Response of Immune System in Type 1 Diabetes Patients

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Abstract

Immune systems are documented as suppressors of immunity. Thus decrease in GM loss of control of immune system -followed by immune cell actions against cells of self,-ultimately T1D. Correlation of early fruit introduction relates to increase in autoimmunity to β-cells .Possibly abnormal immune response to solid food antigens in immature gut immune system in children that possess HLA susceptibility to DM. Moreover over load hypothesis points that environmental food exposures might over stimulate β- cell =>increased autoimmune mediated damage. Similarly increased amounts of bovine milk products increased risk of autoimmunity in children that possess HLA susceptibility. This might be due to insulin auto antibody in view of cross reactivity between bovine as well as human insulin. Gluten foods(cereals) in children <3yrs significant increase in islet autoantibody synthesis .DM patients with HLA-DR allele have increased Tcell reactivity to gluten derived polypeptides .This is secondary to interferonγ(IFNγ) as well as IL-17 liberation .Intestinal inflammation as well as T cell activation induced by gluten => β-cell autoimmunity. Vit D can modify T as well as Bcells function. VDR agonists => Treg cell induction. By stimulation of tolerance as well as stop differentiation as well as maturation of DC's, downregulate expression of costimulatory molecules like CD40, CD80 and CD 86 and decrease IL-10 production,Viruses might => T1D by 2 modes)a direct cytolytic action on β-cells(like ds RNA virus-fig1) or ii)Indirect triggering of a DM –related autoimmune process against β-cells that=> β-cells destruction. This is due to structural similarity of some viral structures as well as β-cells antigen. Persistent virus infection may=> β-cell autoimmunity. Enterovirus, rotavirus, cytomegalovirus (CMV), mumps, rubella virus, retrivirus etc.60 Genes identified by gene wide association system (GWAS).Genetic factors –HLA &non HLA. Genetic factors of genomic locus of HLA-50%of genetic risk of T1D- Most correlations with HLA-class II genes, that get expressed in APC's like DC, macrophages &thymus epithelium .In thymus epithelium they cause presentation of self-antigen that self-tolerance. Inefficient HLA-class alleles –in interacting &presenting insulin in thymic epitheliumare relatively related to T1D-This may insulin negative T cells to escape negative selection. Absence of insulin expression in thymus might hamper negative selection. Polymorphisms of in protein tyrosine phosphatase non-receptor22 (PTPN22) gene – encodes lymphocyte specific tyrosine phosphatase (LYK)-might alter immune self-tolerance. LYP-negative controller of Tcell receptor (TCR) signalling –hyperactive LYP –encoded via PTPN22-risk variant-can inhibit TCR signalling in negative selection. Polymorphisms of cytotoxic lymphocyte associated protein 4 gene (CTLA4)-related to T1D. CTLA4-has immunoregulatory role in effector T cells by suppression of T cells response. CTLA4-key for regressive function of Treg in mice- CTLA4 dampens immune response via both effector& Treg.BTB &CNC homology 1 gene (BACH2) expresses transcription factor that controls Treg action. T1D risk related variant of BACH2 =>abnormal Treg->can stimulate autoimmunity- secondary to improper control on inflammatory responses[16].Various IL & ILR genes like IL10, IL12 & IL2RA(codes-αsubunit of IL2R)-are genetic risk factors for T1D. Polymorphisms of interferon induced with the helicase C domain 1 gene (IF1H1) might explain interaction bet genetic &environmental factors of T1D. IF1H1 evokes immune response against RNA viruses. IF1H1 variants decreased expression protective against T1D. Immune β-cell destruction->mediated by extrinsic apoptotic pathway involves FAS mediated T cell interaction and pro inflammatory cytokines like IL-1β &IFNγ. BACH2-also inhibits BIM activation& JNK1 phosphorylation via β-cell response to proapoptotic signals it cross talks with PTPN22 as an inhibitor of pro apoptotic protein JNK. This pathway targeted by other T1Dgenes like CTSH&GLIS3. TNFAIP3another T1Dgene gives negative feedback loop for pro apoptotic action of NFKB. Hence efforts are further being made to deeply explore this though some partial positive effects obtained by earlier studies, use of formula of Orban etal. T1DM metabolic recovery index (DMMRI) using 3 studies using studies on abatacept, rituximab and glutamic acid decarboxylase(GAD) vaccine(sincethese 3 studies they used C peptide ,and Hb A1c and decrease in insulin& placebo controlledtrial rev in ref 1). Thus sustainance or enhancement of the positive index (DMMRI>5)-maximum seen in abatacept, rituximab while in GAD vaccine DMMRI<5observed.Further studies using controls needed to ultimately achieve the final immunotherapy that we get insulin independentt therapy of T1D. Therapy of persons having Type1 Diabetes mellitus (T1DM)has advanced ,much more from the time when insulin was given to a child with T1DM.Increased years of life spent ,with associated chronic complications like cardiovascular disease(CVD)and renal diseases at older age group and Diabetic ketoacidosis (DKA) and hypoglycaemia at a younger age are the major challenges. People suffering from T1DM in routine daily practice have to bear the massive alterations in glucose levels that is frustrating and depressing but further markedly enhancement of their body weight with overweight in 42% and obesity in 23.8% of people who have T1DM. Empaglifozin is an SGLT 2 Inhibitor which is in common with other agents in this class and decreases the elevated blood glucose levels by inhibiting SGLT2 ,that is the main transporter

needed for reabsorption of glucose On the basis of 2 phase2 and 3 studies namely EASE trials were evaluated and demonstrated definite advantage of use of Empaglifozin as an adjuvant to insulin in reducing blood glucose levels, Hb A1c,weight ,need for insulin dosages .The only worrying problem remains is the fear of unrecogized Diabetic ketoacidosis (DKA) in view of clinicians not accustomed to dealing with DKA with such lower blood glucose levels like 250 mg that has been named by FDA as ''euglycaemic DKA''. This can be overcome by training the patient along with treating physician how to suspect ,recognize and treat it in time. Advantage of EASE was the usage of very low dosage of Empaglifozin 2.5mg as well that is not the therapeutic dosage but can help physicians to work out the best dosage and plan to recognize ,prevent and treat DKA to prevent any mishap as occurred in 25mg arm of EASE-2 25mg arm.Till date Empaglifozin is not approved for T1D treatment but it holds promise to gradually overcome the little lacunae left and try to improve life of T1DM subjects in aiding in reducing insulin dosage ,decrease HbA1C,increased variability of glucose prevention along with reduce weight.