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Type I Diabetes

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- Diabetes Mellitus: systemic disease with multiple metabolic abnormalities, mainly elevation in plasma glucose (lipid metabolism, ketones)
- Classification
    - Type I
        A. Immune Mediated - 85%
        B. Idiopathic - 15%
    - Type II
    - Other types (MODY, secondary DM)
- Signs of Type I: Polyuria; Polydipsia (thirst); Polyphagia (hunger); weight loss; fatigue; increased frequency of infections; rapid onset (type II is much slower progressing); insulin dependent; early onset
- Differences btwn type I and II: type I has islet cell antibodies and patients are typically thin
    - HLA related genetic background, no insulin secretion, non-insulin resistant, non-responsive to oral meds, ketosis prone
    - Type I is only 5% (1.5-2mm cases)
- Type I is chronic autoimmune disease but can also develop in adults/elderly
    - Polygenic: HLA linkage, non-MHC genes
    - Autoimmune etiology: antibodies to islet autoantigens, autoreactive T cells
    - Immune modulation alters course: antigen vaccination, general immunosuppression
- Graph on pg. 297
    - Will see multiple antibodies during beta cell injury phase
    - Declining beta cell mass
    - Loss of first phase insulin response (pre-diabetes)
    - Diabetes full blown once mass is below 10%
- Type I
    - Insulin resistance
    - β cell hypertrophy
    - Islet inflammation, pathogenic T cells, β cell decomposition
    - Impaired glucose tolerance
    - Autoimmune diabetes, insulitis, β cell death
- Genetic Links
    - Lifetime empiric risk increases w/ close relatives
        - Father has greater effect than mother --> imprinting
        - HLA class II genes have highest incidence
    - HLA complex: (DQ2, DQ8), DR3, DR4 are most associated w/ Type I
    - Sibling sharing 2 HLA haplotypes w/ type I affected sibling at much higher risk of developing
- Multiple factors
    - Autoreactive T cells --> islet autoantibodies (not shown to directly kill β cells)
        - Eleavated cytokines (IFNγ, IL-1β, TNFα, etc.)
        - Increased apoptosis/necrosis, decreased neogenesis
        - Hyperglycemia --> glucose toxicity
        - Environmental Factors
    - All combine to lead to β cell death
- Environmental factors
    - Congential rubella syndrome - similar antigens to those in Type I DM --> immune response
    - Cocksakie B virus?
    - Enterovirus?
    - Streptozotocine (low doses)?
- Loss of self tolerance to self-antigens

    - Insulin - main antigen in T1DM
    - GAD65
    - ICA512/IA-2
    - Znt8 - 60% of Type I
    - Can be one or multiple antigens
        - Starts w/ insulin --> epitope spreading to GAD, Znt8, IA2
    - Theory is that not enough insulin enters thymus during T cell development --> recognition as non-self
- T Cells
    - Cell-mediated immunity
        - CD4
        - CD8
        - NK cells?
        - M'phages?
        - Dendritic cells?
    - Normal individuals have balance btwn pathogenic and regulatory T cells
        - T1D prone express too much pathogenic/too little regulatory
        - T1D protected are reverse
    - XLAAD
        - FOXP3 stop codon
        - Genetic defect can lead to type 1 diabetes in presence of other autoimmune disorders for abnormalities in regulatory T cell maturation
        - Tregs may play role in suppressing possible autoimmune disorders
- Cytokines: CD4 T cells
    - IL-12 --> Th1 --> IFN-γ, IL-2 --> cell-mediated immunity, autoimmunity, pro-inflammation, allograft rejection
    - IL-10 + IFN-α --> Tr1 --> IL-10 + TGF-b --> suppression/regulation
    - IL-4 --> Th2 --> IL-4/5 --> humoral immunity/anti-inflammatory
    - IL-β, IFN-γ, TNF-α --> oxidative stress --> NO production --> β cell death
- Role of Autoantibodies
    - Markers of disease
    - GAD65, IA-2, Insulin, Islet cell
    - Assays
        - Immunoprecipitation for GAD-65, IA-2 antibodies
        - Radioimmunoassay for insulin antibodies
        - Immunoperoxidase staining for islet cell antibodies
    - More antibodies --> increases probability of developing type II
- Conclusions
    - Type I DM is a polygenic disease w/ HLA DR3, DR4 having the strongest effect
    - CD4 and 8 T cell responses to islet autoantigens are pathogenic
    - Defect of Reg T cells in suppressing pathogenic autoimmune responses is assoc w/ Type I DM
    - Proinflammatory cytokines IL-β, IFN-γ, TNF-α can cause β cell death
    - Gene defects in FOXP3 and AIRE cause multiple autoimmune diseases incl. T1DM
    - Presence of antibodies to insulin, GAD-65, IA-2 are high risk markers of T1D progression