

Type 1 diabetes pathogenesis – Prevention???

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ABSTRACT

Pathogenesis of type 1 diabetes is multi-faceted, including, autoimmunity, genetics and environment. Autoimmunity directed against pancreatic islet cells results in slowly progressive selective beta-cell destruction (“Primary autoimmune insulinitis”), culminating over years in clinically manifested insulin-dependent diabetes mellitus (IDDM). Circulating serum autoantibodies directed against the endocrine cells of the islets of Langerhans (Islet cell autoantibodies - ICAb) are an important hallmark of this disease. Assays for islet cell autoantibodies have facilitated the investigation and understanding of several facets in the pathogenesis of autoimmune diabetes. Their applications have extended into clinical practice and have opened new avenues for early preclinical prediction and preventive prophylaxis in IDDM/type 1 DM. Recently, surprisingly, differences in insulin content between T1DM islets, as well as, ‘patchy’ or ‘lobular’ destruction of islets have been described. These unique pathobiological phenomena, suggest that beta cell destruction may not always be inexorable and inevitably complete/total, and thus raise hopes for possible therapeutic interruption of beta cell autoimmunity – destruction and cure of type 1 diabetes. “Recurrent or secondary autoimmune insulinitis” refers to the rapid reappearance of islet cell autoantibodies post pancreas transplant, and selective islet beta cell destruction in the grafted pancreas [never forgetting or “anamnestic” beta cell destructive memory], in the absence of any graft pancreas rejection [monozygotic twin to twin transplantation]. The one definite environmental factor is congenital rubella, because of which a subset of children subsequently develop type 1 diabetes. The putative predisposing factors are viruses, gluten and cow’s milk. The putative protective factors include gut flora, helminths, viral infections, and Vitamin D. Prevention of T1DM can include: Primary prevention strategies before the development of autoantibodies and Secondary prevention regimens after autoantibody development. Once islet cell autoantibodies have developed, the goal is to establish a therapeutic regimen to preserve at least 90% of the beta cells, and prevent the development of hyperglycaemia. The targets for T1DM reversal should include autoimmunity, beta cell regeneration and protection of beta cell mass. Anti-CD3 teplizumab and anti-CD3 oteplizumab have been shown to provide C-peptide preservation. The unanswered questions in diabetes research include elimination of autoimmune memory responses, reestablishment of immune self-tolerance, and mechanisms of disease initiation.

Key words: Type 1 diabetes mellitus, pathogenesis, prediction, prevention, autoimmunity, islet cell autoantibodies, beta cell, beta cell destruction

PATHOGENESIS OF TYPE 1 DIABETES

Autoimmune beta cell destruction and pre type 1 diabetes mellitus

Autoimmunity directed against pancreatic islet cells results

in slowly progressing beta-cell destruction, culminating over years in clinically manifested insulin-dependent diabetes mellitus (IDDM). Circulating serum autoantibodies directed against the endocrine cells of the islets of Langerhans are an important hallmark of this disease.^[1-39]

Before 1982, type 1 diabetes was diagnosed on the basis of clinical knowledge, with acute hyperglycemia and ketoacidosis being the major manifestations. Around 1982, the entity of pre-type 1 diabetes was discovered, which was asymptomatic and was the result of slowly progressive autoimmune beta cell destruction spread over 5–10 years or more.^[5-10,15-17,19-20,22,26-29,34,37,40]

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Assays for islet cell autoantibodies (ICA) have facilitated the investigation and understanding of several facets in the pathogenesis of autoimmune diabetes [Figure 1]. Their applications have extended into clinical practice and have opened new avenues for early preclinical prediction and preventive prophylaxis in IDDM/type 1 diabetes mellitus (T1DM).^[40]

Type 1 diabetes: Pathogenesis: Genetics–environment-autoimmunity

A series of seminal discoveries in the 1980’s, paved the way for the current model of type 1 diabetogenesis, consisting of sequential pathogenetic steps, beginning from birth: (1) Genetic predisposition; (2) initiation – Triggering; (3) autoimmunity; (4) beta cell dysfunction – destruction; and (5) clinical diabetes. This landmark model and concept are continuing to pave the way, for all subsequent global research efforts toward better understanding of the pathogenesis and possible prevention/cure of type 1 diabetes, till today.^[40]

Traditionally, it is considered that there is a genetic predisposition from birth, followed by initiation or triggering by unknown or partly known environmental factor(s), of a cascade of autoimmune responses, giving rise to progressive beta-cell dysfunction-destruction, which finally leads to clinical diabetes. This led to the first ever prospective pre type 1 diabetes mellitus (T1DM) registry at Joslin and kindled our and global scientific efforts towards finding an antigen-specific immunotherapy for the prevention of T1DM.

Another important, but less known, discovery at this period, shed additional novel insights for type 1 autoimmune diabetogenesis. Investigating the pathogenetic mechanisms for rapid failure of initially successful (“type 1 diabetes “cured”) monozygotic twin to twin pancreas transplants (expected absence of rejection, thus obviating

the need for post transplant immunosuppression), we also discovered the phenomenon of “recurrent or secondary autoimmune insulinitis.” This refers to the rapid reappearance of ICA post-transplant, and selective islet beta cell destruction in the grafted pancreas (never forgetting or “anamnestic” beta-cell destructive memory), in the absence of any graft pancreas rejection.^[12]

Insulinitis

In the early 1970’s, the first demonstration of insulinitis was made. Various stages of insulinitis namely pre-insulinitis, peri-insulinitis, intra-insular insulinitis and complete islet destruction have been demonstrated both in animal models and humans. Recently, surprisingly, differences in insulin content between T1DM islets, as well as, “patchy” or “lobular” destruction of islets have been described, (i.e., in few pancreas lobules all islets have preserved beta cells, while in other lobules, islets have no beta cells) – reminiscent of autoimmune vitiligo and patchy skin lesions (? scientific basis of “patchiness” in a systemic autoimmune disease unexplained; also possible recovery and relapse, and simultaneous/parallel target cell destruction and regeneration). These unique pathobiological phenomena, suggest that beta cell destruction may not always be inexorable and inevitably complete/total, and thus raise hopes for possible therapeutic interruption of beta cell autoimmunity– destruction and cure of type 1 diabetes [Figure 2].^[41]

A very interesting recent study has indicated that MRI can be used to visualize inflammation in the pancreas that leads to type 1 diabetes. The researchers investigated the possibility of using MRI and ferumoxytol, a coated iron nanoparticle used as an iron replacement therapy, to image inflammation in the pancreas. Ferumoxytol leaks from blood vessels in areas of inflammation and is taken up by immune cells called macrophages, which accumulate at

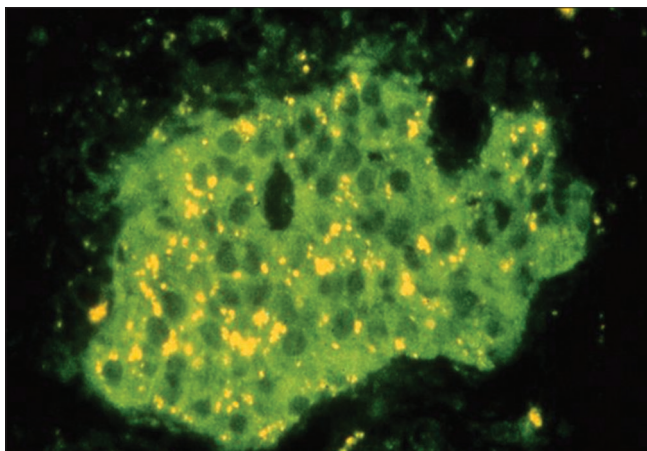


Figure 1: Immunofluorescence: Cytoplasmic islet cell autoantibodies

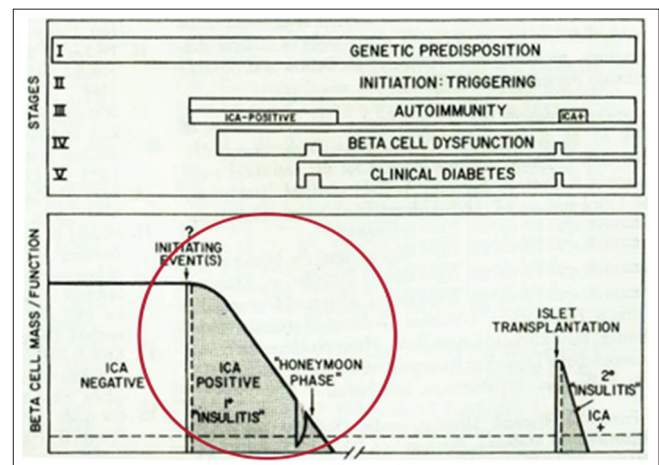


Figure 2: Model of Type 1 diabetogenesis [Genetically determined autoimmune beta cell destruction; pre-type 1 diabetes; primary and recurrent insulinitis]

sites of inflammation. Ferumoxytol-MRI of the patient group showed clear evidence of ferumoxytol accumulation in the pancreas, indicating ongoing inflammation. MR images from the control group did not show the same accumulation. The MRI technique could help better define which patients will progress to diabetes and classify subgroups of patients who might benefit from different therapeutic strategies.^[42]

Islet cell autoantibodies

The corresponding islet cell autoantigens include, insulin antibodies (IAA), glutamic acid decarboxylase (GAD), tyrosine phosphatase-like protein (ICA 512 and IA-2) and zinc transporter 8 (ZnT8). Like in other autoimmune diseases, islet cell autoantigens are proving not to be only passive targets for beta cell destruction, but many [?] all of them seem to have significant physiological functions in the β -cells.

In a representative study, the prevalence of diabetes-associated autoantibodies in children with newly diagnosed type 1 diabetes was as follows: Islet cell cytoplasmic antibodies (ICA): 92.3%, glutamic acid decarboxylase antibodies (GADA): 67.0%, insulinoma-associated autoantibody (IA-2A): 76.0%, IAA: 44.8% and zinc transporter 8 A (ZnT8A): 62.7%. It was also found that 98% of newly diagnosed children had one or more antibodies, and 34% of children had nearly 4 antibodies.

Each antibody has different characteristics and possibly different pathophysiologic roles in type 1 diabetogenesis. The prevalence of all islet cell antibodies, except GAD, decreases with age in T1DM. Once the β cells are destroyed, the antibodies also subside. It is also found that younger the age, higher is the prevalence and titers of insulin antibodies, and faster is the β -cell destruction. However, this relation does not exist for GAD65 and ICA512 antibodies.

Persons with the A/A genotype for the insulin gene have higher IAA levels than people with A/T or T/T type. MHC haplotype sharing increases the risk of developing diabetes in DR3/4-DQ8 siblings, who also have higher percentage of autoantibodies. Risk is greater with those who share 2 MHC haplotypes, as opposed to those who share 1 or none. Beta cells for people with ICA + 0602 + DQ allele are apparently protected, and hence there is a lack of progression to diabetes in them.

Following the pioneering Joslin Prediabetes Registry Study of the 1980s,^[16] a number of natural history studies, including the Diabetes and Autoimmunity Study in the Young, Diabetes Prevention Trial Type-1, TrialNet, The

Environmental Determinants of Diabetes in the Young, Prospective Assessment in Newborns for Diabetes Autoimmunity etc. have been conducted and data published on genetic, environmental and autoimmune determinants of type 1 diabetes.

Environment

The only definite environmental factor is congenital rubella, because of which children subsequently develop type 1 diabetes (an increased incidence of IDDM has been reported in patients with congenital rubella syndrome [CRS]. Diabetes can be classed among the delayed complications of CRS, but the overall incidence of insulin-requiring childhood-onset diabetes is more likely to have been in the range 1-3%, compared with higher values (20%) cited in the earlier literature]. The putative predisposing factors are viruses (enteroviruses and rotaviruses) and components of infant diet including gluten and cow's milk. The putative protective factors are gut flora, helminths, viral infections, and sunlight (Vitamin D).

Prospective Finnish studies indicate that there is a temporal association between enteroviral infections and the first appearance of diabetes-associated antibodies. An antidiabetogenic vaccine is potentially feasible based on a few enterovirus serotypes.

The type 1 diabetes prediction and prevention study has shown that: (a) Infants start developing islet cell antibodies as early as 3 months after birth; and (b) seroconversion of enterovirus RNA in serum to autoantibody positivity is higher in T1DM cases than in controls.

Another study showed that IgG antibodies to bovine insulin are higher in those infants who were introduced to formula-feeds before 3 months of age than in those who were exclusively breast-fed for 3 months or more. Those infants with beta-cell autoimmunity had a rise in these antibodies to bovine insulin over the study period 18 months. The relative risk of developing T1DM in relation to: (a) Early (<4 months of age) exposure to cow's milk was 1.6, and (b) short (<3 months) duration of breastfeeding was 1.5.

Studies are in progress to evaluate the possibility to reduce the frequency of diabetes-associated autoantibodies by excluding dietary cow's milk proteins over the first 6–8 months of life in subjects at increased risk of T1DM. The TRIGR study showed that children, who were given casein hydrolysate up to 8 months, had decreased prevalence of ICA, compared with the control group. Further studies are underway where infants are given a highly hydrolyzed formula (casein hydrolysate) for 6 months, and observed

whether this could be correlated with a delay in the development of antibodies and consequently delayed development of diabetes. A number of theories exist about the protective nature of the hydrolyzed formula against autoantibody production, including decreased gut permeability, maturation of regulatory T-cells in gut-associated lymphoid tissue, elimination of early exposure to intact bovine insulin, and effects on gut microbiota.

Vitamin D supplements have also been shown as an important factor in protecting T1DM development in early infancy.

PREVENTION OF TYPE 1 DIABETES

Next big idea??? hope and dream?

This includes both type 1 diabetes “prevention” and “intervention” approaches.

Prevention of T1DM can include: Primary prevention strategies before the development of autoantibodies and secondary prevention regimens after autoantibody development. Once ICA has developed, the goal is to establish a therapeutic regimen to preserve at least 90% of the beta cells and prevent the development of hyperglycemia.

The targets for T1DM reversal should include autoimmunity, beta cell regeneration and protection of beta cell mass. Studies showed that delayed exposure to gluten did not delay development of T1DM. Neither parenteral insulin nor oral insulin delayed development of T1DM, overall. In the oral insulin trial, the children with baseline IAA ≥ 300 had delayed type 1 diabetes development for up to 10 years.

Numerous intervention immunotherapy trials have been conducted in new onset T1DM with the goal of preserving/increasing residual beta cell mass, and hopefully “switching off” of islet cell autoimmunity and beta cell destruction.

Immunotherapy intervention trials in new onset type 1 diabetes mellitus

- MMF and DZB – Peter Gottlieb, TrialNet
- HSP 65 p227 s.c. (Peptor) – Jerry, Palmer, Seattle
- Multi-dose DZB – Henry Rodriguez, Indiana
- Exenatide and DZB – David Harlan, NIH
- Oral hIFN – alpha – Kristina Rother, NIH
- Anti-CD20 – Mark Peskovitz, Indiana, TrialNet
- Anti-CD3 – Protégé Macrogenics
- Multidose anti-CD3 hOKT – Kevan Herold, ITN
- Rapamycin and IL-2, Greenbaum – ITN
- CTLA4Ig – Tihamer Orban, TrialNet

- glutamic acid decarboxylase 65 in Alum – Diamyd
- Pro-insulin DNA Vaccine – Bay Hill
- ATG (Sandostat) – Steve Gitelman, UCSF, ITN, TrialNet
- Gastrin and EGF– Phase I Trial
- Alpha 1 anti-trypsin trials: Peter Gottlieb – BDC and ITN.

Cyclosporine immunotherapy was associated with an increased remission rate in recently diagnosed T1DM (approach abandoned because of associated nephrotoxicity). Anti-CD3 teplizumab and anti-CD3 oteplizumab have been shown to provide C-peptide preservation. Potential of combination therapies are being explored (combination of immunotherapy, beta cell protection/regeneration therapies etc).

Future need and developments in the field will include: Assays for insulinitis; better quantitation of beta cell mass, beta cell death or survival; and better assays for autoantibodies and for pathogenic T-cells. The unanswered questions in diabetes research include elimination of autoimmune memory responses, re-establishment of immune self-tolerance, and mechanisms of disease initiation.

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REFERENCES

1. Srikanta S, Ahuja MM, Malaviya AN, Mehra NK, Vaidya MC. Type I (insulin-requiring) diabetes mellitus in North India: HLA and autoimmunity. *N Engl J Med* 1981;304:1175-6.
2. Srikanta S, Malaviya AN, Mehra NK, Vaidya MC, Geevarghese PJ, Ahuja MM. Autoimmunity in type I (insulin-dependent) diabetes mellitus in North India. *J Clin Immunol* 1981;1:169-73.
3. Srikanta S, Mehra NK, Vaidya MC, Malaviya AN, Ahuja MM. HLA antigens in type I (insulin-dependent) diabetes mellitus in North India. *Metabolism* 1981;30:992-3.

4. Srikanta SS, Malaviya AN, Rajagopalan P, Bhuyan U, Ahuja MM. Association of Type I diabetes mellitus, antinuclear antibody, autoimmunity and membrano-proliferative glomerulonephritis. *Diabetes Care* 1983;6:71-4.
5. Srikanta S, Ganda OP, Eisenbarth GS, Soeldner JS. Islet-cell antibodies and beta-cell function in monozygotic triplets and twins initially discordant for Type I diabetes mellitus. *N Engl J Med* 1983;308:322-5.
6. Srikanta S, Ganda OP, Jackson RA, Gleason RE, Kaldany A, Garovoy MR, *et al.* Type I diabetes mellitus in monozygotic twins: Chronic progressive beta cell dysfunction. *Ann Intern Med* 1983;99:320-6.
7. Ganda OP, Srikanta S, Brink SJ, Morris MA, Gleason RE, Soeldner JS, *et al.* Differential sensitivity to beta-cell secretagogues in “early,” type I diabetes mellitus. *Diabetes* 1984;33:516-21.
8. Srikanta S, Eisenbarth GS. Disappearing anti-islet antibodies? *Lancet* 1984;1:1176-7.
9. Srikanta S, Ganda OP, Gleason RE, Jackson RA, Soeldner JS, Eisenbarth GS. Pre-type I diabetes. Linear loss of beta cell response to intravenous glucose. *Diabetes* 1984;33:717-20.
10. Srikanta S, Ganda OP, Jackson RA, Brink SJ, Fleischnick E, Yunis E, *et al.* Pre-type 1 (insulin-dependent) diabetes: Common endocrinological course despite immunological and immunogenetic heterogeneity. *Diabetologia* 1984;27 Suppl:146-8.
11. Bhuyan UN, Dash SC, Srikanta S, Malaviya AN, Malhotra KK. Occurrence of glomerulonephritis and autoantibodies in diabetes mellitus. *J Assoc Physicians India* 1984;32:171-5.
12. Sutherland DE, Sibley R, Xu XZ, Michael A, Srikanta AM, Taub F, *et al.* Twin-to-twin pancreas transplantation: Reversal and reenactment of the pathogenesis of type I diabetes. *Trans Assoc Am Physicians* 1984;97:80-7.
13. Srikanta SS, Rabizadeh A, Omar MA, Eisenbarth GS. Assay for islet cell antibodies; Evidence that the target antigen is a sialo-glycoconjugate. *Diabetes* 1985;34:617-9.
14. Nayak RC, Omar MA, Rabizadeh A, Srikanta S, Eisenbarth GS. “Cytoplasmic” islet cell antibodies. Evidence that the target antigen is a sialoglycoconjugate. *Diabetes* 1985;34:617-9.
15. Eisenbarth GS, Srikanta S, Fleischnick E, Ganda OP, Jackson RA, Brink SJ, *et al.* Progressive autoimmune beta cell insufficiency: Occurrence in the absence of high-risk HLA alleles DR3, DR4. *Diabetes Care* 1985;8:477-80.
16. Srikanta S, Ganda OP, Rabizadeh A, Soeldner JS, Eisenbarth GS. First-degree relatives of patients with type I diabetes mellitus. Islet-cell antibodies and abnormal insulin secretion. *N Engl J Med* 1985;313:461-4.
17. Soeldner JS, Tuttleman M, Srikanta S, Ganda OP, Eisenbarth GS. Insulin-dependent diabetes mellitus and autoimmunity: Islet-cell autoantibodies, insulin autoantibodies, and beta-cell failure. *N Engl J Med* 1985;313:893-4.
18. Eisenbarth GS, Srikanta S, Jackson R, Rabinowe S, Dolinar R, Aoki T, *et al.* Anti-thymocyte globulin and prednisone immunotherapy of recent onset type 1 diabetes mellitus. *Diabetes Res* 1985;2:271-6.
19. Srikanta S, Ricker AT, McCulloch DK, Soeldner JS, Eisenbarth GS, Palmer JP. Autoimmunity to insulin, beta cell dysfunction, and development of insulin-dependent diabetes mellitus. *Diabetes* 1986;35:139-42.
20. Eisenbarth GS, Srikanta SS, Rabinowe SL, Jackson RA, Ganda OP, Soeldner JS. Restoration of first phase insulin secretion by daily prednisone in two islet cell antibody positive non-diabetic individuals. *Transplant Proc* 1985;XVIII: 305-808.
21. Srikanta S, Eisenbarth GS. Islet cell antigens. Initial studies of their biology and function. *Mol Biol Med* 1986;3:113-27.
22. Rabinowe SL, Srikanta SS, Jackson RA, Nayak RC, Ganda OP, Soeldner JS, Eisenbarth GS. “Prediction” of Overt Type I Diabetes and Pilot Trials of Immunomodulation. Proceedings of the 12th Congress of the International Diabetes Federation. Madrid, Spain: Elsevier Science Publishers, BV Amsterdam, The Netherlands; 1985.
23. Srikanta S, Krisch K, Eisenbarth GS. Islet cell proteins defined by monoclonal islet cell antibody H1SL-19. *Diabetes* 1986;35:300-5.
24. Krisch K, Buxbaum P, Horvat G, Krisch I, Neuhold N, Ulrich W, *et al.* Monoclonal antibody H1SL-19 as an immunocytochemical probe for neuroendocrine differentiation. Its application in diagnostic pathology. *Am J Pathol* 1986;123:100-8.
25. Nayak RC, Spitalnik SL, Rabizadeh A, Srikanta SS, Eisenbarth GS. Islet Cells Autoantigen (s) in Type I Diabetes Mellitus. Preliminary Biochemical Characterization. Proceedings of the Second International Conference on Human Tissues and Organs for Research Interchange, Washington, DC, USA; 1985.
26. Ganda OP, Srikanta S, Gleason RE, Soeldner JS, Eisenbarth GS. Diminished A-cell secretion in the early phase of type I diabetes mellitus. *Metabolism* 1986;35:1074-7.
27. Kaye WA, Adri MN, Soeldner JS, Rabinowe SL, Kaldany A, Kahn CR, *et al.* Acquired defect in interleukin-2 production in patients with type I diabetes mellitus. *N Engl J Med* 1986;315:920-4.
28. Omar MA, Srikanta SS, Eisenbarth GS, Human islet cell auto antibodies: Immunoglobulin class and subclass distribution defined by monoclonal antibodies. *Diabetes Res* 1987;4:155-8.
29. Baekkeskov S, Landin M, Kristensen JK, Srikanta S, Bruining GJ, Mandrup-Poulsen T, *et al.* Antibodies to a 64,000 Mr human islet cell antigen precede the clinical onset of insulin-dependent diabetes. *J Clin Invest.* 1987;79:926-34.
30. Srikanta S, Telen M, Posillico JT, Dolinar R, Krisch K, Haynes BF, *et al.* Monoclonal antibodies to a human islet cell surface glycoprotein: 4F2 and LC7-2. *Endocrinology* 1987;120:2240-4.
31. Dotta F, Nayak RC, Dib SA, Di Bella E, Krisch K, Posillico JT, *et al.* A novel neuroendocrine cell surface glycoprotein: Identification, isolation, and initial characterization. *Endocrinology* 1988;122:1263-8.
32. Vardi P, Dib SA, Tuttleman M, Connelly JE, Grinbergs M, Radizabeh A, *et al.* Competitive insulin autoantibody assay. Prospective evaluation of subjects at high risk for development of type I diabetes mellitus. *Diabetes* 1987;36:1286-91.
33. Krisch K, Dibella E, Buxbaum P, Horvat G, Krisch I, Neuhold N, *et al.* Islet cell proteins defined by monoclonal islet cell antibody H1SL-19: Further characterisation; 1986.
34. Bakkeskov S, Kristensen JK, Srikanta SS, Poulsen TM, de Beaufort C, Soeldner JS, *et al.* Antibodies to a Mr 64000 human islet cell antigen precedes the clinical onset of insulin-dependent diabetes. *J Clin Invest* 1987;79:934.
35. Karasik A, O’Hara C, Srikanta S, Swift M, Soeldner JS, Kahn CR, *et al.* Genetically programmed selective islet beta-cell loss in diabetic subjects with Wolfram’s syndrome. *Diabetes Care* 1989;12:135-8.
36. Catalano PM, Bernstein IM, Wolfe RR, Srikanta S, Tyzbit E, Sims EA. Subclinical abnormalities of glucose metabolism in subjects with previous gestational diabetes. *Am J Obstet Gynecol* 1986;155:1255-62.
37. Pre-hyperglycemic diabetes mellitus. Soeldner JS, Srikanta S, Eisenbarth GS, Gleason RE. *Clin Chem.* 1986 Oct; 32 (10 Suppl):B7-18. Review.
38. Raju R, Srikanta S, Kharbanda K, Kochupillai N. Islet Cell antigens and autoantigen (s): Monoclonal antibodies and further characterization, *J Biosci* 1992;17:313-23.
39. Raju R, Srikanta S, Shah P, Kochupillai N. I-45 islet cell antigen is a 68kD neuroendocrine protein. *Immunol Invest* 1995;24:573-82.
40. Vardi P, Dibella EE, Pasquarello TJ, Srikanta S. Islet cell

autoantibodies: Pathobiology and clinical applications. *Diabetes Care* 1987;10:645-56.

41. Jeffrey A. Bluestone, Kevan Herold, and George Eisenbarth. Genetics, pathogenesis and clinical interventions in type 1 diabetes. *Nature* 2010;464:1293-300.
42. Noninvasive mapping of pancreatic inflammation in recent-onset type-1 diabetes patients. Jason L. Gagliaa, Mukesh Harisinghanib, Iman Aganjc,

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