of T1DM

1. Specific disease-associated auto-antibodies
 - Islet cell antibodies (ICA)
 - Insulin auto-antibodies (IAA)
 - Glutamic acid decarboxylate antibodies (GAD)
 - Tyrosine phosphatase antibodies (IA-2)
 - Zinc transporter antibodies (ZnT8)
2. Greater number, higher titer of auto-antibodies is more suggestive of autoimmune etiology

H. Recent Key Clinical Studies of T1DM Prevalence

1. EURODIAB
2. Swedish Childhood Diabetes Study
3. SEARCH for Diabetes in Youth Study
4. TEDDY

I. "Hybrid" Diabetes (SEARCH study)

1. Features of both type 1 and type 2 present
 - Obesity + autoantibodies
2. Prevalence - unknown
3. Clinical course - unknown
4. Etiology - unknown
 - T1DM with obesity?
 - T2DM with auto-antibodies?
 - Something else altogether?
5. May be more common in non-whites

J. Latent Autoimmune Diabetes in Adults (LADA)

1. Fairly common, but often goes unrecognized
2. Associated with auto-antibodies
3. Often requires insulin for adequate treatment
4. Progression halted by earlier use of insulin or other modifiers?
5. Predictive Clinical Features
 - Age <50 yo
 - BMI <22
 - Subacute onset
 - Low stimulated C-peptide level
 - Auto-antibodies (ICA, GAD)
 - Personal or family history of other autoimmune disorders

K. Sample Cases

L. Summary

1. Prevalence of autoimmune DM is increasing in all age groups.
2. During recent decades, rate of increase in diabetes in the young has been accelerating worldwide.
3. "Hybrid" diabetes in the young may be new clinical syndrome.
4. Latent autoimmune diabetes affects up to 10% of US adults now classified with T2DM.
5. Consider LADA in thin adults with worsening glucose control, initiate insulin at low doses.
6. Ongoing clinical research may give clues as to course, optimal management, prevention of atypical forms of autoimmune DM.