ECRONICON OPEN ACCESS

EC DIABETES AND METABOLIC RESEARCH

Research Article

Path Directed towards a Stage when we almost Cure Type1 Diabetes Mellitus (T1dm) after a Century of Insulin Advent

Kulvinder Kochar Kaur[1]*, Gautam Allahbadia[2] and Mandeep Singh[3]

[1]*Scientific Director, DR Kulvinder Kaur Centre For Human Reproduction, Jalandhar, Punjab, India*

[2]*Scientific Director, Rotunda-A Centre for Human reproduction, Mumbai, India*

[3]*Consultant Neurologist, Swami Satyanand Hospital, Jalandhar, Punjab, India*

***Corresponding Author:** Kulvinder Kochar Kaur, Scientific Director, DR Kulvinder Kaur Centre For Human Reproduction, Jalandhar, Punjab, India.

Received: February 22, 2020; **Published:** May 30, 2020

Abstract

Following the discovery of insulin lives of type 1 diabetes mellitus (T1DM) patients changed dramatically so that what was literally a death warning became a disease that could be controlled although still remaining a chronic disease, with insulin not curing the disease process, rather only its consequences i.e. blood sugars. Noticeably insulin does not achieve normoglycaemia. Despite maximum sophisticated, practically 'near closed loops' ways, glucose homeostasis does not get back to normal. Both short as well as long term complications are incurred by T1DM patients, with hypoglycaemic as well as hyperglycaemic events as well as long term effects of enhanced glycosylation of proteins resulting in eye, renal, central nervous system (CNS) as well as other complications. These sequelae are correlated with marked morbidity as well as mortality despite following aggressive insulin treatment. Practically a century after insulin discovery, we still battle with the hurdle of addressing disease process by itself, just to make the life of these patients better. Lot of work have been done to be able to totally arrest the autoimmune mechanism damaging the insulin synthesizing cells within the pancreas, or minimum at least reduce the speed of the process for blunting as well as delaying short as well as long term complications. Basic idea is to discuss a method that might aid in quantitative result measurements by particular therapies, short or clinical cure might be contrasted and exact advantage of their help in DM treatment might get assessed by the T1DM metabolic recovery index (DMMRI).

Keywords: *T1DM; Autoimmune Process; Metabolic Checking; DMMRI*

Introduction

Before insulin [1] was discovered, survival of type 1 diabetes mellitus (T1DM) patients was just few years maximum with only available therapy method was forcible starvation. With the advent of insulin as replacement treatment patients lives changed as did their prognosis. Still till date with utilization of methods that are much more sophisticated [2] still hurdles of abnormal blood sugars [3], with their short as well as long term complications exist [4-6]. Still no permanent treatment is there either for patients/clinicians.

Earlier we had reviewed the etiopathogenesis as well as the management of T1DM in details besides role of carbohydrate therapy along with use of SGLT2 inhibitors in T1DM and recently on immunotherapies that are getting tried to get an insulin independent status [7-10].

In this minireview we analyze how one can optimize the recent advances to develop almost complete cure in T1DM.

Methods

We did a pubmed search regarding optimization of recently used trials for advances in T1DM therapy and update over what we had reviewed earlier.

Results and Discussion

We found a total of 67 articles. No meta-analysis was done.

Etiopathogenesis of T1DM (Genetic and environmental factors)

T1DM forms via elimination of the immune system against the β-cell antigen along with provocation of proinflammatory responses. Following presentation of beta-cell antigens to the immune system via antigen presenting cells (APC), chronic immunological responses start secondary to improper control of immunological reactions that result in the β-cell destruction. β-cell death through virus directed/physiological modes stimulates liberation of antigens as well as onset of immune responses against other β-cells. Mostly dendritic cells (DC's) take up these Antigens, presenting them to T-cells. Possibility of any autoimmune process can be there only if autoreactive T-cells have escaped thymic negative selection. Autoreactive T-cells, that get activated via DC's stimulate Autoreactive T as well as B-cells. Ultimately effector mechanisms of the β-cell destruction need the collective action of DC's, macrophages, T as well as B cells and natural killer (NK) cells [11]. Of the environmental factors decrease in gut microbiota (GM), obesity, early fruit introduction or cow milk in childhood, gluten, toxins, absence of vitamins as well as viruses [12-14]. Moreover, pancreas take part in etiopathogenesis of T1D. Immune cell confrontation with GM occurs early in childhood, that activates immunocontrolling modes that control autoimmune reactions-a phenomenon called "hygiene-hypothesis". Toll like receptor 4 (TLR4), stimulating lipopolysaccharides (LPS), as well as other bacterial products which have contact with immune system are documented as suppressors of immunity [15]. Thus, decrease in GM loss of control of immune system followed by immune cell actions against cells of self-ultimately T1D [16]. 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, overload 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 autoantibody, in view of cross reactivity between bovine as well as human insulin [12]. Gluten foods (cereals) in children < 3 yrs =>significant increase in islet autoantibody synthesis. DM patients with HLA-DR allele have increased T-cell reactivity to gluten derived polypeptides. This is secondary to interferon ɣ (IFNɣ) as well as IL-17 liberation. Intestinal inflammation as well as T cell activation induced by gluten β-cell autoimmunity [17]. Vit D can modify T as well as B-cells function. VDR agonists Treg cell induction. By stimulation of tolerance [18] 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 i) a direct cytolytic action on β-cells 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, retrovirus etc [19]. 60 Genes identified by gene wide association system (GWAS). Genetic factors-HLA and 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 and thymus epithelium. In thymus epithelium they cause presentation of self-antigen that self-tolerance. Inefficient HLA-class alleles-in interacting and presenting insulin in thymic epithelium are relatively related to T1D [20]. 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 T-cell 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 [21]. CTLA4-key for regressive function of Treg in mice- CTLA4 dampens immune response via both effector and Treg. BTB and 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 [22]. Various IL and ILR genes like IL10, IL12 and 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 and environmental factors of T1D. IF1H1-evokes immune response against RNA viruses. IF1H1 variants-decreased expression-protective against T1D [23]. Immune β-cell destruction mediated by extrinsic apoptotic pathway involves FAS mediated T cell interaction and proinflammatory cytokines like IL-1β and IFNɣ [18]. BACH2-also inhibits BIM activation and JNK1 phosphorylation via β-cell response to proapoptotic signals. It cross-talks with PTPN22-an inhibitor of proapoptotic protein JNK1 [24]. This pathway targeted by other T1D genes like CTSH and GLIS3 [25]. TNFAIP3 another T1D gene gives negative feedback loop for proapoptotic action of NFκB [26].

Modulation of microbiota

It is well known that both small and large intestine house a trillion microorganisms that belong to over 100 species. Changes in intestinal bacteria has a role in development of obesity and glucose tolerance along with NAFLD has been proven [27-33]. In case of TID more important publications in both mice models as well as humans benefit of *Akkermansia muciniphila* administration insulin sensitivity as well as glucose homeostasis, healthier lipid profile with a proinflammatory tone besides other changes [34]. Giongo., *et al.* used samples

from 8 Finnish children of which 4 cases later developed T1D with rest 4 being controls showed that the case children's samples had an unsatisfactory formation of GM diversity, that did not become as complex as that of controls as well as had heterogeneity among cases [34]. They emphasized on the significance of a compromised phylogenetic diversity in a risk of forming autoimmune DM and lay down the basis of potential screening criteria. This was corroborated by a Chinese study [35]. Long cohort studies, and RCT like FINDIA (Finnish Dietary Intervention Trial for the Prevention of type 1 diabetes), BABYDIET (in German infants), TRIGR (Trial to Reduce IDDM in the Genetically at Risk)and TEDDY of other lots gave important knowledge as to the natural history of T1D along with how GM participate [36]. More information about enriched intestinal segmented filamentous bacteria (SFB) was provided by Krigel., *et al.* [37] regarding formation as well as propagation of DM in NOD mice. Though a protective role of SFB's could not be assumed, their conclusions were that SFB's in certain ways ameliorated the propagation of T1D as well as facilitate a boost in certain T-helper cell sub-populations. Earlier SFB's were thought to be latent but present proof gives clues that they; possess part in mucosal immunity as well as immune response.

Summary

From these observations it is clear that GM should not be ruled out regarding management of T1D. With the information present, mainly the protective human studies. point to a major part of GM in the risk as well as formation of autoimmune disorders. Trying to find specific targets in the GM would aid to increase the efficacy of these innovative methods and give diabetic patients alternative medical therapy.

Problems with immunotherapy

The key pitfall of the immune cells targeted therapies is the absence of finding the T1DM particular immune cells taking part in and causing the autoimmunity. What we understand today is that TIDM particular CD4+T cells [12] that are not controlled by the regulatory T cells [38], get stimulated with antigen presenting cells (APC) [39], CD8+T cells [40] and possibly other parts from the immune system collect with the music system that take part in the autoimmune damage of the pancreatic beta cell. Till one knows the exact T1DM particular T cells as well as other immune cells taking part in the widening orchestra of autoimmunity when the disease propagates, it is just not feasible to form any particular immune repressive therapies. Blanket immune suppression have been utilized by certain trials like ATG (Anti-thymocyte globulin) [41], whereas other ones utilized ones with specificity that are T-cell or APC (B-cell) particular -therapies like anti- CD3 [42], CTLA4-Ig like abatacept [43] or antiCD20 with Rituximab B [44].

Regulatory T cells (Tregs) have been demonstrated to be defective in the autoimmune disease setting. Hence, attempts to repair or replace Tregs in T1D might reverse autoimmunity as well as protect the remnant insulin producing beta cell. On this basis of this premise, a robust method has been formed regarding isolation as well as expansion of Tregs from patients having T1D. These expanded Tregs retained their T-cell receptor diversity and displayed increased functional action. Bluestone., *et al.* reported a phase 1 trial for assessment of safety of Tregs adoptive immunotherapy in T1D. 14 adult subjects with T1D, in 4 dosing cohorts, received *ex vivo* -expanded autologous CD4+CD127lo/-CD25+polyclonal Tregs (0.05×10^8 to 26×10^8 cells). A subset of the adoptively transferred Tregs was long lived, with upto 25% of the peak level remaining in the circulation at 1 year following transfer. Immune studies illustrated transient escalation in Tregs in recipients and retained a broad Tregs FOXP3+CD4+CD25hiCD127lo phenotype long term. No infusion reactions or cell therapy -associated high grade side effects were observed. C-peptide levels persisted out to 2+ year after transfer in various individuals. These results supported the formation of a phase 2 trial for evaluating the efficiency of Treg therapy [45]. T cells have been identified as key players in the pathogenesis of type 1 diabetes. However, the exact role of T-cell subpopulations in this pathway is presently unknown. The purpose of this study was to assess the expression pattern of two lineage-specifying transcription factors GATA-3 and T-bet, which are important in T helper type 1 (Th1) and Th2 cell development, respectively. Gene expression analysis of peripheral blood mononuclear cells (PBMCs) was performed using reverse transcription-quantitative polymerase chain reaction (RT-qPCR). Plasma levels of IFN-γ and IL-4 were also determined by ELISA. T-bet and IFN-γ gene expression was significantly lower in patients group compared with healthy controls ($p < 0.05$). The expression of GATA-3 was relatively similar in patients and controls; however, IL-4 mRNAs were significantly increased in the PBMCs from patients as compared with normal controls ($p < 0.05$). In addition, a marked increase in plasma IL-4 levels were observed in patient group compared with controls ($p < 0.001$). To the contrary, IFN-γ protein levels were decreased in patients in comparison with controls ($p < 0.001$). These data suggest additional implications of the role of Th1/Th2 imbalance for the immunopathogenesis of type 1 diabetes [46].

There are many aspects regarding getting cure i) immunological ii) clinical iii) metabolic, all needing proper analyses. Immunological cure means to arrest the markedly auto aggressive immune response by either immune cells taking part in the pathological process are totally removed, incapacitated or repressed totally. Clinical cure means total lack of symptoms of DM, without need of therapy, insulin or

other means. This doesn't imply that the pancreatic beta cells are totally functional. Metabolic cure means a stage when the total initial β cell mass and its function are totally replenished. This covers both immunological as well as clinical cure (Figure 1).

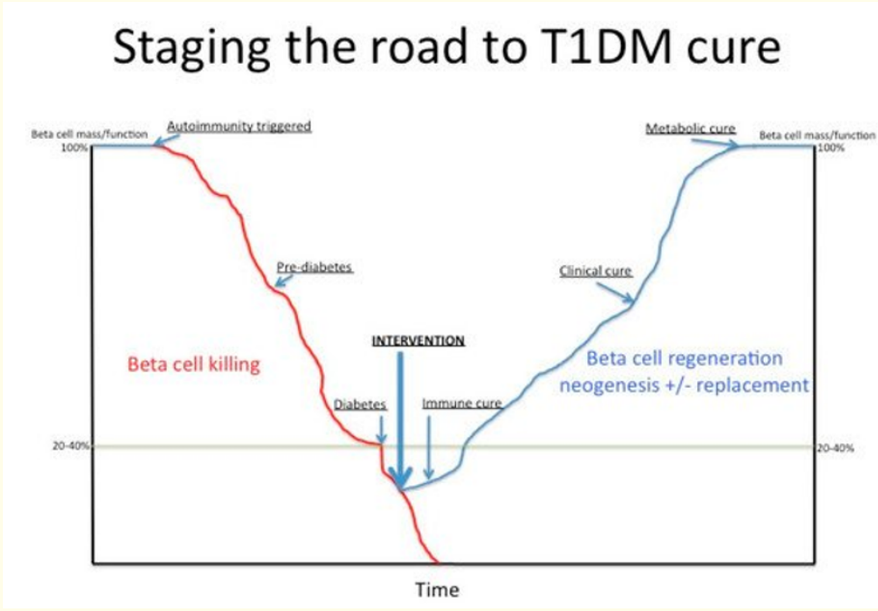

Figure 1: *Courtesy reference number [48]: The road to clinical type 1 diabetes (T1DM) and stages of recovery from the disease.*

In 1984 Eisenberth elaborated the various phases of the autoimmune procedure [47] in T1DM. With this newer understanding of the natural disease propagation was yielded. This now recently got further supplemented by Orban., *et al.* [48] by a method of the recovery phase from the autoimmune damage. With novel potentially cures available and being concentrated on in research need of the hour is to get a method that quantifies as well as anticipates the stages of recovery from T1DM. Hence their innovative conceptual strategy for better staging as well as characterizing both therapies as well as other interventional methods which could change T1DM autoimmunity in a helpful method. Need for an objective as well as quantitative evaluation of the progress, or its absence, in clinical interventional trials. Further also there is requirement of comparison of interventions to see the ones giving the maximum benefit and potentially club them together for obtaining a synergism.

To develop the T1DM metabolic recovery index (DMMRI) Orban., *et al.* utilized the outcome of 3 published clinical trials [55,56,64] which documented stimulated C peptide area under the curve, HbA1c as well as insulin dosages. Utilization of 3 recent trials was done in view of them being most recent as well as comprehensive, having quiet similar clinical protocol designs as well as had all these factors evaluated. Their concept was dependent on the belief that C peptide is associated with lower HbA1c as well as insulin dosages. Combination of these3 factors into one formula gives the best way in testing total outcomes.

The formula that was posited by Orban., *et al.* for T1DM metabolic recovery index (DMMRI) is displayed in Equation (1)

D HbA1c (P □ T) + (5 _ (1 □ D Insulin dose (T □ P)/1 □ D Stimulated C-peptide AUC (T □ P)) (1)

P-placebo, T-treated.

Value of 5 is indicating no effect for the intervention; Value > 5 indicates proportional improvement; Value < 5 indicates proportional worsening of the metabolic status due to intervention.

For checking immunological cure all immune cells taking part in β cell injury require to be isolated and assays formed to evaluate their no's activity, actions as well as crosstalk. Currently these represent high headed aims or theoretical thought process not converted to practice. Since T1DM particular pathological immune cells have not been isolated, a proper immunological cure remains not in site. Surrogate markers like enhanced number as well as function of regulatory T-cell cytokine profile alterations although very useful, remains unable to find correctly the immunological cure.

Clinical cure is much simpler to define i. e no symptoms, normal blood sugars (normal HbA1c) with no therapy of any kinds, which includes insulin. This does not imply that β cell health got fully recovered. β cell function might vary among 50% and 100% since it is in the so-called prediabetes state. It might also get known as 'post diabetes state'.

Metabolic cure can also be simply stated. Normal insulin amounts point to normal endogenous insulin synthesis. A normal amount of 1st phase insulin response to glucose is nearest that we can estimate β cell function that is replenished.

In the past 5 decades increased as well as concerted actions have been taken to tackle T1DM autoimmunity with 2 typical strategies, immune cell targeted therapies, or antigen concentrated treatments. All these methods do not allow getting clinical cure or metabolic cure.

The key pitfall of the immune cells targeted therapies is the absence of finding the T1DM particular immune cells taking part in and causing the autoimmunity. What we understand today is that TIDM particular CD4+T cells [49] that are not controlled by the regulatory T cells [50], get stimulated with antigen presenting cells (APC) [51], CD8+T cells [52] and possibly other parts from the immune system collect with the music system that take part in the autoimmune damage of the pancreatic beta cell. Till one knows the exact T1DM particular T cells as well as other immune cells taking part in the widening orchestra of autoimmunity when the disease propagates, it is just not feasible to form any particular immune repressive therapies. Blanket immune suppression have been utilized by certain trials like ATG (Anti-thymocyte globulin) [53], whereas other ones utilized ones with specificity that are T-cell or APC (B-cell) particular -therapies like anti- CD3 [54], CTLA4-Ig like abatacept [55] or antiCD20 with Rituximab B [56]. Of these anti- CD3 as well as CTLA4-Ig could change but not halt the course of the specific autoimmunity with certain essential advantages as well as understanding.

Antigen concentrated treatments have not proved to be more beneficial. The biggest hurdle is 2 times, i) isolating the correct antigen (s) and ii) detected the proper delivering system. Some of the explanations support a main part of insulin or associated antigen (s) in originating autoimmunity are convincing. Of these one being that the damage is limited and particular to the insulin developing beta cell within the pancreatic islet. This gets further compounded by the fact that an epitope is present along with antigen Spreading once the disease progresses [57]. It has to be thought that till one intercepts this before it occurs at the initial phase of the disease, aid might be got by utilizing combined key antigens in an individualistic way. In avoiding oral insulin has been tried in this setting [58], with post hoc evaluation showing some preventive actions in a subgroup [58]. In a recent Bayesian meta-analysis GAD vaccine in alum in Type 1 diabetes demonstrated modest benefits [59]. Insulin B chain utilization in an incomplete Freunds adjuvant (IFA) in a phase 1 clinical trial demonstrated a good immune effect by escalating insulin B chain specific regulatory T-cells [60]. To get an administration system that is powerful and targeted that much to move the immune system back towards immune tolerance is the basic part of an antigen dependent strategy. The answer might lie in IFA or equivalent strong adjuvants. By reduction in the amounts as well as function of the auto-aggressive immune cells might deactivate them and hence help in getting the balance as well as tolerance back is crucial. The objective is to mimic the thymic education of immune cells within the peripheral circulation.

Clinical cure of Type 1 diabetes was neither attained by immune cells targeted, nor by antigen concentrated therapies. Although some changed the pathology they couldn't halt the autoimmunity. But still they have ended up giving certain good clinical results, Now the biggest challenge is how to capitalize on these partial yet very emphatic results as well as comparison of success in trials that have different methods that will help in giving direction to future trials.

The basic crucial metabolic factor of the disease is damage to the insulin synthesis. Measuring self-insulin synthesis should be assumed would help in the centre of success finding. But alone this is not enough and needs additional clinical as well as laboratory tests to be combined. Right now the best of the lot for checking self-insulin synthesis is serum C peptide. The rest of clinically essential laboratory tests are the metabolic effects of self-laboratory tests, i.e. blood sugar level (HbA1c), levels of externally administered insulin, how frequent hypoglycaemic as well as hyperglycaemic events ([diabetic ketoacidosis (DKA)]). These parameters are self-connected and it might be said that they have gone in "linkage disequilibrium". The link among C peptide, (HbA1c as well as insulin dosage is possibly tighter as compared to connection of this group with rest of parameters (like hypoglycaemic episodes as well as hyperglycaemic events (DKA). Get-

ting more insight regarding fragile association among surrogate markers of DM control will help in contrasting newer therapy methods and thus formatting newer treatments.

Regarding the preDM setting lot of work has been put in to check the metabolic deterioration towards T1DM. Measuring alterations in stimulated C peptide over time singly [61,62] or together with HbA1c [63] gave assurance in enhancing anticipation of the initiation of T1DM beyond the usual autoantibody evaluations. Till date nobody has tried to check the dynamic of the metabolic decline or getting better comprehensively in T1DM patients.

Maximum clinical trials in T1DM patients utilize stimulated C peptide as the primary outcome result along with insulin as well as HbA1c as secondary ones to know the efficacy, but not in combination. It is quiet possible that a trial in which C peptide conservation also yields more effective HbA1c and would result in influence on patients short as well as long term health. Once these 2 changes take place along with insulin utilization, it might point benefit from the therapy utilized. It would be better to combine these factors into a formula.

The potential utilization of the proposed index by Orban., *et al.* [48] would be to give the quantification of the amount of desirable treatments, just little prior to clinical cure. Thus, sustainance or enhancement of the positive index (DMMRI > 5) could point to total immune cure, while improved but then deterioration over time would point effective but temporary change of the autoimmune mechanism. The index might also point to negative influence of accelerating autoimmunity and hence worsened metabolic status (DMMRI < 5). Other probable utilization of the index is to aid in selection of the best, most promising combination treatments. Further besides the chances of addition as well as/or synergism of various therapies, this index might aid in choosing best therapies, the ones possessing the maximum indices.

Still lot of lacunae are there in this index. It can only get used in placebo controlled interventional clinical trial settings. This has been applicable to the 3 trials where it has been tried. Still the indices obtained appear to corroborate the usefulness of this method. The 2 trials that proved to be of success, namely abatacept as well as Rituximab B gave indices 5. The abatacept index is as compared to that for Rituximab B supposedly pointing to more advantages for the patients. The GAD vaccine trial was found to be not efficacious as corroborated by DMMRI < 5. In future, more checking will be required to check the applicability of the index with its usefulness.

Lot of work has been done to be able to cure this dreaded disease are going on with newer trials under way having planning, getting insight of the relative advantages of these novel methods are required markedly to help in formatting strategies as well as designs for more drugs as well as combination therapies to be formed for future. Thus, this innovative index which helps in contrasting of similar studies will aid both current as well as future attempts to abrogate which and ultimately cure T1DM patients the final objective.

Conclusion

Thus, utilizing the innovate approach regarding characterization as well as stage recovery from autoimmune damage in T1DM by Orban., *et al.* helps in aiding in the stages of deterioration that had been given by erstwhile Eisenbarth. This staging aids in classification of the effectiveness of any action taken with the objective of halting the decline which might act as a quantitative metabolic measure of results through which treatments might get contrasted and actual help given by DM therapy found. Further role of CD28 is critical for regulatory T cell survival and the maintenance of immune homeostasis. Esensten., *et al.* [65] outlined the roles that CD28 and its family members play in human disease and reviewed the clinical efficacy of drugs that block CD28 ligands. Despite the centrality of CD28 and its family members and ligands to immune function, many aspects of CD28 biology remain unclear. Translation of a basic understanding of CD28 function into immunomodulatory therapeutics has been uneven with both successes and failures (See figure 2). Such real-world results may stem from multiple factors including complex receptor-ligand interactions among CD28 family members, differences between the mouse and human CD28 families, and cell-type specific roles of CD28 family members. Moreover phase 2 trials of Polygonal T-cells will further help in understanding role of these besides trials on omega acids and Vitamin D [66,67].

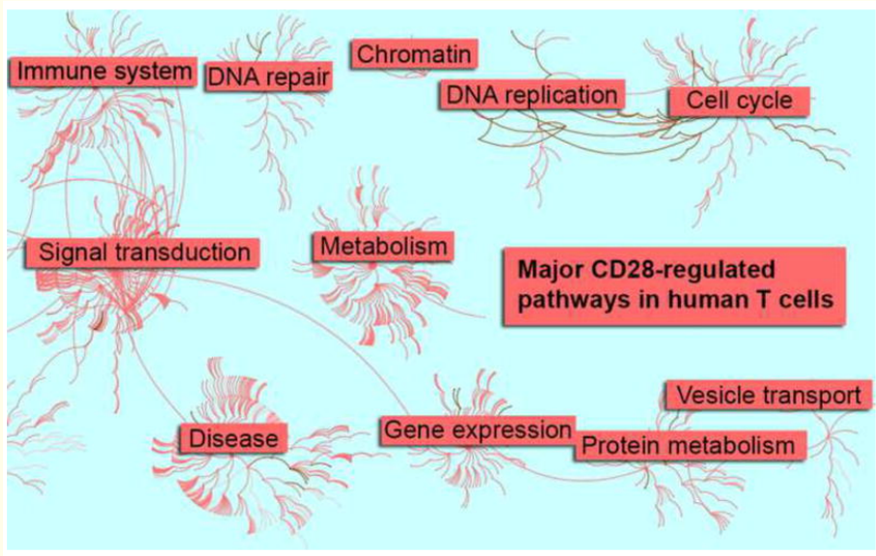

Figure 2: *Courtesy reference number [65]: Major CD28 pathways in human T cells. CD4+CD45RA+ human T cells were stimulated with anti-CD3 antibodies or anti-CD3 and anti-CD28 antibodies for 24 hours before harvest and transcriptome analysis. Differentially regulated genes were mapped to specific pathways (nodes), which are connected to each other based on common function (edges) using the Reactome pathway database (Croft., et al. 2014; Milacic., et al. 2012). Top-level nodes are categorized by a collection of pathways specific to its category (e. g. Immune System includes CD28 and TCR stimulation and cytokine signaling pathways, among others). The major pathway categories are indicated by pop-out text boxes in the network above. The density of connected nodes indicates the relative enrichment of a given class of pathways in T cells after CD28 stimulation.*

Bibliography

1. Banting FG., *et al*. "Pancreatic Extracts in the treatment of Diabetes Mellitus". *Canadian Medical Association Journal* 12 (1922): 141-146.

2. Thabit H and Hovorka R. "Coming of age :The artificial pancreas fortype1 Diabetes". *Diabetologia* 59 (2016): 1795-1805.

3. Home PD. "Plasma insulin profiles after subcutaneous injection: How close can we get to physiology in people with diabetes?" *Diabetes, Obesity and Metabolism* 17 (2015): 1011-1020.

4. De Boer LH., *et al*. "Long term renal outcomes of patients with type 1 diabetes mellitus and microalbuminurea: An analysis of the diabetes control and complications Trial /Epidemiology of diabetes Interventions and Complications Trial/Epidemiology of diabetes Interventions and complications cohort". *Archives of Internal Medicine* 171 (2011): 412-420.

5. White HN., *et al*. "Effect of prior intensive therapy in type 1 diabetes on 10year ;progression and retinopathy in the DCCT /EDTC: Comparison of adults and adolescents". *Diabetes* 59 (2010): 1244-1253.

6. Alberts JW., *et al*. "Effect of prior insulin treatment during the diabetes control and complications Trial(DCCT)on peripheral neuropathy in type 1 diabetes during the Epidemiology of diabetes Interventions and Complications(EDIC) Study". *Diabetes Care* 33 (2010): 1090-1096.

7. Kulvinder Kochar Kaur., *et al*. "An Update on Etiopathogenesis and Management t of Type 1 Diabetes Mellitus". *Open Access Journal of Endocrinology* 1.2 (2017): 1-23.

8. Kulvinder Kochar Kaur., *et al*. "Restricting Carbohydrates in the Diet-A Possible Method of Meeting the Challenges of Increasing Diabesity in Type1 Diabetes along with Meeting Exercise Performances Requirements-A Review". *Open Access Journal of Endocrinology* 3.1 (2019): 000138.

9. Kulvinder Kochar Kaur., *et al*. "How can we use Empagliflozin as an adjuvant in reducing required need of insulin in type1 diabetes along with lowered HbA1c,weight without fear of DKA.-A Minireview''. under publication in press accepted (2019).

10. Kulvinder Kochar Kaur., *et al*. "An update on the Immunotherapy Strategies for the treatment of Type 1 Diabetes(TID)-How far have we reached in reaching insulin independency in TID therapy.-A Systematic Review''. *Journal of Endocrinology* (2020).

11. Wallberg M and Cooke A. "Immune mechanisms in Type 1 Diabetes". *Trends in Immunology* 34.12 (2013): 583-591.

12. Knip M and Smell O. "Environmental triggers of Type 1 Diabetes". *Cold Spring Harbor Perspectives in Medicine* 2.7 (2012): 176-185.

13. Adamczak DM., *et al*. "The roll of Toll like receptors and Vitamin D in Diabetes mellitus Type 1-a review". *Scandinavian Journal of Immunology* 80.2 (2014): 75-84.

14. Norris JM., *et al*. "Timing of initial cereal exposure in infancy and risk of islet autoimmunity". *The Journal of the American Medical Association* 290.13 (2003): 1713-1720.

15. Itoh A and Ridgway WM. "Targeting innate immunity to downregulate adaptive immunity and reverse Type 1 Diabetes and reverse Type 1 Diabetes". *ImmunoTargets and Therapy* 6 (2017): 31-38.

16. Kondrashova A and Hyoty H. "Role of viruses and other microbes in the pathogenesis of Type 1 Diabetes". *International Reviews of Immunology* 33.4 (2014): 284-295.

17. Mojlibian M., *et al*. "Diabetes specific HLA-DR-restricted proinflammatory T cell response to wheat polypeptides in tissue transglutaminase antibody –negative patients with Type 1 Diabetes". *Diabetes* 58.8 (2009): 1789-1796.

18. Adorini L. "Interventions in autoimmunity: the potential of Vitamin D receptor agonists". *Cellular Immunology* 233.2 (2005): 115-124.

19. Knip M. "Autoimmune mechanism s in Type 1 Diabetes". *Autoimmunity Reviews* 7.7 (2008): 550-557.

20. Zhou Z and Jensen PE. "Structural characteristics of HLA-DQ that may impact DM editing and susceptibility to Type 1 Diabetes". *Frontiers in Immunology* 4 (2013): 262.

21. Wing K., *et al*. "CTLA-4 control over Foxp3+regulatory T cell function". *Science* 322.5899 (2008): 271-275.

22. Roy Chaudhary R., *et al*. "BACH2 represses effector programs to stabilize Treg- mediated Immune homeostasis". *Nature* 498.7455 (2013): 506-510.

23. Downes K., *et al*. "Reduced expression of ifih1 is protective for Type 1 Diabetes". *PLoS One* 5.9 (2010): e12469.

24. Wachlin G., *et al*. "IL-1β ,IFNγ and TNFα increase vulnerability of pancreatic beta cells to autoimmune destruction". *Journal of Autoimmunity* 20.4 (2003): 303-312.

25. Marroqli L., *et al*. "BACH2-a candidate risk gene for Type 1 Diabetes, regulates apoptosis in pancreatic β-cells via JNK 1 modulation and crosstalk with the candidate gene PTPN2". *Diabetes* 63.7 (2014): 2516-527.

26. Naguiera TC., *et al*. "GLIS3.a susceptibility gene for Type 1 and type2 Diabetes modulates pancreatic β-cells apoptosis via regulation of a splice variant of the BH3-Only protein bim". *PLoS Genetics* 9.5 (2013): e1003532.

27. Kulvinder Kochar Kaur., *et al*. "An Update on Aetiopathogenesis and Management of Obesity". Obesity and Control Therapies: Open Access 3.1 (2016): 1-17.

28. Kulvinder Kochar Kaur., *et al*. "Hypothalamic inflammation and glioses as aetiopathogenetic factor inhigh fat diet induced obesity and various therapeutic options to resolve it". *Obesity Research and Clinical Practice Journal* 4.2 (2017): 44-60.

29. Kulvinder Kochar Kaur., *et al*. "Current advances in pathogenesis in obesity: Role of Hypothaalamic gliosis". *Journal of Obesity and Weight Loss* 3.008 (2018): 1-11.

30. Kulvinder Kochar Kaur., *et al*. "Have Probiotics and Synbiotics passed the test of time to be implemented in management of obesity and related metabolic disorders-a comprehensive review". *Obesity, Weight Management and Control Advances* 9.1 (2019): 21-28.

31. Kulvinder Kochar Kaur., *et al*. "Weight loss Associated with high protein Intake in Obesity:Interactions of Gut Microbiota in Protein Sources influencing this positive effect". *Acta Scientific Nutritional Health* 2.7 (2018) : 80-89.

32. Kulvinder Kochar Kaur., *et al*. "Will Probiotics Provide the Answer for Therapy of Non-alcoholic Fatty Liver Disease (NAFLD)? – A Systematic Review". *Biochemistry and Physiology* 9 (2020): 257.

33. Depommier C., *et al*. "Supplementation with *Akkermansia muciniphila* in overweight and obese human volunteers :A proof of concept exploratory study". *Nature Medicine* 25 (2019): 1096-1103.

34. Giongo A., *et al*. "Toward defining the autoimmune microbiome for type 1 diabetes". *The ISME Journal* 5 (2011): 82-91.

35. Huang Y., *et al*. "Gut microbiota profiling in Han Chinese with type 1 diabetes". *Diabetes Research and Clinical Practice* 141 (2018): 256-263.

36. Paun A., *et al*. "The influence of microbiome on type 1 diabetes". *Journal of Immunology* 198 (2017): 590-595.

37. Kriegel MA., *et al*. "Naturally transmitted segmented filamentous bacteria segregate with diabetes protection in non obese diabetic mice". *Proceedings of the National Academy of Sciences of the United States of America* 108 (2011): 11548-1563.

38. Parikka V., *et al*. "Early seroconversion and rapidly increasing autoantibody concentrations predict pubertal prepubertal manifestation of type 1 diabetes in children at genetic risk". *Diabetologia* 55 (2012): 1926-1936.

39. Krischer JP., *et al*. "The 6 year incidence of diabetes-associated autoantibodies in genetically at risk children: the TEDDY study". *Diabetologia* 58 (2015): 980-987.

40. Bosi E., *et al*. "Impact of age and antibody type on progression from single to multiple autoantibodies in type 1 diabetes relatives". *The Journal of Clinical Endocrinology and Metabolism* 102 (2017): 2881-886.

41. American Diabetes Association. "2 Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2019". *Diabetes Care* 42 (2019): S13-S28.

42. Herold KC., *et al*. "Teplizumab(antiCD3mAb) treatment preserves C-peptide responses in patients with new –onset type 1 diabetes in a randomized controlled trial: Metabolic and immunologic features at baseline identify a subgroup of responders". *Diabetes* 62 (2013): 3766-3774.

43. Rigby MR., *et al*. "Targeting of memory T cells with alefacept in new –onset type 1 diabetes (TIDAL study):12 month results of a randomized, double blind placebo controlled phase 2 trial". *The Lancet Diabetes and Endocrinology* 1 (2013): 284-294.

44. Mahon JL., *et al*. "The Trial Net Natural History Study of the Development of type 1 diabetes: Objectives, design and initial results". *Pediatrics and Diabetes* 10 (2009): 97-104.

45. Bluestone JA., *et al*. "Type 1 Diabetes Immunotherapy using polyclonal regulatory T Cells". *Science Translational Medicine* 7.315 (2015): 315ra189.

46. Vaseghi H., *et al*. "T helper cell type1-Transcription factor T-Bet is downregulated in Type 1Diabetes". *Iranian Journal of Allergy, Asthma and Immunology* 15.5 (2016): 386-393.

47. Eisen barth GS. "Autoimmune beta cell insufficiency". *Triangle* 23 (1984): 111-124.

48. Orban T., *et al*. "A novel quantitative approach to staging and assessing recovery from type 1 diabetes mellitus: the type 1 diabetes mellitus metabolic recovery index". *International Journal of Molecular Sciences* 21 (2020): 992.

49. Walker LS and Von Herrath. "CDT4 cell differentiation in type 1 diabetes". *Clinical and Experimental Immunology* 183 (2016): 16-29.

50. Bluestone JA., *et al*. "Type 1 diabetes immunotherapy using polyglonal regulatory T cell". *Science Translational Medicine* 7 (2015): 315ra189.

51. Calderon B., *et al*. "The central role of antigen presentation in islets of langerhans in autoimmune diabetes". *Current Opinion in Immunology* 26 (2014): 32-40.

52. Abreu JR., *et al*. "CD8T cell autoreactivity to proinsulin epitopes with very low human leukocyte antigen class1 binding affinity". *Clinical and Experimental Immunology* 170 (2012): 57-65.

53. Gitelman SE., *et al*. "Antithymocyte globulin treatment for patients with recent onset Type 1 diabetes: 12 mths results of a randomised ,placebo controlled ,phase 2 trial". *The Lancet Diabetes and Endocrinology* 1 (2013): 306-316.

54. Keymeulen SE., *et al*. "Insulin needs after CD3 –antibody in new onset Type 1 diabetes". *The New England Journal of Medicine* 352 (2008): 2598-2608.

55. Orban T., *et al*. "Costimulation modulation with abatacept in patients with recent onset Type 1 diabetes: a randomised, double blind , placebo controlled trial". *Lancet* 378 (2011): 412-419.

56. Pescovitz MD., *et al*. "B lymphocytes depletion and preservation of beta cell function". *The New England Journal of Medicine* 361 (2009): 2143-2152.

57. Brooks-Worrell B., *et al*. "Intermolecular Antigen Spreading Occurs during the preclinical period of human Type 1 diabetes". *Journal of Immunology* 166 (2001): 5265-5270.

58. Skyler JS., *et al*. "Effects of oral insulin in relatives of patients with diabetes :The diabetes prevention trial- Type 1". *Diabetes Care* 28 (2005): 1068-1976.

59. Beam C., *et al*. "GAD vaccine reduces insulin loss in recently diagnosed Type 1 diabetes: Findings from a Bayesian meta-analysis". *Diabetologia* 60 (2016): 43-49.

60. Orban T., *et al*. "Autoantigen –specific regulatory Tcells induced in patients with type 1 diabetes mellitus by insulin B chain immunotherapy". *Journal of Autoimmunity* 34 (2010): 408-415.

61. Sosenko JM., *et al*. "The development and utility of a novel scale that quantifies the glycaemic progression towards type 1 diabetes over 6 mths". *Diabetes Care* 38 (2015): 940-942.

62. Sosenko JM., *et al*. "A new approach for diagnosing type 1 diabetes in autoantibody –positive individuals based on prediction and natural history". *Diabetes Care* 38 (2015): 271-276.

63. Krischer JP. "The use of intermediate endpoints in the design of type 1 diabetes prevention trials". *Diabetologia* 56 (2013): 1919-1924.

64. Wherett DK., *et al*. "Antigen –based therapy with glutamic acid decarboxylase(GAD) vaccine in patients with recent onset type 1 diabetes mellitus: A randomised double blind trial". *Lancet* 378 (2011): 319-327.

65. Esensten JH., *et al*. "CD28 Costimulation: From Mechanism to therapy". *Immunity* 44.5 (2016): 973-988.

66. Issazadeh-Navikas S., *et al*. "Influences of dietary components on regulatory T cells". *Molecular Medicine* 18 (2012): 95-110.

67. Gutierrez S., *et al*. "Effects of omega-3 fatty acids on immune cells". *International Journal of Molecular Sciences* 20 (2019): E5029.

Volume 4 Issue 6 June 2020