Autoimmune aspect of type 2 diabetes: Diagnostic and therapeutic perspective

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Introduction:

Type 2 diabetes (T2D) is a multifactorial and multilayer disease, characterized by an altered metabolism of glucose, fat, and proteins. Hyperglycemia is the main common feature defining T2D, and clusters of patients are identifiable according to the specific combination of insulin resistance (IR) and absolute or relative insulin deficiency (1).

Autoimmune etiology has long been associated with type 1 diabetes (T1D), whereas T2D has historically been considered a metabolic disease. However, recent discoveries identify the involvement of the immune system in the development of T2D and in the progressive deterioration of b-cell function in T2D (2, 3).

The increased production of cytokines characterizing the chronic inflammatory state in T2D concur to destroy pancreatic b cells, and induced tissue damage leads to the release of “self” antigens that promote autoimmune activation. In turn, autoimmunity further impairs insulin secretion in b cells and promotes hyperglycemia (4, 5).

Characteristic features of Autoimmune aspect of type 2 diabetes (6)

T2D patients with a significant autoimmune component:

a- Need insulin earlier during disease progression,

b- Are likely to poorly respond to classical anti-diabetic medications,

c- May be highly responsive to immunomodulator therapy.

Autoimmune Activation in T2DM

1-Chronic inflammation and islet autoimmunity

The development of T2D has now been linked to the establishment of chronic obesity-associated inflammation in the visceral adipose tissue (7, 8). As an individual becomes obese, several changes occur within the adipose tissue, leading to a shift from an anti-inflammatory to an inflammatory milieu These changes include: (Figure 1)

1- Adipocyte hypertrophy.
2- A decrease in adiponectin.
3- Increase in plasma C-reactive protein (CRP) levels.
4- Increased levels of proinflammatory cytokines such as interleukin (IL)-6, tumor necrosis factor (TNF)-a and IL- 1b.
5- Activation of the transcription factor nuclear factor (NF)- kB, infiltration of proinflammatory macrophages (M1), and infiltration of proinflammatory CD8+ and CD4+ T cells into the adipose tissue (9, 10).

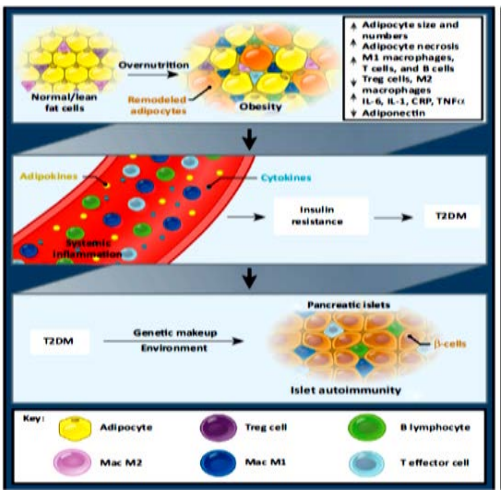

Figure (1): changes occur within the adipose tissue.

2-Lymphocyte alteration in T2DM

Evidence of lymphocytic infiltrates in target organs such as the pancreas, underlines the idea of autoimmune participation in T2DM pathogenesis. Interleukin-10 (IL-10) secreted by B cells is important for controlling autoimmune processes (11). When compared to B cells of healthy subjects, B cells of patients with T2DM fail to secrete the anti-inflammatory IL-10 in response to stimulation. (IL-10). Accordingly, low IL-10 production in response to stimulation with lipopolysaccharide was associated with a high risk for T2DM in elderly subjects (12). Brooks-Worrell et al. demonstrated that islet-reactive T cells can be found in phenotypic T2DM patients, and the presence of such cells is associated with a more severe β-cell lesion and lower residual insulin secretion. (13)

3-Role of macrophage

Inflammation in adipose tissue, liver, muscle, and pancreas has been clearly established in patients with obesity and T2DM. An infiltration of macrophages into these tissues is observed in human obesity, metabolic syndrome, and T2DM. Activated macrophages infiltrate adipose tissue, pancreatic islets, liver, and skeletal muscle and stimulate the production of pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β. Which promote insulin resistance by interfering with insulin signaling in peripheral tissues.(14) and trigger β-cell apoptosis, leading to a decrease in islet mass, which are all critical events in the progression of T2DM.(15)

The diagnostic perspective of autoimmunity in type 2 DM

Measurements of adiponectin, CRP, IL-6, and IL-1b have been used primarily to identify T2D patients with active inflammation. There is evidence suggesting that the efficacy of immunotherapy for T2D is greatest in patients with active islet inflammation and/or autoreactivity, thus, it may be useful to stratify patients according to immune status before initiation of immunotherapy. determining the presence or absence of islet autoantibodies (Abs) and islet-specific T cell responses provides a good measure of islet autoimmune status. Patients negative for both islet Abs and islet-reactive T cells are considered nonautoimmune, whereas patients with islet autoimmunity could be positive for islet Abs and/or islet-reactive T cells. Future clinical trials should focus on determining the importance of islet autoimmunity when evaluating immunotherapies in phenotypic T2D patients. (16) (Figure 2)

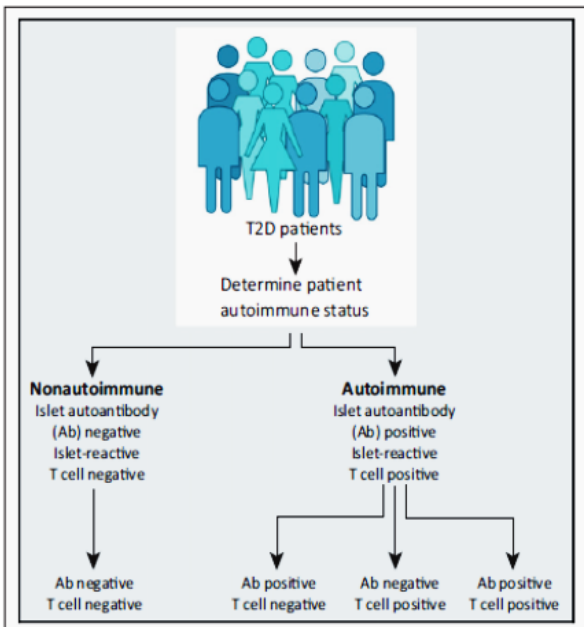

Figure (2): determining autoimmune status in patients with T2D.

Biomarkers for Immune Therapy Efficacy

- Equally beneficial is using specific immune biomarkers to monitor the immune and clinical responses of the immunotherapies.
- Previously, the levels of circulating soluble inflammatory mediators such as IL-1, IL-6, TNF-a, CRP, and adiponectin have been used. However, various trials have shown limited ability to predict the efficacy of immunotherapeutic treatments using these biomarkers. (17, 18).
- Other potential biomarkers, which have been used to evaluate specific therapies include endogenous IL-1Ra serum levels to predict responsiveness to anti-IL-1 therapies, and sCD26/DPP-4 for evaluating the clinical efficacy of sitagliptin (a DPP-4 inhibitor) (19, 20).

Therapeutic perspective of autoimmunity in type 2 Diabetes:

Considering the fact that autoimmune reactions contribute to the pathogenesis of T2DM as well, but to a limited extent, antigen-specific therapies are still not in sight for prevention or treatment of T2DM. However, keeping in mind the prominent role of innate immune system activation in adipose tissue inflammation and T2DM, anti-inflammatory and immunomodulatory therapeutic approaches may be beneficial in improving metabolic regulation in T2DM.

1-Clinical Trials of immunomodulatory therapies for T2D

A- IL-6 blockers

Tocilizumab is humanized anti-IL-6R antibody has been approved for the treatment of Rheumatoid Arthritis (RA). Tocilizumab inhibits the binding of IL-6 to both membrane-bound non signaling IL-6R (mbIL-6R) and soluble form (sIL-6R) and thereby results in complete blockade of IL-6 signaling. (21, 22).Tocilizumab has been reported to improve insulin sensitivity and decrease glycated hemoglobin (HbA1c) levels in humans (23, 24).Taken together, these findings support the idea that IL-6 signaling is a potential therapeutic target for the treatment of inflammatory-associated disorders including T2D.

sgp130Fc protein is a recombinant version of sgp130, which consists of the extracellular portion of gp130 fused to the Fc region of a human immunoglobulin G1 (IgG1) antibody. Sgp130Fc specifically blocks IL-6 trans-signaling, without affecting classical IL-6 signaling. Therefore, sgp130 inhibits the pro-inflammatory actions of IL-6, while

leaving its anti-inflammatory and protective activities intact. Sgp130Fc has demonstrated robust efficacy in the treatment of many autoimmune and inflammatory diseases, with better side effect profile than global blockers of IL-6 signaling (22, 25).

Using sgp130Fc, which is the only available therapeutic agent for specific blockade of IL-6 trans-signaling, in combination with other anti-inflammatory treatments, such as anti-IL-1β agents, could lead to the development of more efficacious strategies for treatment of T2D (25).

B- IL-1b and IL-1b receptor antagonist (IL-1bRa)

IL-1β Is inflammatory cytokine with a pivotal role in islet inflammation in T2DM (10). anakinra canakinumab and are IL-1R antagonist which antagonizing IL-1β effects. These agents have shown a significant beneficial effect on HbA1c, IR, and b cell secretory function(26, 27).

Anakinra proved favorable improvement of glucose control in T2DM patients randomized to receive either the drug or placebo for 13 weeks (27). Also cause significant reduction in HbA1c levels and increase in circulating C-peptide concentration and proinsulin, at the end of the treatment, During the follow-up period, which lasted 39 weeks and was intervention- free, patients showed a pronounced decrease in C-peptide levels and a lower ratio of proinsulin to insulin (27). Emerging evidence also suggests that anti-IL-1β therapy may dramatically decrease the risk of macrovascular and microvascular complications of diabetes(28, 29). In contrast, Ridker et al. did not find alterations in HbA1c, glucose, and insulin levels after canakinumab treatment in well-controlled T2D patients with high cardiovascular risk (30).

C- CTLA4 immunoglobulin

Abatecept is CTLA4 immunoglobulin that showed a dramatic improvement of insulin sensitivity after 12 weeks of treatment in a severely insulin-resistant patient suffering from rheumatoid arthritis which attributable to T-cell suppression (31)

D-TNF-a blockers (infliximab, adalimumab, and etanercept)

TNF-a is produced by adipocytes early in tissue inflammation and TNF-a levels are elevated in T2D and obesity(32, 33). In theory, blocking TNF-α may improve insulin sensitivity by increasing the tyrosine kinase activity of the insulin receptor and thus could promote glucose uptake in peripheral tissues (34).

TNF-α inhibition leads to a significant reduction in HOMA (Homeostatic Model Assessment for Insulin resistance) and QUICKI (Quantitative Insulin Sensitivity Check Index) indices, which are surrogate markers for IR (35), Also show significant reduction in fasting glucose levels and an increased ratio of high molecular weight adiponectin to total adiponectin in obese individuals with metabolic syndrome (36).

Conversely, infliximab did not alter insulin secretion in patients with Crohn's disease (37) Furthermore, a treatment with TNF-α did not improve fasting insulin, glucose, and C-peptide over a period of 4 weeks in patients with obesity and T2D (38).

E- Anti-IL-17

It was shown that anti-IL-17 treatment in T2D increased serum adiponectin levels while reducing serum TNF-α concentration. Thus, therapy with antibodies blocking IL-17 improves adipose tissue functionality, resulting in the release of the anti-inflammatory and insulin-sensitizing adipokine adiponectin (39).

F-Targeting T and B lymphocytes

Anti-CD3 therapies: Targeting T lymphocytes through anti-CD3 therapy (teplizumab, otelixizumab, and visilizumab) and B lymphocytes through anti-CD20 therapy (rituximab) has demonstrated clinical efficacy in treating the islet autoimmunity associated with T1D (40, 41).Studies have demonstrated marked improvement of insulin sensitivity in the diet-induced obesity mouse model with anti-CD3 and anti-CD20 therapies suggesting that, if these results are applicable to humans, targeting T and B lymphocytes in adipose tissue may be beneficial (18, 42).

A note of caution when considering using anti-CD3 or anti- CD20 antibodies to treat T2D patients would be the potential risk of future development of leukoencephalopathy in treated patients. Since antigens in T2DM are not well defined, induction of antigen nonspecific Tregs by oral anti-CD3 is preferable to parenteral administration and will be the focus of intense research in the future.

New immunotherapies for the treatment of T2D

Toll-like receptor (TLR) inhibitors

In fact, newly diagnosed T2D patients have been demonstrated to have an increased expression of TLR2 and TLR4 in monocytes(43) . Inappropriate activation of TLRs by self-components can result in inflammation or autoimmunity and has been hypothesized to play a role in the development of T2D (44, 45).

Angiotensin receptor blockers (ARBs), which downregulate TLRs, are commonly used to treat hypertension and diabetic nephropathy. In mice, ARB treatment protects pancreatic islet and adipose tissue from inflammatory consequences of a high-fat diet (46) Thus, inhibiting TLR receptors may offer new immunological agents in the treatment of both T2D and obesity.

Resolvin (Rv)

RvD1 is a newly acknowledged enzyme that blocks the arrival of leukocytes into tissues and promotes macrophage phagocytosis. In studies using obese/diabetic mice, treatment with RvD1 increased adiponectin levels and decreased proinflammatory cytokines in adipose tissue (47).

Histone deacetylase (HDAC) inhibitors

In 2009, Lawless et al. (48) described the clinical potential of HDACs for the treatment of proinflammatory diseases such as T2D, and Christensen et al. (49)provided compelling evidence for testing HDAC inhibitors as a novel therapy for the treatment of T2D. Currently, HDAC exhibits anti-inflammatory and neuroprotective properties and subsequently suppress the

autoimmune attack associated with development of MS (50)

Sirtuin activators

Sirtuins represent a family of enzymes involved in metabolism and metabolic disease Activation of one member of the family of sirtuins (SIRT1) leads to decreased glucose levels, improved insulin sensitivity, and decreased adiposity in mice (51).

Side Effects of ant-cytokine Therapies

Take into consideration that anti-cytokine therapies are not devoid of side effects; thus, benefits should be carefully weighed against potential harms related to the use of these drugs. Critical adverse events deriving from the use of these drugs (ranging across different biological agents) include infections (including reactivation of latent tuberculosis and hepatitis B), rare demyelinating disorders of the central nervous system, and liver and cardiac injury (56). Therefore, these aspects need further investigation in future studies.

2-Salicylates

High doses of salicylates block the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway and increase circulating adiponectin, an important adipokine counteracting insulin resistance.

Salsalate is a prodrug of salicylate which does not inhibit the Cox enzyme pathway and thus does not prolong bleeding times. Also, it is insoluble in the acidic environment of the stomach and therefore may result in reduced undesirable bleeding and gastrointestinal effects emphasizing its use as an insulin sensitizer. In a randomized clinical trial, a high dose of salsalate improved metabolic control and HbA 1c levels in T2DM patients (52). the glucose-lowering action of salsalate is due to activation of Adenosine Monophosphate (AMP) kinase (53).

3-Anti-inflammatory effects of antidiabetic agents:

Many pharmacological agents have been developed for the treatment of DM and there is evidence to show that these may have intrinsic anti-inflammatory properties independent of their effect on glycemia. It was suggested that a therapeutic agent that can ameliorate the inflammatory response independent of their glycemic response may have additional beneficial effects on the prevention of diabetic complications (table 1) (54).

Table (1) Anti-inflammatory effects of antidiabetic agents	
Antidiabetic agents	**Anti-inflammatory effects**
Insulin	Prevents ICAM-1, MCP-1, TNF-α, NF-κb, and TLRs expression, and induces NO release
Biguanides	Suppress inflammation by inhibition of oxidative stress, IL-1β, TNF-α, (MMP-9), COX-2, IL-10, NF-κb, and rise in NO bioavailability; decrease the neutrophil to lymphocyte ratio
Sulfonylureas	Prevent inflammatory responses by MAPKs/NF-κb-dependent pathway; suppress Th2 cytokines, VCAM-1, p-STAT6, TNF-α, NF-κb, caspase-3, PGE2, and IL-10 expressions; inhibit NLRP3 inflammasome; ameliorate oxidative stress
DPP-4 inhibitors/GLP-1 receptor agonists	Prevent; adipocyte and hepatocyte inflammation and inhibit the inflammatory cytokine expression through NF-κb inhibition in renal glomeruli, sitagliplin reduces autoimmunity by decreasing the homing of CD4+ cells into pancreatic β cells in non-obese diabetic (NOD) mice and helps preserve islet cell mass (55).
Alpha-glucosidase inhibitors	Reduce ICAM-1, VCAM-1, IL-6, IL-1β, TNF-α, and CRP expression
SGLT2i	Downregulate MCP-1, TGF-1β, IL-6, TNF-α, and CRP expression
Meglitinides	No verified effects

ICAM-1: intercellular cell adhesion molecule-1, **MCP-1:** monocyte chemoattractant protein-1, **TNF-α:** Tumor Necrosis factor α, ***NF-κb*:** Nuclear factor kappa-light-chain-enhancer of activated B cells**, MAPKs:** Mitogen-activated protein kinases, **VCAM-1:** Vascular cell adhesion protein 1, **p-STAT6:** Polyclonal Antibody for studying *Stat6,* **PGE2:** Prostaglandin E2**, NLRP3:** NLR family pyrin domain containing 3 **TGF-1β*:*** Transforming growth factor *beta* 1

Future Prospects in management of autoimmunity in T2DM:

• Two alternative approaches to target LGI without suppressing immune function may be represented by:

a- The removal of the pro-inflammatory triggers.

b- The selective modulation of immune cells function.

• The first approach is already being exploited with specific interventions known to target LGI and to improve diabetes outcomes, e.g., diet, exercise, and bariatric surgery (56, 57) Also, innovative molecules aimed at attenuating fundamental triggers of LGI are going to be tested in T2D, e.g., microbiota modulators, epigenetic-modifying, and senescence-targeting drugs (56, 58).

• On the other hand, increasing evidence suggests that immune response can be selectively modulated, rather than suppressed. There is emerging role of extracellular vesicles (EV)s for the regulation of immune cell behavior. Qualitative and quantitative alterations regarding EVs in settings of T2D are constantly emerging (59, 60) as well as their central role in the

regulation of immune function (61-63). Finally, a deeper understanding of this newly described extracellular vesicle-based cell-cell communication machinery will probably enable the design of specific nanodrugs able to produce a long-lasting beneficial effect on the pathological inflammatory component of T2D.

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