**Primary, Secondary and Tertiary Prevention of Type 1 Diabetes Mellitus**

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**Abstract: Objective:** Studying prevention of type 1 diabetes mellitus: primary, secondary, and tertiary. **Background:** Diabetes is an increasingly important metabolic disease, globally In 2013 there are 382 million people with diabetes and this is expected to rise to 592 million by 2035. Type 1 diabetes (T1DM) is an immunologically mediated disease, prevention studies undertaken is (primary, secondary and tertiary prevention). **Materials and Methods:** All available published articles were reviewed including Textbooks, Journals, and Website for conduction of the research. **Results:** Advances in treatment for subjects with T1DM are not yet sufficient to prevent the harmful effects of diabetes and the early morbidity and mortality still associated with the disease. Increased understanding of the natural history of the T1DM disease process expanded the concept of prevention to include primary, secondary and Tertiary prevention. **Conclusions:** A variety of immune interventions have been used some immunosuppressive and some immunomodulatory drugs. A lasting clinically beneficial response has not yet been forthcoming.

[Sanaa S. Gazareen, Ahmed A.M. Shoaib, Alaa A.E. Dawood and Samy M. Haggag. **Primary, Secondary and Tertiary Prevention of Type 1 Diabetes Mellitus.** *Nat Sci* 2015;13(2):122-127]. (ISSN: 1545-0740). <http://www.sciencepub.net/nature>. 20

**Key words:** Primary, Secondary, Tertiary, Prevention, Type 1 Diabetes.

1. **Introduction:**

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction and failure of different organs especially the eyes, kidneys, nerves, heart, and blood vessels(1).

T1DM is an autoimmune condition in which the insulin-producing β-cells of the pancreas are destroyed and hence the body loses its ability to produce insulin(2).

Its diagnosis based on plasma glucose criteria either the fasting plasma glucose or the 2-h plasma glucose value after a 75-g oral glucose tolerance test. Recently, the International Expert Committee added the A1C (threshold ≥ 6.5%) as a third option to diagnose diabetes. The A1C test should be performed according to National Glycohemoglobin Standardization Program and standardized to the Diabetes Control and Complications Trial reference assay(3).Figer (1).

The highest reported incidences of T1DM occur in Finland and Sardinia (37- 65 per $10^{(5)}$children ≤15 years). Rates in these countries are almost 400 times that of Venezuela and parts of China which have the lowest incidence (0.1 - 0.5 per $10^{(5)}$ children) The age of presentation of childhood onset T1DM has a bimodal distribution, with one peak at (4-6) years of age and a second in early puberty (10 - 14 years of age). Overall, about 45 % of children present before 10 years of age.(4).

It is generally believed that β-cell autoantigens, macrophages, dendritic cells, B lymphocytes, and T lymphocytes are involved in the β-cell-specific autoimmune process. It is necessary to determine what exact factors are causing the immune system to become unregulated in such a manner as to promote an autoimmune respons (5).

Diabetes is a group of chronic diseases characterized by hyperglycemia, generally the injurious effects of hyperglycemia are separated into macrovascular complications (coronary artery disease, Peripheral arterial disease and stroke) and microvascular complications (diabetic nephropathy, neuropathy and retinopathy)(6).

Type 1 diabetes is an immunologically mediated disease, immune intervention should alter the natural history of the disease. prevention studies undertaken either prior to any evidence of autoimmunity (primary prevention) or after the development of islet autoantibodies (secondary prevention) and halting or reversing β-cell loss after clinical presentation of T1D (tertiary intervention)(7).

**2. Materials and Methods**

This research was written at Internal Medicine Department. After approval of the Local Institutional Ethical Committee of Menoufia University Hospital and all available published articles were reviewed including Textbooks, Journals, and Website for conduction of the research.

**3. Results and Discussion:**

Type 1 diabetes results from the destruction of pancreatic β-cells by a β-cell-specific autoimmune process. The mechanisms involved in the β-cell destruction are still not clear. It is necessary to determine what exact factors are causing the immune system to become unregulated in such a manner as to promote an autoimmune respons(5).

*Complications***:**

*Diabetic Nephropathy*:

Diabetic nephropathy occurs in 20–40% of patients with diabetes and is the single leading cause of end stage renal disease. Persistent albuminuria in the range of 30–299 mg/ 24 h has been shown to be an early stage of diabetic nephropathy in T1DM and a marker for development of nephropathy in type 2 diabetes. (8).

*Diabetic Retinopathy*:

In younger patients with T1DM, micro aneurysms count predicts long-term incidence of proliferative diabetic retinopathy and diabetic macular edema. This demonstrates that early DR is a warning sign of late retinopathy complications and that the number of micro aneurysms is an important factor for long term outcome (9).

*Diabetic Neuropathy*:

A prospective study of patients with T1DM reported that the overall prevalence of diabetic neuropathy ranged from 18% to 58 % at baseline, in patients with type 2 diabetes the prevalence was 28 %(10).

There are almost 500,000 children aged under 15 years with T1DM worldwide, the largest numbers being in Europe and North America. The United States, India and Brazil were the highest Countries estimated numbers of new cases annually, the numbers have increased in most of the IDF Regions when compared with the prevalence estimates made in previous editions. Monogenic diabetes is increasingly being recognized as genetic studies become available(10).

*Prediction of T1DM:*

Diabetes progresses from genetic risk to immune activation to β-cell injury to impaired insulin secretion to glucose intolerance and finally to frank disease. Identifying individuals at risk for T1DM before substantial islet injury is our best chance for diabetes prevention, If diabetes can be predicted earlier it may be possible to prevent disease progression while an adequate islet mass remains to maintain eugly­cemia throughout a patient’s lifetime. (11).

There is a need for diagnostic biomarkers to detect more accurately individuals with prediabetes to accelerate targeting for prevention and intervention strategies. The researches generated five major categories of markers (genetic, autoantibody, risk score quantification, cellular immunity and β-cell function). The current standard used to assess T1DM onset or predisposition focuses on autoimmune pathology and disease-associated autoantibodies. Thus, novel techniques are discussed with the potential to estimate degrees of β-cell stress and failure via protein, RNA and DNA analyses.(12).

*Genetic Prediction:*

The first-degree relatives have a higher risk than the general population, siblings have a higher risk (6%) than offspring and there is a high concordance rate in identical twins with diabetes(approximately 50%)(13).

The genetic screening for susceptible HLA-DQB1 alleles and the follow-up of higher-risk newborn Finnish children identified 77% of those who developed the disease before 3 years of age.(14).

*Autoantibody Prediction:*

Diabetes Autoimmunity Study in the Young (DAISY) study demonstrated that over 70% of children expressing multiple islet auto antibodies progress to T1DM in 10 years compared to 15% of those with one autoantibody. Once islet autoimmunity spreads to more than one auto antigen, the progression to T1DM is only a matter of time and the rate of progression is linear and hardly influenced by the HLA-DR,DQ genotype or family history of T1DM (15).

Zinc transporter-8(ZnT8) recently identified as an autoantigen in T1DM, ZnT8A complements and GADA increases the diagnostic sensitivity for detection of autoimmunity in T1DM. Inclusion of ZnT8A increases the proportion of patients with antibody positivity to nearly 80%. ZnT8A can replace IA2A as a serological marker for autoimmunity in T1DM patients without loss of sensitivity and specificity. Combined use of ZnT8A and GADA could detect 97% of antibody positive patients (16).

*Prevention of T1DM:*

Increased understanding of the natural history of the T1DM disease process expanded the concept of prevention to include (primary Prevention) in which the goal is to stop the initiation of autoimmunity (Secondary Prevention) in which the goal is to stop the progression of immune-mediated beta cell destruction and prevent clinical disease and (Tertiary Prevention) with the aim of easing daily management of diabetes and diminishing its complications (17).figer (2, 3).

*Primary Prevention:*

As primary prevention is directed at individuals with no signs of autoimmunity or metabolic impairment and uncertainty as to whether they will actually develop T1DM. Interventions tested must be extremely safe. All primary prevention trials to date have involved dietary interventions designed to interrupt putative environmental triggers of T1DM. No specific dietary factor has been shown to be an obvious risk factor for β-cell autoimmunity or T1DM (18).

*The Trial to Reduce T1DM in the Genetically at Risk:*

This is the first ever primary prevention trial for T1DM and if completed successfully will provide a definite answer and determine whether weaning to a formula comprised of hydrolyzed protein compared with a standard intact foreign cow’s milk protein formula reduces the cumulative incidence of diabetes predictive auto antibodies and/or clinical diabetes over the first 6 years of life and to assess whether weaning to the hydrolyzate reduces the cumulative incidence of T1DM in these participants by 10 years of age. The first endpoint of TRIGR meaning positivity for two or more T1DM -associated auto antibodies and/or clinical diabetes by the age of 6 years. The primary and final endpoint of TRIGR will be reached early in 2017(19)**.**

*BABYDIET Study:*

A nutritional interventions primary prevention studies aiming to determine whether delaying the introduction of gluten in infants with a genetic risk of islet autoimmunity may reduce the risk of T1DM associated islet autoimmunity. The primary end point was the development of persistent auto antibodies to one or more of the antigens insulin, GAD65 or IA-2A. Some children developed islet auto antibodies during the first 3 years, some children developed more than one islet autoantibody, the probability of developing any islet autoantibody by the age of 3 years in the total cohort was 12%. concluding that this primary dietary prevention trial had no effect on appearance of islet antibodies(20).

*Vitamin D and Prevention of T1DM****:***

Both forms of immunity (adaptive and innate) are regulated by 1, 25(OH) 2D3. The immune-modulatory properties of vitamin D suggest that it could play a potential therapeutic role in prevention of T1DM. It is postulated that large doses of vitamin D supplementation may influence the pattern of immune regulation and subsequent progression to T1DM in a genetically susceptible individual. More studies are required to demonstrate the relation between T1DM and vitamin D/vitamin D analogues in the pattern of immune regulations in susceptible individuals (21).

*Secondary Prevention of T1DM:*

Secondary prevention is targeted at individuals with persistent islet autoantibodies. The goal of such intervention is to arrest the immune process and thus prevent or delay clinical disease, ongoing trials involve the use of nicotinamide or antigen-specific therapies, including parenteral, oral and nasal insulin or the intradermal proinsulin peptides and a vaccine with (GAD). When clinical symptoms are observed the autoimmune process is markedly advanced (60- 80% of the ß-cell mass have been destroyed at the time of diagnosis) (22).

*Nicotinamide*

The effects of nicotinamide in at-risk relatives of individuals with T1DM, after following up for about 4 years was shown that the rates of T1DM development in nicotinamide and placebo groups were essentially the same. Nicotinamide thus had no effect on the prevention or delay of T1DM development in at-risk relatives(23).

Insulin is a β-cell-specific antigen so multiple approaches have been conducted for the interventions using it. It is quite advantageous to employ the insulin therapy in individuals with anti-islet autoimmune responses. Firstly the β-cell load will be reduced in the state of subclinical T1DM. Secondly immunological tolerance is expected to be induced. In fact delayed disease progression was observed in pilot studies of parenteral insulin as prophylaxis among first-degree relatives of T1DM patients with anti-islet cell autoantibodies(24)**.**

*Nasal insulin:*

The Intranasal Insulin Trial is an ongoing randomized placebo-controlled trial with nasal insulin at either 1.6 mg or 16 mg to evaluate whether nasal insulin is effective on anti-islet autoimmune responses. The Diabetes Prediction and Prevention trial in Finland was using nasal insulin in children with genetic risk of T1DM who were positive for islet cells and anti-insulin autoantibodies, the trial showed that the nasal insulin had no effect on the protection of the disease and the modulation of the anti-insulin autoantibodies indicating that the anti-insulin autoimmunity was already mature at the start of the intervention (25).

*Autologous Infusion Followed By Oral (DHA) and Vit D****:***

Stimulated C-peptide to determine if autologous umbilical cord blood(UCB) infusion followed by 1 year of supplementation with vitamin D and Docosoahexaenoic acid (DHA) can preserve C-peptide in children with T1DM. Autologous UCB infusion one year of daily oral Vit D (2,000IU) and DHA (38mg/kg) and intensive diabetes management. Primary analyses were performed 1 year following UCB infusion. The result was that autologous UCB infusion followed by daily supplementation with Vit D and DHA was safe but failed to preserve C-peptide, lack of significance may reflect small sample size. Future efforts will require expansion of specific immunoregulatory cell subsets, optimization of combined immunoregulatory and anti-inflammatory agents and larger study group (26).

*Tertiary Prevention:*

The goal of tertiary intervention trials at or after disease onset is to halt the destruction of remaining β-cells perhaps allowing these residual β-cells to recover function hopefully reducing the severity of clinical manifestations and disease progression. A variety of immune interventions have been used some immunosuppressive and some immunomodulatory drugs, unfortunately a lasting clinically beneficial response has not yet been forthcoming (27).

*Anti-CD3(Teplizumab):*

Three intravenous teplizumab dosing regimens administered daily for 14 days at baseline and after 26 weeks in new-onset UCB. After 2 years of follow-up. Teplizumab (14-day full-dose) reduced the loss of C-peptide mean area under the curve (AUC), exogenous insulin needs tended to be reduced versus placebo, antidrug antibodies developed in some patients without apparent change in drug efficacy, no new safety or tolerability issues were observed during year 2, in summary anti-CD3 therapy reduced C-peptide loss 2 years after diagnosis using a tolerable dose (28).

*Anti-CD20 (Rituximab):*

By investigating the role of follicular helper T (Tfh) cells and the effect of(Rituximab) on Tfh cells from T1DM patients demonstrated that the frequencies of circulating Tfh cell and serum IA2A were decreased, the levels of IL-21, IL-6 and Bcl-6 mRNA were decreased after treatment. β-cell function in 10 of 20 patients was improved, indicating that Tfh cells may participate in the T1DM-relateded immune responses and β-cells might play a role in the development of Tfh responses in the disease progression(29).

*Abatacept:*

**Figure (1): Criteria for diagnosis of diabetes**

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| Criteria for Diabetes Diagnosis: 4 options |
| A1C ≥6.5%\*method and standardized to DCCT assay |
| FPG ≥126 mg/dL (7.0 mmol/L)\* Perform in lab using NGSP-certifiedFasting defined as no caloric intake for ≥8 hrs |
| 2-hr PG ≥200 mg/dL (11.1 mmol/L) during OGTT (75-g)\* |
| Random PG ≥200 mg/dL (11.1 mmol/L)In persons with symptoms of hyperglycemia or hyperglycemic crisis |
| \*In the absence of unequivocal hyperglycemia results should be confirmed using repeat testing |

DCCT=Diabetes Control and Complications Trial; FPG=fasting plasma glucose; OGTT=oral glucose tolerance test; PG=plasma glucose

***(American Diabetes Association, 2014).***



**(Wherrett & Daneman., 2011).**(17)

**Figure (2): Natural history of type 1 diabetes and prevention opportunities**.



**(Wherrett& Daneman., 2011).**(17)

**Figure (3): Natural history of type 1 diabetes**

Co stimulation blockage by Abatacept significantly slows decline of β-cell function after diagnosis of T1DM by evaluating peripheral blood immune cell subsets (CD4, CD8 naïve, memory and activated subsets,…..) by following up at baseline, 3, 6, 12, 24 and 30 months after treatment there was an increase in central memory,CD4 T-cells and significantly associated with C-peptide decline at the subsequent visit, so the quantification of CM CD4 T-cells can provide a substitute immune marker for C-peptide decline after diagnosis of T1DM and that co-stimulation blockade may exert its beneficial therapeutic effect via modulation of this subset (30).

**Conclusions:**

Type 1 diabetes or more accurately type 1A diabetes is thought to arise from selective immunologically mediated destruction of the insulin- producing β-cell with consequent insulin deficiency. Prevention of T1DM would require interventions aimed to avoiding exposure to environmental triggers early in life(primary prevention), interfering with the autoimmune cascade that occurs during β-cell destruction (secondary prevention) and halting or reversing β-cell loss after clinical presentation of T1DM (tertiary intervention). Once T1DM has developed, immune interventions are unlikely to be effective. Genetic engineering and stem cell biology hold out the most hope in the long run for a cure for T1DM and elimination of the need to inject insulin, however successful therapy for diabetes and other immune disorders remains indefinable.

**No funds.**

**Conflicts of interest:** No

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2/16/2015