

The Role of Inflammation in Diabetes: Current Concepts and Future Perspectives

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Abstract

Diabetes is a complex metabolic disorder affecting the glucose status of the human body. Chronic hyperglycaemia related to diabetes is associated with end organ failure. The clinical relationship between diabetes and atherosclerotic cardiovascular disease is well established. This makes therapeutic approaches that simultaneously target diabetes and atherosclerotic disease an attractive area for research. The majority of people with diabetes fall into two broad pathogenetic categories, type 1 or type 2 diabetes. The role of obesity, adipose tissue, gut microbiota and pancreatic beta cell function in diabetes are under intensive scrutiny with several clinical trials to have been completed while more are in development. The emerging role of inflammation in both type 1 and type 2 diabetes (T1D and T2D) pathophysiology and associated metabolic disorders, has generated increasing interest in targeting inflammation to improve prevention and control of the disease. After an extensive review of the possible mechanisms that drive the metabolic pattern in T1D and T2D and the inflammatory pathways that are involved, it becomes ever clearer that future research should focus on a model of combined suppression for various inflammatory response pathways.

Keywords

Inflammation, diabetes, obesity, metabolic disorders, adipose tissue, anti-inflammatory treatment

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Diabetes is a multifaceted metabolic disorder affecting the glucose status of the human body. Impaired glucose tolerance and hyperglycaemia are the main clinical and diagnostic features and the result of an absolute or relative insulin deficiency or resistance to its action. Chronic hyperglycaemia associated with diabetes can result in end organ dysfunction and failure which can involve the retina, kidneys, nerves, heart and blood vessels.¹ The clinical relationship between diabetes and atherosclerotic cardiovascular disease are well established, with the risk for cardiovascular disease (CVD) being significantly elevated in patients with diabetes.^{2,3}

Moreover, CVD typically occurs one to two decades earlier in people with diabetes, with more aggressive, severe and diffuse distribution.^{4,5} The first WHO global report on diabetes published in 2016 demonstrates that the number of adults living with diabetes has almost quadrupled since 1980 to 422 million adults and this is expected to rise to 552 million by 2030.^{6,7} Thus, the need for effective novel therapeutic approaches for the treatment and/or prevention of diabetes and atherosclerotic disease is crucial.

Traditionally, the majority of cases of diabetes fall into two broad pathogenetic categories, type 1 (T1D) and type 2 (T2D). However, in some people this rigid classification is not applicable because other genetic, immunological or neuroendocrinological pathways are involved in its pathogenesis. T1D is related to an absolute lack of insulin

due to a vaguely understood mechanism, where an immune-mediated destruction of pancreatic beta cells is the hallmark of the disorder, with hyperglycaemia only emerging when more than 90% of the beta cells are lost.⁸ T2D is the most common form of diabetes, accounting for 90–95% of cases. Its development is secondary to a relative insulin deficiency but the primary defect is insulin resistance.⁹

Various proposals and hypotheses have been developed to describe the mechanisms which are usually involved in the propagation of diabetes, mainly focusing on T2D. The increase in prevalence of the condition has been related to well-recognised risk factors, such as the adoption of a western lifestyle, sedentary lives, lack of physical activity and an energy-dense diet.^{10,11} Genetic predisposition, ethnicity and ageing are not modifiable risk factors for T2D, while others, such as being overweight or obese, an unhealthy diet, insufficient physical activity and smoking are modifiable through behavioural and environmental changes. However, increasing evidence has shown that inflammatory pathways are the principal, common pathogenetic mediators in the natural course of diabetes under the stimulus of the risk factors described above.¹²

In this article, we will highlight the emerging role of inflammation in the pathophysiology of diabetes and we will analyse the implicated inflammatory pathways and biomarkers of inflammation in diabetes and metabolic diseases. The focus of this article is to provide an

overview of the current state of knowledge on anti-inflammatory therapies for diabetes, along with perspectives on future therapies for the disease.

Historical Perspectives

Observational studies provided the first evidence for the possible association between inflammation and diabetes. Over a century ago, the administration of high doses of sodium salicylate led to decreased glycosuria in people with a suspected or definite diagnosis of diabetes.^{13,14} Later studies on the role of inflammation in diabetes, revealed that this hypoglycaemic action was related to the inhibition of the serine kinase I κ B kinase-beta (IKK β), which correlates with the post-receptor action of insulin.¹⁵

A landmark study to correlate inflammation with diabetes was conducted in animal models by Hotamisilgil et al., in 1993 and it revealed that the role of tumour necrosis factor-alpha (TNF-alpha) in obesity and particularly in insulin resistance and diabetes.¹⁶ Epidemiologic associations of inflammation with obesity and T2D were made when circulating concentrations of markers and mediators of inflammation and acute-phase reactants including fibrinogen, C-reactive protein, interleukin (IL)-6, plasminogen activator inhibitor-1, sialic acid and white cells, have been shown to be elevated in these conditions.¹⁷⁻²¹ Over the next decades, numerous studies on human and animal models provided further supporting evidence for the role of inflammation in the initiation and progression of diabetes.^{12,22} Accumulative evidence suggests that chronic activation of pro-inflammatory pathways in target cells of insulin action may contribute to obesity, insulin resistance and related metabolic disorders including T2D.²² The identification of potential pathways connecting inflammation to diabetes has produced growing interest in targeting inflammation to help prevent and control diabetes and related conditions, as well as improving risk stratification for diabetes by using inflammatory biomarkers as potential indexes.^{23,24}

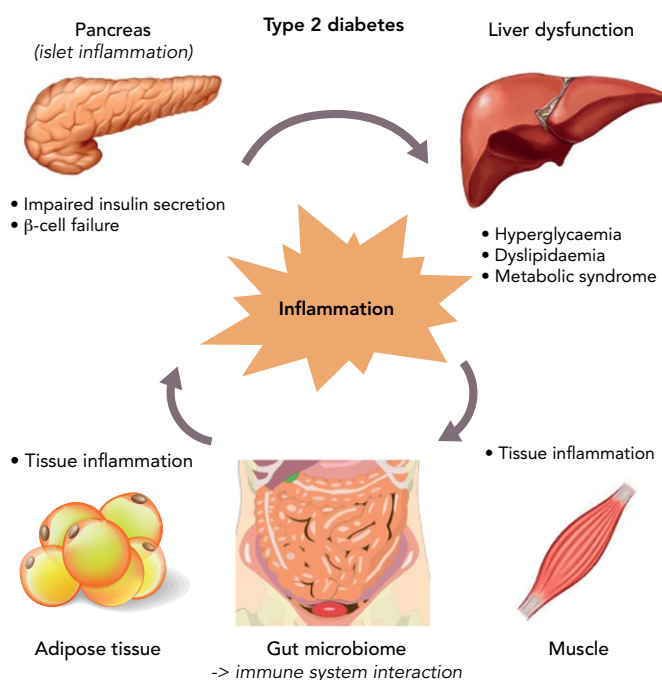
Inflammation in Type 1 Diabetes

T1D is an autoimmune disorder characterised by a selective, specific destruction of insulin-producing pancreatic beta cells, without apparent pathological alterations of other Langerhans cells.²⁵ However, T1D shows significant heterogeneity in regard to the age of onset, severity of autoimmune response and efficacy of therapy, while it has also been demonstrated that both humoral and cellular immunity is involved in the pathogenesis of T1D.²⁶⁻²⁸ The first theories about predisposition support that environmental trigger factors in early life, such as infections, nutrition and chemicals that are able to activate self-targeting immune cascades, remain applicable even though the initial event is still unclear.^{29,30}

Inflammatory Infiltrates in Type 1 Diabetes

Progress in understanding the pathophysiology of T1D has been made in parallel with the advances in the field of immunology. The predominant theory is that the beta cell pancreatic islets in patients with T1D are inflamed, called insulinitis, through the course of T1D. Anderson et al., demonstrated that failure in both central and peripheral immune tolerance mechanisms contribute to the emergence of autoreactive T cells in the periphery of non-obese mice with diabetes.³¹ Regulatory T cells (Tregs) have been shown to also be defective in this autoimmune disease setting, along with evidence from animal models demonstrating the participation of both CD4⁺ and CD8⁺ T cells (effector T-cells/Teff) in the development of T1D as they

Figure 1: Inflammatory Mediators in Type 1 Diabetes



Activation of several immune cells are involved in pancreatic beta-cell death through a variety of inflammatory cytokines. Regulatory T cells are defective in this autoimmune disease, while effector T-cells (Teff) participate in the development of type 1 diabetes targeting several beta-cell autoantigens and related peptide epitopes. The profile of immune B cells also changes during disease progression and macrophages are also critical mediators of islet inflammation due to their direct toxicity on beta-cells by reactive oxygen species. Dendritic cells, natural killer cells and natural killer T cells may have a partial role in the process.

target several beta cell autoantigens and related peptide epitopes.³²⁻³⁵ Moreover, by using adoptive T-cell transfer models of T1D, it has been demonstrated that T-cell subtypes are capable of inducing destructive peri-islet inflammatory infiltrate and overt diabetes.^{36,37} This was further depicted in human studies using pancreas samples obtained post mortem from subjects diagnosed with recent-onset T1D.^{27,38}

Interestingly, the immune B cell (CD20⁺) profile also changes during disease progression, as initial studies found they align closely with the migration of CD8⁺ T cells, following two different patterns, either that of high or low infiltration in islets as reported by Wilcox et al.^{27,38} Macrophages are also critical mediators of islet inflammation due to their ability to secrete cytokines, such as Interleukin 1 beta (IL-1 β) and tumour necrosis factor alpha (TNF-alpha) and produce reactive oxygen species (ROS).^{27,39} Additional studies have shown that the surrounding pancreatic exocrine tissue is abundant in both lymphocytes and neutrophils in T1D and it is suspected that these cells might also contribute to the evolution of disease.^{40,41} In some studies, dendritic cells, natural killer (NK) cells and NKT cells have also been found in the islet infiltrate and may have a partial role in the whole process, however, it seems that overall the interaction among different cell types regulates diabetes progression.^{42,43}

Mediators of Inflammation in Type 1 Diabetes

The three cytokines that seem to be implicated in the inflammation of pancreatic beta cells in T1D, are the synergic action of interferon gamma (IFN- γ) and the innate inflammatory cytokines TNF-alpha and IL-1 β .⁴⁴ The combined action of these inflammatory molecules results in the upregulation of inducible nitric oxide synthase (iNOS), with subsequent production of nitric oxide (NO).⁴⁵ However,

Table 1: Representative Clinical Trials of Anti-inflammatory Treatments on Type 1 Diabetes

Mechanism of action	Drug	Main findings	References
Monoclonal anti-CD20 antibody	Rituximab	Rate of C peptide decline ↓, lower insulin requirements, HbA _{1c} ↓	49,50
Engineered DNA plasmid encoding proinsulin BHT-3021		↓ CD8 ⁺ T cells frequency reactive to proinsulin, C peptide preservation, no change to Interferon-gamma, IL-4, IL-10	51
Proinsulin peptide	Human leukocyte antigen-DR4 (DRB1*0401)	↑ C-peptide, ↑ proinsulin-stimulated IL-10 production, favourable beta-cell stress markers (proinsulin/C-peptide ratio)	189
TNF antagonism	Etanercept	HbA _{1c} ↓, endogenous insulin production ↑	53
Anti-inflammatory serum protein	Alpha 1 antitrypsin (AAT)	IL-1beta response to monocytes and dendritic monocytes ↓, beta-cell function improvement	54
Vitamin D analogue	Alfacalcidol	Beta-cell preservation especially in male subjects	56
Vitamin D analogue	Calcitriol	↑ in fasting C peptide from diagnosis to 1 year, daily insulin dose ↓ in the treatment group	190
IL-1 receptor blockade	Anakinra	No C peptide response	58
IL-1 receptor blockade	Anakinra	↓ insulin requirements compared with controls, ↓ insulin dose adjusted	191
IL-1beta antagonism	Canakinumab	No C peptide response	58
IL-1 receptor blockade IL-1beta antagonism (plasma-induced transcriptional meta-analysis)	Anakinra/canakinumab	Immunomodulation/reverse relationship between inflammation and C peptide stimulation	192
ALPHA ₁ -CD3 mAbs	Teplizumab/otelixizumab		52

CD20 = cluster of differentiation 20, IL = interleukin, mAbs = monoclonal antibodies, TNF = tumour necrosis factor.

even though ROS plays a role in beta cell destruction, more recent studies have demonstrated that NO is not implicated in the damage of pancreatic beta cell.⁴⁶ Furthermore, studies demonstrating that the biology of the beta cell could directly influence the response to an inflammatory environment, through specific gene-guided modulation of beta cell apoptosis induced by IFN-gamma modulated by the PTPN2 gene (Figure 1).⁴⁷

The mechanisms mentioned above strongly suggest that multiple pathways may exist which can contribute to pancreatic beta cell death. During this process, the control and regulation of local inflammatory cytokines production are likely to be critical factors in determining the outcome of the autoimmune progression. The disruptive effects of inflammatory and autoimmune-mediated pancreatic islet attack may lead to a vicious cycle where initial cytokine stress may urge the metabolic stress and an additional loss in beta cell function.⁴⁸

Anti-Inflammatory Trials on Type 1 Diabetes

Given the obvious genetic influences in the initiation and progression of T1D, the immune cell type and the pattern that occurs in any given patient offers an important perspective on the design of clinical trials intended to slow or terminate the progression of the disease. Two initial clinical trials with rituximab, a monoclonal anti-CD20 antibody, were only partially successful.^{49,50} Furthermore, strategies are being developed targeting the antigen-specific T-cell response, such as the application of plasmid DNA (pDNA) vaccination with promising results.⁵¹ Moreover, two humanised anti-CD3 monoclonal antibody (mAbs), teplizumab and oteelixizumab, have been evaluated in people with new and recently diagnosed T1D and showed a reduced rate of loss of beta cell function in the majority of participants.⁵²

Cytokines are another promising target for therapy for T1D, given their involvement in the process of beta cell pathology. IL-1beta and TNF-alpha appear to be attractive initial targets for designing clinical trials based on this concept. A pilot study examined the effects of

an anti-TNF-alpha therapy, etanercept, on paediatric patients newly diagnosed with T1D and demonstrated an increased endogenous insulin production and better metabolic control.⁵³ Administration of alpha-1 antitrypsin (AAT), an anti-inflammatory serum protein, to a small group of people with T1D resulted in a reduced IL-1beta response in monocytes and dendritic cells and improved beta cell function.⁵⁴ Furthermore, given the broad anti-inflammatory properties of vitamin D, it has also been identified as a potential therapeutic target.⁵⁵ However, small studies of vitamin D supplementation in recent onset T1D have only resulted in modest beta cell protection.^{56,57}

On a larger scale, interleukin-1 receptor antagonist (IL-1RN) and human monoclonal IL-1beta antibody were employed in two randomised, placebo-controlled trials in people with recent onset T1D.⁵⁸ Canakinumab and anakinra were found to be safe but they were not effective as single immunomodulatory drugs in recent-onset T1D and they did not result in preserved beta cell function, as measured by stimulated C-peptide area under the curve (Table 1).

In conclusion, the immunotherapeutic trials that have been completed in human T1D have always focused on patients after clinical onset of diabetes, well after the establishment of targeted adaptive immune responses towards beta cell islets. Targeting these factors is likely to preserve remaining beta cell function, but curative treatments can only be realistically achieved by attempting at the same time to replace part of the beta cell mass that has been lost during the autoimmune process.

Metabolic Disorders and Inflammation in Type 2 Diabetes

Inflammation in Type 2 Diabetes

Several pathophysiological studies have strengthened our understanding of insulin resistance and secretion in the course of disease onset and progression.^{59,60} Subjects at risk of T2D display an initial state of insulin resistance compensated by hypersecretion of

insulin in the beta cells. However, in the clinical course of the disease this pancreatic functional reserve is eventually unable to cope with the required insulin secretion and by the time diabetes is diagnosed, beta cells are no longer able to secrete enough insulin.⁶¹ Although the relative contribution of beta cell dysfunction and insulin resistance can vary in people with T2D, it is generally accepted that abnormal insulin sensitivity precedes the clinical diagnosis of diabetes by up to 15 years.⁶² Therefore, along with mechanistic studies investigating mechanisms forming the basis of insulin resistance, more recent research has also focused on the pathways leading to beta cell failure.⁶³

The Role of Adipose Tissue and Obesity

There has been intensive research conducted into the pathophysiology of diabetes and its association with obesity and the biological role of adipose tissue. As addressed before, insulin resistance is a key component in the course of T2D. Liver and muscles have long been recognised as major contributors of systemic insulin resistance.⁶⁴ Fat accumulation in the liver (steatosis) precedes overt T2D, is commonly associated with obesity and is considered a major determinant of the reduced hepatic insulin sensitivity resulting in fasting hyperglycaemia.^{65–67} Furthermore, it is now well accepted that the accumulation of energy due to excessive calorie intake and the lack of physical activity leads initially to fat accumulation in the subcutaneous tissue and later to other tissue compartments such as the liver, pancreas, muscles, perivascular and pericardium.⁶⁷ This fat accumulation increases tissues' insulin resistance, while pancreatic fat accumulation further determines beta cell dysfunction.^{64,68}

Obesity and its associated conditions including metabolic syndrome, hypertension and dyslipidaemia, is positively associated with concentrations of inflammatory biomarkers, which are predictive of insulin resistance and the incidence of T2D and CVD.^{69–71} Obesity and metabolic syndrome specifically comprise a cluster of diseases associated with too much food and insufficient physical activity, conditions where sub-acute chronic inflammation is a common and potentially unifying mechanistic cause, accompanied by activation of at least two major inflammatory pathways, stress-activated Jun N-terminal kinases (JNK) and the transcription factor NF-kappaB.^{12,16,72–77} This inflammatory state via production of pro-inflammatory cytokines, is further amplified by adipokines, though a number of studies have demonstrated that adipokines stimulate additional inflammatory responses in obesity and promote obesity-induced metabolic and cardiovascular diseases.⁷⁸

Animal studies have demonstrated that brown adipose tissue (BAT) has an important role in regulating energy and glucose homeostasis and is associated with peripheral insulin resistance and glucose levels.^{79–81} However, white adipose tissue (WAT) and mainly visceral WAT (around the trunk, upper body or abdomen) appears to be the major source of inflammatory markers in T2D, but also a target of the inflammatory process in people with diabetes. It produces cytokines and several other bioactive substances involved in the inflammatory pathways, such as TNF-alpha, IL-1, IL-6, IL-10, leptin, adiponectin, monocyte chemoattractant protein, angiotensinogen, resistin, chemokines, serum amyloid protein, and many others collectively referred to as adipokines.^{82–85} Further infiltration of adipose tissue by macrophages and immune cells (B cells and T cells) trigger local and systemic chronic low-grade inflammation, by producing more cytokines and chemokines that serve as a pathologic link between obesity, insulin resistance and diabetes.⁸⁶

The Role of Gut Microbiota in Type 2 Diabetes

The role of the gut in the pathophysiology of diabetes can be approached from two different viewpoints. Studies have suggested that several mechanisms may be involved in weight loss and diabetes control after bariatric surgery, beyond malabsorption or anatomical restriction.⁸⁷ Indeed, complex changes in multiple gut hormones have been shown after bariatric procedures and have been proposed as adjunctive mechanisms for short- and long-term positive metabolic effects, serving as possible novel therapeutic approaches to obesity and insulin resistance.^{88,89}

In the past few years, a two-way relationship between the gut microbiome in the host's energy balance and immune function has been demonstrated.⁹⁰ The gut microbiome seems to differ between obese and lean subjects, flora composition influences metabolism and inversely, diet and metabolic status influence the composition of the gut flora, while a faecal microbiome transplantation from lean donors to insulin-resistant subjects results in beneficial metabolic effects.^{91–94} It has been postulated that products from the gut microbiome may interact with the immune system inducing a tissue metabolic modification, which feeds the molecular origin of the low-grade inflammation that characterises the onset of obesity and diabetes.⁹⁵

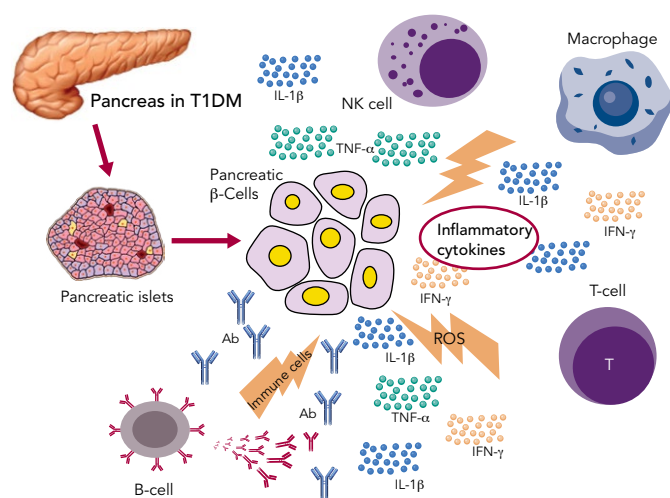
An altered gut microbiota can directly affect immune cells in the gut and indirectly affect immune cells via microbial products including LPS, metabolites and short chain fatty acid (SCFAs), all of which can affect adipogenesis and/or insulin resistance.^{96–101} Lipopolysaccharide (LPS) is believed to cause low-grade inflammation mediated by the induction of inflammatory cytokines by immune cells and adipocytes, while SCFAs can modulate gene expression of human monocytes and reduce pro-inflammatory cytokine and chemokine production.¹⁰² SCFAs can also promote regulatory T-cell generation through several pathways, thereby suppressing the function of inflammatory T cells. These are able to block IFN-gamma inducible protein 10 (IP-10) release in human colonic sub-epithelial myofibroblasts, acting not only on immune cells systemically but also on intestinal tissue cells locally.^{103,104}

The Role of Pancreatic Beta Cell Failure in Type 2 Diabetes

Independent of the aetiopathogenetic mechanism among the different types of diabetes, the common pathway seems to be the inflammation in the pancreatic Langerhans beta cell islets (insulinitis), in the concept of an auto-inflammatory process, which results in reduction in both beta cell number and function.¹⁰⁵ It has been suggested that in people with a genetic predisposition, the 'stressed' beta cell may stimulate local inflammation and modify the balance between beta cell mass and function in the islets of Langerhans.^{106,107} Several experimental models as well as observational studies in humans have demonstrated that macrophages play a key role in the islet inflammation seen in T2D.^{108–111} Inflammasome/IL-1beta signalling is the most common, well-studied and high-impact pathway activated in islets of multiple T2D models that cause beta cell dysfunction.^{112,113} It is likely that other immune cell types are involved in islet inflammation in T2D, while islet autoimmunity has also been suggested to contribute to beta cell functional decline during the course of T2D.^{114,115}

Among factors that stimulate islet macrophages to secrete IL-1beta *in vivo* in human islets are amyloid polypeptide, free fatty acids (FFAs) and endocannabinoids.^{110,111,116} However, it has been assumed

Figure 2: The Vicious Cycle of Inflammation in Various Target Organs in Type 2 Diabetes



Inflammation has a key role in the pathophysiology of type 2 diabetes and its associated metabolic abnormalities.

that hyperglycaemia is produced initially in the inflammation in pancreatic beta cells by inducing apoptotic mechanisms.¹¹⁷ ALPHA particular pathway was proposed by Maedler et al. who showed that hyperglycaemia may induce the production of IL-1beta by stimulating pro-apoptotic receptor FFAs on beta cells.¹¹⁸

FFAs can also produce and secrete IL-1beta and IL-1-dependent pro-inflammatory cytokines in pancreatic islets and thus to reduce the inflammation. In addition, after its initial secretion, IL-1beta regulates its production in pancreatic beta cells by auto stimulation, while this process also increases nitric oxide production leading to reduction in ATP concentration in the mitochondria, which can cause further beta cell dysfunction and reduced insulin secretion.^{119–122} Oxidative stress may also potentiate the generation of ROS along with other pro-inflammatory cytokines and chemokines in the beta cells that disrupts the blood flow into them and destroys their function.^{108,123,124}

Experimental studies have confirmed that IL-6 induces apoptosis in pancreatic islets together with other inflammatory cytokines and acts as a predictor and pathogenic marker for the progression of T2D.^{69,124,125} TNF-alpha is also considered to play an essential role, by creating a linkage among insulin resistance, obesity and islet inflammation.¹²⁵ Its overproduction in adipose tissue seems to feed the inflammation and beta cell death in pancreatic islets and produces additional insulin resistance in peripheral tissues.^{126,127}

Evidence of Inflammation in Other Organs in People with Type 2 Diabetes

Immune system activation is highly related to T2D incidence and progression and adaptive and innate immunity are involved in adipose tissue inflammation. The phenotype switching of macrophages from predominantly anti-inflammatory M2-type to increased proportions of pro-inflammatory M1-type macrophages plays a crucial role in the initiation and amplification of islet inflammation.¹²⁸ However, the evidence shows that the recruitment of B cells and T cells precedes adipose tissue infiltration by macrophages.⁸⁶

Moreover, several other organs have been reported to participate in the metabolic homeostasis and inflammatory state in T2D, such as the

liver, the neural system and possibly skeletal muscle.^{129–133} However, more research is needed to support this evidence (Figure 2).

Current Knowledge on Diabetes Treatments Drugs with Pleiotropic Effects

The current therapeutic approaches to T2D have anti-inflammatory properties in addition to their major modes of action. Non-pharmacological therapies, such as lifestyle interventions, but also pharmacological and bariatric surgical approaches for weight loss, appears to reduce inflammation assessed as circulating CRP and IL-6 concentrations, and improves cardiovascular and all-cause mortality.^{134–138}

Statins also have anti-inflammatory properties beyond their ability to lower levels of low-density lipoproteins (LDL) cholesterol. The Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) demonstrated that rosuvastatin reduced high-sensitivity CRP along with LDL cholesterol, however the effects of statins on glycaemic control are conflicting, implying that targeting inflammation with statins does not improve glycaemia and therefore does not provide an integrated anti-inflammatory approach for diabetes and CVD.^{139–141}

Anti-diabetic agents, including insulin, have intrinsic anti-inflammatory effects associated with their primary mechanisms of action and are also associated with reductions in inflammatory markers. Insulin itself decreases NF-kappaB activity in peripheral blood mononuclear cells which reduces inflammation.¹⁴² The anti-inflammatory actions of thiazolidinediones through binding and activation to the peroxisome proliferator-activated receptor gamma (PPARgamma), seems to be related to trans-repression of NF-kappaB and reduced expression of NF-kappaB targets.¹⁴³

In addition to its metabolic effects, metformin has anti-inflammatory actions that appear to be independent of glycaemia and are most prominent in immune cells and vascular tissues.^{144–150} Dipeptidyl peptidase-4 inhibitors (DPP-4) and GLP-1 receptor agonists also have intrinsic anti-inflammatory properties, however, beyond their anti-diabetic effects, the contribution of inflammation reduction to diabetes and cardiovascular improvements remains unknown.^{151–153} Finally, a new class of anti-diabetic drugs, sodium–glucose cotransporter-2 inhibitors (SGLT2 inhibitors) acts by increasing renal excretion of glucose. Preliminary data in humans demonstrate a possible improvement on the circulating biomarkers of inflammation by SGLT2-inhibitors; however, more studies are needed.¹⁵²

Anti-Inflammatory Drugs in Type 2 Diabetes

Multiple medical approaches that directly target inflammatory pathways have been studied in the past few years supporting the concept of anti-inflammatory treatment for cardiometabolic diseases, such as diabetes and atherosclerotic CVD.^{154–156} For a long time, salicylates, especially aspirin, have been used to treat thrombosis in primary and secondary CVD prevention, as well as to treat rheumatoid diseases.^{157,158} They were the first class of drugs reported to lower glucose in diabetes more than a century ago, however, several studies with salicylate products have demonstrated an improved metabolic profile in patients with obesity and diabetes, suggesting a potential efficacy for diabetes prevention and control.^{159–166}

Methotrexate is a disease-modifying drug broadly used to treat rheumatic diseases among other conditions, while its efficacy on

Table 2: Representative Clinical Trials of Anti-Inflammatory Treatments on Type 2 Diabetes – Metabolic Profile

Mechanism of Action	Drug	Main Findings	Reference
IL-1 receptor blockade	Anakinra	HbA _{1c} ↓, leukocyte ↓, CRP ↓ insulin secretion ↑	182
IL-1 receptor blockade	Anakinra	Sustained CRP ↓, insulin secretion ↑, insulin requirement ↓	181
IL-1 receptor blockade	Anakinra	Insulin sensitivity ↑	193
IL-1 receptor blockade	Anakinra	Insulin secretion ↑ (first-phase insulin secretion improved)	194
IL-1 receptor blockade	Anakinra	Insulin secretion ↑	183
IL-1beta antagonism	Gevokizumab	HbA _{1c} ↓, CRP ↓, insulin secretion ↑	112
IL-1beta antagonism	Canakinumab	Insulin secretion ↑, CRP ↓	185
IL-1beta antagonism	Canakinumab	CRP ↓, HbA _{1c} ↓, insulin secretion ↑ (not statistically significant)	184
IL-1beta antagonism	Canakinumab	Significant CRP and IL-6 ↓, 6 month HbA _{1c} ↓, but not consistent HbA _{1c} ↓ long-term	188
IL-1beta antagonism	Canakinumab	CRP ↓, fibrinogen ↓, IL-6 ↓, no effect on HbA _{1c} , glucose and insulin levels	187
IL-1beta antagonism	LY2189102	HbA _{1c} ↓, CRP ↓, insulin secretion ↑	186
IKKbeta–NF-kappaB inhibition	Salsalate	FBG ↓, CRP ↓, insulin sensitivity ↑, adiponectin ↑	160
IKKbeta–NF-kappaB inhibition	Salsalate	FBG ↓, CRP ↓, adiponectin ↑	159
IKKbeta–NF-kappaB inhibition	Salsalate	FBG ↓, insulin ↑, CRP ↓	195
IKKbeta–NF-kappaB inhibition	Salsalate	HbA _{1c} ↓, FBG ↓, triglyceride ↓, adiponectin ↑	165
IKKbeta–NF-kappaB inhibition	Salsalate	HbA _{1c} ↓, FBG ↓, insulin secretion ↑, triglyceride ↓	162
IKKbeta–NF-kappaB inhibition	Salsalate	FBG ↓, adiponectin ↑	163
IKKbeta–NF-kappaB inhibition	Salsalate	HbA _{1c} ↓, FBG ↓, triglyceride ↓, leukocyte ↓, uric acid ↓, adiponectin ↑	164
TNF antagonism	CDP571	No effect on insulin sensitivity	176
TNF antagonism	Single dose of soluble TNF receptor–Fc fusion protein (Ro 45–2081)	No effect on insulin sensitivity	177
TNF antagonism	Soluble TNF receptor–Fc fusion protein etanercept	CRP ↓, insulin secretion ↑, no effect on insulin sensitivity	178
TNF antagonism	Soluble TNF receptor–Fc fusion protein etanercept	CRP ↓, adiponectin ↑, LDL ↓, no effect on insulin sensitivity	179
TNF antagonism	Soluble TNF receptor–Fc fusion protein etanercept	FBG ↓	180
TNF antagonism	Infliximab	Fasting glucose improvement, ratio of high molecular weight to total adiponectin ↑, sICAM-1 ↑, no effect on CRP	170
Decrease in TNF and IL-1beta levels by an unknown mechanism of action	Diacerein	HbA _{1c} ↓, FBG ↓, insulin secretion ↑	196
DHFR inhibitor – antimetabolite	Low-dose methotrexate	No effects on CRP, IL-1beta or IL-6	168
DHFR inhibitor (DMARD) – combination with sulphasalazine glycocorticosteroids/hydroxychloroquine	Methotrexate	HbA _{1c} ↓	167

CRP: C-reactive protein; DHFR = dihydrofolate reductase inhibitor; FBG = fasting blood glucose; IKKbeta = I-kappaB kinase-beta; IL = Interleukin; mAbs = monoclonal antibodies; NF-kappaB = nuclear factor-kappaB; sICAM-1 = soluble intercellular adhesion molecule-1; TNF = tumour necrosis factor.

glycaemic control was demonstrated in a small cohort study.¹⁶⁷ The preliminary data drove the design and conduction of a large clinical trial with methotrexate among patients with previous MI and either T2D or metabolic syndrome, however, methotrexate had neutral findings on IL-1b, IL-6 and CRP levels, while more data are anticipated for the effects on T2D.¹⁶⁸

Biological Agents as Anti-Inflammatory Therapy in Type 2 Diabetes

Targeting cytokine production and secretion to prevent further activation of inflammation have been proposed with the intention of

stopping the initiation and progression of T2D. TNF-alpha antagonists have been used to treat inflammatory conditions and have been associated with improved glycaemic control and decreased incident of diabetes, while more studies on patients with unfavourable cardiometabolic profile did not demonstrate adequate results, with the exception of a randomised 6-month trial.^{169–180}

The mechanism of action of IL-1beta is consistent with the pathogenesis and progression of T2D is. Improved beta cell secretory function and glycaemia, as well as reduced inflammatory biomarkers in people with diabetes and pre-diabetes have

been demonstrated by IL-1beta antagonists, such as anakinra and gevokizumab.^{112,120,181–6} Studies on CVD and atherosclerosis prevention with IL-1beta antagonists have also been conducted. One study showed that canakinumab reduced the inflammatory proteins CRP, IL-6, and fibrinogen in persons with T2D and high cardiovascular risk with no effect on HbA_{1c}, glucose, and insulin at 4 months, while the large randomised trial with canakinumab – Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) – over a median period of 3.7 years did not reduce the incidence of diabetes in patients with prior MI and high-sensitivity CRP (hsCRP) ≥ 2 mg/l (Table 2).^{187,188}

Future Perspectives for the Treatment of Diabetes

Novel approaches on T2D to evaluate anti-inflammatory diets and modulate an individual's microbiome are under study. Clinical trials investigating the effects of vitamin D supplementation on serum levels of inflammatory markers have provided inconsistent results, with no evidence of effects in most trials, or effects on selected markers in others. There are also studies investigating whether antagonists of leukotriene production enzymes – 5-lipoxygenase (5-LO), 5-LO-activating protein and LTA4 hydrolase – or receptor binding BLT1 have cardiometabolic outcome benefits, however these results

have not yet been reported. The potential for targeting cholinergic pathways, immune modulation or other mediators of inflammation such as JNK and toll-like receptors (TLRs) are also being researched.

Conclusion

The increasing prevalence of diabetes makes it imperative that research should focus on its prevention as well as its treatment. An improved understanding of the mechanisms linking inflammation to diabetes and related complications has stimulated interest in targeting inflammatory pathways as part of the strategy to prevent or control diabetes and its complications.

T1D is considered to be more of an immunological response rather than a metabolic disorder and the preliminary results of trials using anti-inflammatory and immunomodulatory medication are promising. These treatments in combination with possible use of stem cells to regenerate pancreatic beta cells could potentially be the key to permanent treatment of T1D. Therefore, after a holistic review of the possible mechanisms that lead to T1D and T2D and the numerous already described inflammation pathways that are involved, it becomes more and more clear that future research should focus on simultaneous suppression of various inflammatory response pathways rather than focusing on one pathway at a time. ■

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