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### GUEST EDITORIAL

#### INFLAMMATION IN DIABETES AND PRE-DIABETES

Vivian Fonseca, MD

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Over the last decade, evidence has linked chronic low-grade inflammation with diabetes; inflammation has also been closely linked with cardiovascular disease (CVD) and is considered one of the earliest abnormalities in atherosclerosis. Therefore, it has been proposed that inflammation is the “common soil” linking diabetes and CVD.

Interest in inflammation arose with studies suggesting that chronic sub-clinical inflammation may be part of the insulin resistance syndrome—the more features of the syndrome present, the higher the mean value of inflammatory markers such as C-reactive protein (CRP) (click on the PubMed ID number to read more: [PMID 10880413](#), [11128362](#)). Subsequent studies demonstrated that chronic inflammation in insulin-resistant patients preceded development of diabetes. This finding has been confirmed in several studies using a wide variety of inflammatory markers ([PMID 14769830](#)). Indeed, even simple indices of chronic inflammation, such as white blood count, predict incident diabetes on follow up.

Interest in these hypotheses grew when it was recognized that adipose tissue secretes a number of cytokines, particularly interleukin-1 (IL-1) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), that stimulate several downstream inflammatory proteins involved in the pathogenesis of diabetes ([PMID 18987272](#)). More intriguing is the finding that fat tissue itself accumulates macrophages, indicating inflammation; this may perpetuate the

problem of diabetes and CVD ([PMID 16823477](#)). Richard Pratley explores this topic in his article on obesity.

While many investigators focus on the relationship of insulin resistance and inflammation, others have suggested that inflammation also occurs in the pancreatic  $\beta$ -cells and that islet inflammation is common to both type 1 and type 2 diabetes, with different degrees of severity. This is discussed in more detail by Marc Donath later in this issue.

A key factor in the development of inflammation is nuclear factor kappa B (NF $\kappa$ B), which is normally inactive in the cytoplasm until activated by a variety of signals that lead to its translocation into the nucleus to stimulate production of inflammatory proteins by serving as a transcription factor. Several of these proteins are involved in diabetes as well as CVD. Thus, NF $\kappa$ B may serve as the “master switch” in the process of inflammation and may, therefore, prove to be an important therapeutic target. Interestingly, several approaches to block inflammation by suppression of

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**EDITORIAL CORRESPONDENCE**

*CADRE'S Current Diabetes Practice*  
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NfκB entering the nucleus are possible—this key process is blocked by anti-inflammatory drugs, insulin, and some, but not all, drugs used in the treatment of diabetes ([PMID 14704745](#)).

It is noteworthy that low-fat diets and weight loss, as used in the Diabetes Prevention Program, are capable of significant suppression of inflammation; evidence for the Mediterranean Diet also exists. In addition, insulin, insulin sensitizers, and statins reduce inflammation. The JUPITER trial showed that the statin rosuvastatin could reduce cardiovascular events in patients with moderately elevated CRP and low LDL cholesterol who would not otherwise be treated with a statin ([PMID 18997196](#)). Thus statins targeting inflammation may reduce CVD. On the other hand, blood glucose in the JUPITER trial actually went up, suggesting that modulating inflammation may affect glucose metabolism in different ways, and that further study is needed in this area.

If there is overlap between inflammation and diabetes, what would happen if anti-inflammatory drugs were given to patients with diabetes? Indeed, high doses of aspirin have been shown to have insulin-sensitizing effects, but such doses are not practical in clinical practice. However, salicylates have been described in the literature for over a century as being useful in lowering blood glucose. This anti-inflammatory property is being explored in various clinical approaches to treating diabetes. These include use of the salicylate dimer salsalate, which does not cause gastrointestinal side effects and bleeding and has been used for rheumatologic conditions. In addition, drugs that block the interleukins, such as anakinra, have been shown to improve blood glucose. Preliminary studies with salsalate have been conducted ([PMID 17959861](#)) and a large clinical trial using salsalate to treat type 2 diabetes has been launched ([www.tinsalt2d.org](http://www.tinsalt2d.org)). In addition, salsalate has the potential to modulate CVD by addressing low-grade inflammation in the vasculature. Beginning on page 6, Drs. Smiley and Umpierrez discuss the anti-inflammatory effects of diabetes treatments.

Finally, it has been postulated that low-grade inflammation in the mouth, including teeth and the gums, may affect glucose control. To this end, a number of studies have suggested that periodontal treatment may improve glucose control ([PMID 20103557](#); [19909640](#)). This hypothesis is being tested in a large clinical trial.

In summary, a number of investigations have linked diabetes and CVD with low-grade inflammation, and research is being undertaken so that we may use this information to find better ways to target these common conditions.

*Dr. Fonseca has no commercial relationships to disclose related to the content of this article.*

**Suggested Reading**

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**LITERATURE CORNER**

**ISLET INFLAMMATION IN TYPE 2 DIABETES**

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The concept of islet inflammation or insulinitis is traditionally associated with type 1 diabetes. However, increasing evidence points to a pathological activation of the innate immune system in the pancreatic islets of patients with type 2 diabetes mellitus (T2DM), leading to an auto-inflammatory response (click on the PubMed ID number to read the article/abstract: [19996363](#)). Here, we revisit the pathology of islet failure in T2DM and highlight evidence that this process includes an inflammatory response to metabolic stress. It follows that specific anti-inflammatory strategies may prevent this process, thereby improving insulin secretion and glycemia.

**Evidence For Islet Inflammation in Type 2 Diabetes**

Inflammation is defined as the local response to tissue injury. Characterized by immune cell invasion and local release of cytokines and chemokines, it is accompanied by functional or structural damage to the invaded tissue. Inflammation is not, in itself, a disease, but a manifestation of disease. It has beneficial effects such as preventing the spread of infections and promoting regeneration; equally, it may exacerbate disease by tissue destruction due to

*Continued*

inflammatory mediators, reactive oxygen species, and complement components.

In T2DM, metabolic stress causes islet injury; elevated glucose levels, free fatty acids, adipokines (eg, leptin), and LDL cholesterol have all been shown to impair insulin secretion and induce  $\beta$ -cell death, eventually leading to decreased functional  $\beta$ -cell mass. Whether metabolic stress is the primary cause of  $\beta$ -cell failure or a secondary precipitating factor remains unclear. In response to this stress,  $\beta$ -cells produce interleukin-1 $\beta$  (IL-1 $\beta$ ), which has the ability to induce its own production. Thus, strong or prolonged metabolic stress will lead to IL-1 $\beta$  production, which in turn engenders a vicious cycle of auto-induction and possible  $\beta$ -cell injury.

In type 1 diabetes, IL-1 $\beta$  has been shown to have direct toxic effects on  $\beta$ -cells. Recently it has become apparent that IL-1 $\beta$  is a master regulator of tissue inflammation responsible for production of several cytokines and chemokines. Thus, rather than simply being directly cytotoxic, IL-1 $\beta$  may regulate a broad inflammatory response that amplifies the adverse effects on  $\beta$ -cell function and survival.

Although immune cells are an inherent part of tissue inflammation, it was only in 2007 that they were investigated in the islets of patients with T2DM (PMID 17579207) and the presence of increased numbers of islet-associated macrophages detected. The precise role of these cells remains unclear, however. Several animal studies have shown that macrophages and other bone marrow-derived cells may contribute to  $\beta$ -cell regeneration (PMID 12819790). It is possible that macrophages are initially recruited to the islets in an attempt to cope with increased metabolic stress. However, if this response becomes prolonged, macrophages may become activated and thus harmful to organ function. In line with this hypothesis, low concentrations of IL-1 $\beta$  promote  $\beta$ -cell function and survival, while high concentrations are deleterious.

Fibrosis is pathognomonic for the end stage of a chronic inflammatory process and autopsy studies show that the presence of fibrosis with amyloidosis is a hallmark pattern for islets from patients with T2DM. This simple observation may be the strongest support for the claim of insulinitis in T2DM; it is surprising that this obvious link was not made earlier.

### Therapeutic Implications

Cytokine modulation is a recent and rapidly expanding therapeutic area. Specific cytokine antagonists have been successfully used or are under investigation for an increasing number of diseases. Based on the hypothesis of islet inflammation with a predominant role for IL-1 $\beta$ , clinical trials of IL-1 antagonism in T2DM have been initiated. In a proof-of-concept study, administration of IL-1Ra, the naturally occurring receptor antagonist of IL-1 $\beta$ , led to improvements in glycated hemoglobin due to enhanced  $\beta$ -cell secretory function (PMID 17429083). Remarkably, the improvement promoted by IL-1 blockade lasted for at least 39 weeks following treatment withdrawal, possibly reflecting a break in the vicious cycle of IL-1 $\beta$  auto-induction, and indicating the disease-modifying potential of this therapy. Rather than just palliating hyperglycemia, IL-1 antagonism may represent a novel treatment directed against the underlying pathogenesis of diabetes mellitus, whereby the progressive decline in functional  $\beta$ -cell mass could be prevented or even reversed. Due to the auto-inflammatory nature of the metabolic syndrome and based on preclinical

*Continued*

## SPECIAL REPORT

### C-REACTIVE PROTEIN (CRP) AS A PREDICTOR OF CARDIOVASCULAR DISEASE (CVD) RISK

Recent clinical and population studies have linked inflammation to CVD risk. The most reliable marker of inflammation, C-reactive protein (CRP), is simple and inexpensive to measure, and the blood test can be performed without regard to the patient's fasting status. The American Heart Association recommends a high-sensitivity CRP (hs-CRP) assay for patients at intermediate CVD risk (ie, the possibility of developing CVD is 10% to 20% within the next 10 years). The test should be done twice, about 2 weeks apart, and the results averaged. Patients with an active infection, systemic inflammatory processes, or trauma should not be tested until the conditions have resolved. Table 1 shows the CVD risk associated with hs-CRP

measurements; a hs-CRP >10 mg/L should be discarded and the test repeated in 2 weeks. Knowledge of hs-CRP levels may help motivate patients to implement or improve lifestyle modifications shown to reduce CRP levels, including:

- weight loss, if overweight or obese
- increased physical activity
- smoking cessation
- a healthful diet of fresh fruits and vegetables, low-fat foods, healthy oils, and fish (especially fatty fish), and reduced intake of processed foods, saturated fat, and animal fat
- compliance with drug therapy, particularly statin, fibrate, and/or niacin therapy

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**Table 1. Cardiovascular disease (CVD) risk based on high-sensitivity C-reactive protein (hs-CRP) assay**

hs-CRP (mg/L)	Risk of Developing CVD
<1	Low
1 – 3	Average
>3	High

American Heart Association. Inflammation, heart disease, stroke: the role of C-reactive protein. <http://www.americanheart.org/presenter.jhtml?identifier=4648>.

studies, it is conceivable that IL-1 antagonism will also enhance insulin sensitivity and prevent complications like blindness, cardiovascular events, and nephropathy. Numerous ongoing clinical studies are based on this assumption and will uncover the real potential of this therapeutic approach.

A limitation for the use of IL-1Ra is its short half-life of 4 to 6 hours and weak efficiency that requires a 500-fold molar excess to block IL-1 action. In development are novel therapeutic approaches designed to modulate IL-1 activity with agents lasting a month or longer. IL-1 antagonism may also be potentiated by targeted modulation of other cytokines. Alternatively, tissue inflammation in T2DM may be treated by other anti-inflammatory drugs, including salicylate or other NF- $\kappa$ B modulators. Several drugs used frequently in patients with T2DM, such as statins, have profound secondary anti-inflammatory effects ([PMID 12879149](#)).

### Conclusion

Decreases in both secretory function and mass of insulin-producing  $\beta$ -cells contribute to the pathophysiology of T2DM. The histology of islets from patients with T2DM displays an inflammatory process characterized by the presence of cytokines, apoptotic cells, immune cell infiltration, amyloid deposits, and eventually fibrosis. This process is probably the combined consequence of hyperglycemia, dyslipidemia, and increased circulating adipokines. Therefore, modulation of intra-islet inflammatory mediators, particularly IL-1 $\beta$ , appears to be a promising therapeutic approach. In the future, anti-inflammatory drugs may represent a primary treatment directed at the underlying pathogenesis of diabetes mellitus.

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## LITERATURE CORNER

### OBESITY: A CHRONIC INFLAMMATORY CONDITION

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Obesity increases the risk for a number of chronic conditions including insulin resistance, type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, atherosclerosis, some types of cancer, and respiratory disorders such as asthma. Recently, a large and growing body of research addressing the role of adipose tissue in promoting obesity-associated complications has led to important new insights into the biology of the adipocyte.

Adipose tissue used to be viewed as a passive storage depot; we now know it is a complex, metabolically active tissue that secretes a wide variety of signaling molecules to regulate feeding behavior, energy expenditure, metabolism, endocrine function, and immune function. A large proportion of these secreted molecules are cytokines or cytokine-like molecules that modulate immune and inflammatory response, including leptin, adiponectin, resistin, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), and others. These adipokines contribute to a chronic, low-grade inflammatory state in obesity and may play a central role in the pathogenesis of many of the complications of obesity that are also characterized

by evidence of chronic inflammation, including T2DM and atherosclerosis.

### Obesity Is a State of Chronic, Low-Grade Systemic Inflammation

Substantial evidence accumulated over the last 2 decades indicates that obesity is associated with a state of chronic, low-grade systemic inflammation. In the early 1990s, we and others demonstrated a direct correlation between total leukocyte count and obesity in young, healthy men and women. In our study, the total leukocyte count also was directly related to the insulin concentration and insulin resistance, measured using the glucose clamp technique (click on the PubMed ID number to read more: [8653533](#)). Other studies established an association between the total leukocyte count and risk factors for atherosclerosis, as well as for mortality.

Circulating cytokines and other markers of inflammation are also increased in obesity. A direct correlation between fasting plasma IL-6 concentrations and obesity has been demonstrated ([PMID 11445664](#)); elevated plasma TNF- $\alpha$  levels have also been associated with obesity. C-reactive protein (CRP), a major acute-phase reactant, is increased in obesity, as are other acute-phase reactant proteins including serum amyloid A and fibrinogen. IL-6 and TNF- $\alpha$  promote hepatic production of CRP, so higher levels of CRP in obese persons may be due, in part, to higher circulating levels of these cytokines. CRP levels are also higher in patients with metabolic syndrome, diabetes, and atherosclerosis and are predictive of development of diabetes and acute coronary events. High-sensitivity CRP (hs-CRP) is a non-specific but sensitive marker of infection and tissue inflammation. CRP has a number of diverse effects including activating the complement system, modulating phagocytosis, and regulating inflammation. Not surprisingly, other proteins involved in the innate immune response, such as complement component 3 (C3), and the thrombotic-fibrinolytic pathways, such as plasminogen activator inhibitor-1 (PAI-1), are also increased in obesity. Thus, a large number of studies in

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different populations, using a wide variety of markers, indicate that obesity is a state of chronic, sub-clinical systemic inflammation.

**Adipose Tissue Secretes Cytokines and Other Molecules That Induce a Pro-inflammatory State in Obesity**

The discovery of leptin in 1995 was a pivotal point in the evolution of adipose biology. Almost overnight, the prevailing view that adipose tissue was merely a passive storage depot shifted, as it became rapidly apparent that adipocytes secrete a large number of proteins involved in endocrine and metabolic function—including leptin, which plays a key role in regulating appetite and energy expenditure. We and others demonstrated that leptin was secreted in direct proportion to the degree of obesity in humans (PMID 7584987). The observation that leptin and its receptor were similar to certain cytokines also suggested a role for adipose tissue in modulating immune function. Subsequently, a microarray gene expression profiling study demonstrated that a large number of cytokines were expressed in human adipocytes (PMID 16059715). Remarkably, 52 of 54 genes in the inflammation/immune response category that were differentially expressed were upregulated in the adipocytes of obese compared with nonobese persons. It is now apparent that adipocytes secrete many of these, including TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-8,  $\alpha$ 1-acid glycoprotein, as well as complement proteins involved in the innate immune system, and PAI-1, which plays a critical role in coagulation. Of note, expression of a number of molecules implicated in macrophage function, including monocyte chemoattractant protein-1 (MCP-1), macrophage migration inhibitory factor (MIF) and macrophage inflammatory protein (MIP)-1 $\alpha$  are also upregulated in adipocytes in obesity.

Another pivotal development in adipocyte biology was the discovery of adiponectin. In contrast to leptin, adiponectin is downregulated in obesity and may have both anti-inflammatory and insulin sensitizing effects. We demonstrated that adiponectin levels were negatively correlated with obesity,

whereas they were directly correlated with insulin action in young, healthy individuals (PMID 11344187).

Thus, both an expanded adipose tissue mass, as well as alterations in secretion and expression of adipokines from adipose tissue, may contribute to higher circulating levels of multiple adipokines in obese individuals, leading to the development of a chronic, low-grade pro-inflammatory state.

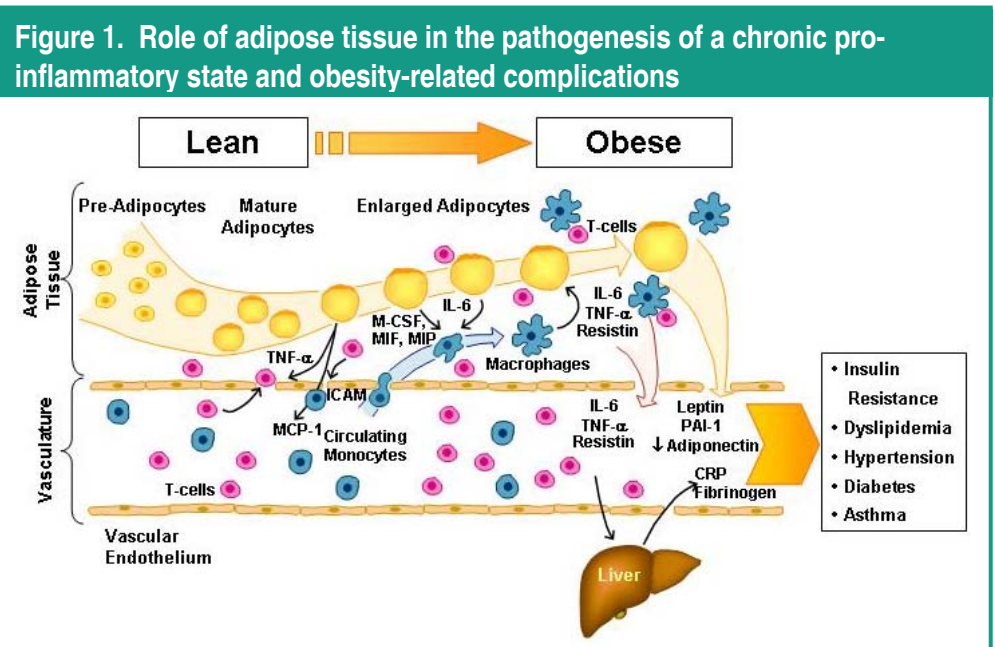
**Cellular Contributions to Obesity-Associated Inflammation**

Besides mature, lipid-laden adipocytes, adipose tissue contains a large variety of stromal vascular cells (SVC), including preadipocytes, fibroblasts, macrophages, mast cells, lymphocytes, and vascular cells. It is now clear that these cells play an integral role in the development of obesity-associated inflammation. Like adipocytes, the SVC compartment of adipose tissue is dynamically regulated and responsive to obesity. For example, extent of macrophage infiltration in adipose tissue is directly correlated with degree of obesity. Moreover, macrophages in adipose tissue from obese individuals are activated and express a number of proteins, such as MIP-1 $\alpha$ , MCP-1, Mac-1, and related inflammatory markers, which may play a role in development of obesity-induced insulin resistance. Almost all adipose tissue

TNF- $\alpha$  and significant amounts of inducible nitric oxide synthase (iNOS) and IL-6 appear to be expressed by adipose tissue macrophages, rather than adipocytes. These data indicate that adipose tissue resident macrophages contribute significantly to the increased inflammatory state in obesity. The infiltration of macrophages into adipose tissue and their involvement in the inflammatory process is similar to that observed in atherosclerosis and may suggest a common mechanism linking obesity and atherosclerosis.

It has become evident that T-cells play an important role in generating the inflammatory phenotype in adipose tissue. In response to a high-fat diet, CD4<sup>+</sup> helper T-cells are diminished whereas CD8<sup>+</sup> effector T-cells are markedly increased in adipose tissue, leading to macrophage infiltration and adipose tissue inflammation in mice. The loss of a specific population of CD4<sup>+</sup> T-cells in adipose tissue has also been associated with development of insulin resistance in obese animals. Collectively, these data reinforce the concept that adipose tissue is a complex organ and that the genesis of the pro-inflammatory state in obesity depends on the interactions of multiple cell types.

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Adapted from Lee YH and Pratley RE. Abdominal obesity and cardiovascular disease risk: the emerging role of the adipocyte. *J Cardiopulm Rehabil Prev.* 2007;27:2-10; used with permission.

**Conclusion**

During the last 2 decades, a number of pivotal studies have helped clarify the central role of adipose tissue in the pathogenesis of a chronic pro-inflammatory state and many obesity-associated complications, including T2DM and atherosclerosis. A simplified schema is depicted in Figure 1 (previous page). Expansion of adipocyte cell size and tissue mass in response to over-nutrition leads to increased production of leptin, TNF- $\alpha$ , and other cytokines by adipocytes. This leads to an increase in T-effector cells and a decrease in certain T-regulatory cells that, in turn, promotes migration of monocytes across the endothelial wall. Once in the tissue, other factors produced by adipocytes and T-cells, including MIP, MIF and macrophage-colony stimulating factor (M-CSF), cause the monocytes to differentiate into macrophages and become activated. These activated

macrophages secrete a large number of cytokines including IL-6 and TNF- $\alpha$ , inducing insulin resistance in adipocytes through paracrine mechanisms. Macrophages also contribute substantially to overall adipose tissue secretion of these pro-inflammatory cytokines; this leads to increased circulating levels in obese individuals and promotes enhanced production of CRP and fibrinogen from the liver. Leptin, and potentially other cytokines, may also contribute to the increased total leukocyte count in obese individuals.

Together, these alterations in cytokines and cellular mediators of immunity produce a chronic, low-grade pro-inflammatory milieu that adversely affects insulin action, endothelial function, and lipid metabolism, resulting in diabetes, dyslipidemia, hypertension, metabolic syndrome, and atherosclerosis.

*Dr. Pratley has received research grants from Eli Lilly, GlaxoSmithKline, MannKind, Merck, Novartis, Novo Nordisk, Pfizer, Roche, sanofi-aventis, and Takeda; has served as a consultant and/or is on an advisory board and/or speakers' bureau for AstraZeneca/Bristol Myers Squibb, Eisai, GlaxoSmithKline, Glenmark, Merck, Novartis, Novo Nordisk, Roche, and Takeda; and holds stock in Novartis.*

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**PRACTICE POINTERS**

**POTENTIAL TREATMENTS FOR UNDERLYING INFLAMMATION IN TYPE 2 DIABETES**

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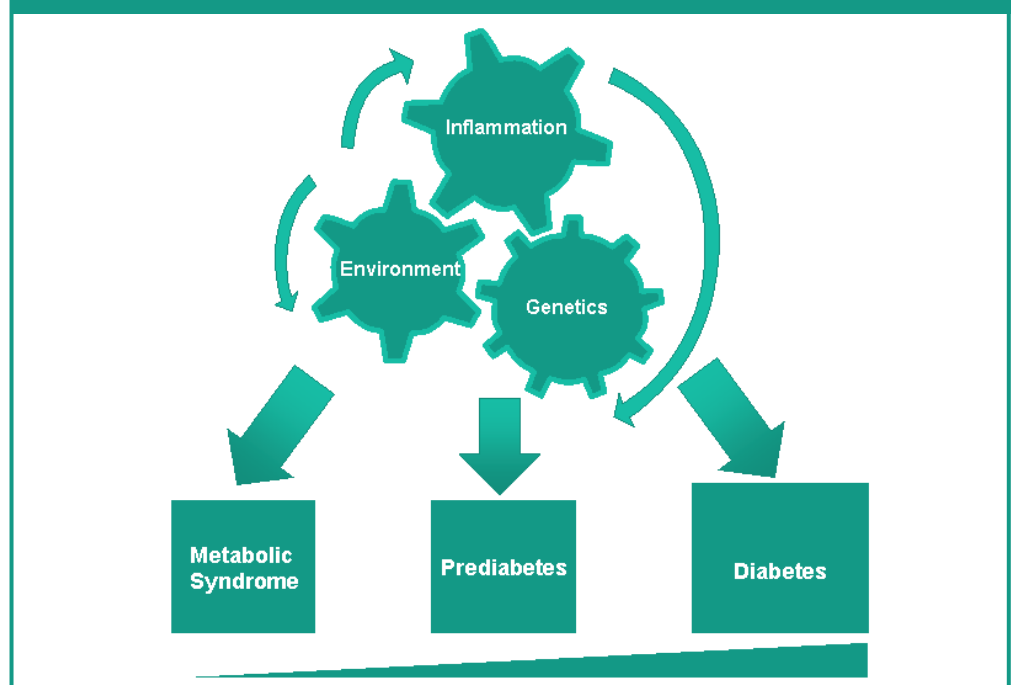
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Chronic inflammation, characterized by an increase in C-reactive protein (CRP), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and interleukins (IL-1 $\beta$ , IL-6, IL-8, IL-12) (Table 1, page 7), has been associated with poor glycemic control and T2DM complications such as retinopathy and neuropathy, endothelial dysfunction,

and atherosclerotic disease. Increasing evidence suggests that chronic inflammation precedes T2DM onset by several years and may be linked to genetic predisposition (Figure 1) (click on the PubMed ID number to read the article/ abstract: [15864529](https://pubmed.ncbi.nlm.nih.gov/15864529/)). Increased

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**Figure 1. The components leading to diabetes**



Insulin resistance and  $\beta$ -cell dysfunction have been the traditional etiologic cornerstones of type 2 diabetes mellitus (T2DM); increasing evidence, however, supports the role of inflammation and oxidative stress underlying the disease, its progression, and its associated chronic complications. The mechanisms that trigger inflammation at the level of the pancreatic  $\beta$ -cells and endothelium in T2DM are not well understood, but it is suspected that a combination of genetic, hormonal, and environmental factors leads to the unbalanced production of pro-inflammatory acute phase reactants and cytokines.

amounts of visceral adipose tissue can produce IL-6, TNF- $\alpha$ , and other adipokines; these mediators of inflammation in turn mediate production of CRP and other inflammatory cells (ie, macrophages), leading to insulin resistance and worsening pancreatic  $\beta$ -cell function. Studies of mice fed a high-fat diet suggest that altering inflammatory responses can prevent insulin resistance, carbohydrate intolerance, and diabetes; clinical studies have shown that reduction of inflammation in subjects with T2DM is associated with reduced incidence of microvascular and macrovascular disease. The current T2DM armamentarium focuses primarily on improving A1C, blood pressure, and lipid profiles, however the use of agents with anti-inflammatory properties may

further improve glycemic outcomes and cardiovascular risk factors.

### Current Treatments With Anti-Inflammatory Actions

A number of treatments used in T2DM have anti-inflammatory actions (Table 2). Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), frequently employed as first-line agents for management of hypertension in T2DM, appear to have anti-inflammatory benefits. Several ACE inhibitors improve oxidative stress and systemic inflammation in normotensive and hypertensive T2DM patients (PMID 18046434, 17404826). ACE inhibitors and ARBs may also exert beneficial effects on carbohydrate metabolism through a variety of mechanisms such as increased blood flow to skeletal muscle, increased bradykinin levels, and more efficient insulin release (PMID 18370775). These mechanisms are directly related to inhibition of angiotensin II; however, it remains to be established whether these drugs' effects on carbohydrate metabolism have long-term influence.

Since 1987 when the first FDA-approved HMG-CoA reductase inhibitor became commercially available, statins have

been in the forefront due to their ability to significantly decrease fatal and non-fatal cardiac event rates (relative risk reduction, 17% to 47%) in patients with diabetes. In addition to LDL-lowering effects, the pleiotropic, independent effects of statins, including anti-oxidant, anti-inflammatory, and anti-atherogenic properties, make this class of medications a formidable opponent in the fight against cardiovascular disease. Statins reduce inflammation, as shown by decreased levels of high-sensitivity CRP (hs-CRP), soluble tissue factor, and platelet-activating factor acetyl hydrolyase. Interestingly, statin use has been associated with elevations in fasting blood glucose levels in patients with and without diabetes; this effect is independent of age or the use of aspirin, angiotensin-converting enzyme inhibitors, or  $\beta$ -blockers (PMID 19188844).

Fibrates, commonly used to combat low high-density lipoprotein cholesterol and hypertriglyceridemia in patients with diabetes via a different lipid-lowering pathway than statins, also have anti-inflammatory properties. Okopień and colleagues reported that, compared with the American Heart Association Step 1 diet, 30 days of fenofibrate treatment resulted in lower hs-CRP and monocyte

*Continued*

**Table 1. Inflammatory markers that can be elevated in diabetes**

Acute phase proteins
C-reactive protein (CRP)
Fibrinogen
Serum amyloid A protein
Haptoglobin
$\alpha$ -1 Acid glycoprotein
Orosomucoid
Systemic cytokines
Interleukin-6 (IL-6)
Soluble IL-6 receptor
Tumor necrosis factor- $\alpha$ (TNF- $\alpha$ )
Soluble TNF- $\alpha$ receptors 1 and 2
IL-1+IL-6
IL-18
Macrophage migration inhibitory factor (MIF)
Monocyte chemotactic protein-1 (MCP-1)
Regulated upon activation normal T-cell expressed and secreted (RANTES)
Endothelial/blood molecules
Soluble intercellular adhesion molecule-1 (ICAM-1)
Soluble vascular cell adhesion molecule-1 (VCAM-1)
Plasminogen activator inhibitor-1 (PAI-1)
Thrombin-activatable fibrinolysis inhibitor (TAFI)
Tissue plasminogen activator (t-PA)
Soluble E-selectin
Soluble P-selectin
Soluble CD40 ligand
von Willebrand factor

Adapted from Kolb H, *Diabetologia*. 2005;48:1038-1050; used with permission.

**Table 2. Anti-inflammatory properties of common treatments in diabetes**

Agent	Inflammatory Markers					
	CRP	IL-1	IL-6	TNF- $\alpha$	PAI-1	ICAM-1
<b>Biguanides</b>	↓↔			↔	↓	↓
<b>Sulfonylureas</b>	↓↔			↓		
<b>Thiazolidinediones</b>	↓	↓	↓	↓	↓	
<b>GLP-1 analogs</b>			↔	↔	↔	
<b>DPP-4 inhibitors</b>			↔	↔	↔	
<b>Insulin</b>	↓	↓	↓	↓	↓	↓
<b>Statins</b>	↓		↔*	↔*		
<b>ACE inhibitors/ARBs</b>	↓		↓	↓		
<b>Fibrate</b>		↓	↓	↓		
<b>Lifestyle modification</b>	↓	↓	↓	↓	↓	↓

↓↔= no effect or only modest decrease

↔\*=decrease in ex vivo effects but no effect on circulating levels

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CRP, C-reactive protein; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; lifestyle modification, weight loss and/or physical exercise; PAI-1, plasminogen activator inhibitor-1; TNF- $\alpha$ , tumor necrosis factor-  $\alpha$

Adapted from: Kolb H, *Diabetologia*. 2005;48:1038; Deans KA. *Diabetes Technol Ther*. 2006;8:18; Courreges JP. *Diabet Med*. 2008;25:1129; Caballero, AE. *J Clin Endocrinol Metab*. 2004;89:3943.

TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and monocyte chemoattractant protein-1 (MCP-1) (PMID 16492702). The recent DIACOR (Diabetes and Combined Lipid Therapy Regimen) trial found that fibrates lower lipoprotein-associated phospholipase A2 (Lp-PLA2) following 12 weeks of therapy (PMID 16843192). Since fibrates modify lipids via activation of the peroxisome proliferator-activated receptor type alpha (PPAR $\alpha$ ) pathway, it is not surprising that they, like their PPAR $\gamma$  counterparts, thiazolidinediones (TZDs), lower fasting blood glucose levels. Of note, the study group found that the glucose-lowering benefit of fibrate therapy due to improved insulin sensitivity correlated more closely with anti-inflammatory than with lipid-lowering effects.

TZDs are PPAR $\gamma$  agonists frequently used as monotherapy or combination therapy for glycemic control in patients with T2DM. These agents have been shown to reduce blood glucose and free fatty acids, as well as levels of various inflammatory markers such as hs-CRP, TNF- $\alpha$ , and plasminogen activator inhibitor-1 (PAI-1), independent of effect on glycemic control. TZDs reduce blood pressure, improve endothelial function, and exert a number of anti-atherogenic effects on the vascular wall, including modulation of smooth muscle proliferation and migration, reduction of cytokine production and macrophage activation, and suppression of matrix metalloproteinase production in macrophages.

Concerns for cardiovascular safety were raised in 2007 by a meta-analysis of 42 controlled trials that investigated cardiovascular morbidity and mortality in patients with T2DM treated with rosiglitazone. The results revealed that patients treated with rosiglitazone for >24 weeks had an odds ratio for myocardial infarction of 1.43 (confidence interval, 1.03-1.98;  $P=0.06$ ) and had a statistical trend ( $P=0.03$ ) toward increased cardiovascular death (PMID 17517853). In contrast, the >6-year results from the ADOPT (A Diabetes Outcome Progression Trial) and RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation

of glycaemia in Diabetes) trials did not show any increased ischemic risk with rosiglitazone use relative to that noted in the metformin or glyburide treatment arms (PMID 12351470, 19501900). Moreover, the 2005 PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) study reported that pioglitazone was not associated with increased risk of cardiac ischemic events, and a recent meta-analysis evaluating pioglitazone found that patients receiving this drug had a significantly lower risk of death, myocardial infarction, or stroke compared with other patients evaluated (PMID 16214598, 17848652). Despite a lengthy FDA review concluding that TZDs, including rosiglitazone, are safe in patients with T2DM when used as directed, the agents are no longer used as frequently in the United States due to concerns regarding cost and side effects (ie, weight gain, lower extremity edema, and volume overload).

Lifestyle modification still stands as the primary, and most frequently revisited, intervention in patients with T2DM. In patients with T2DM who have undergone bariatric procedures, the impact of decreasing weight and the resultant improvement in panmetabolic targets (glycemia, lipids, blood pressure) speaks to the direct link between weight, inflammation, and oxidative stress. Even in less aggressive instances of lifestyle modification, investigators have found that 5% to 10% loss of body weight (PMID 18452840) or exercise for 45 to 60 minutes per day, 4 times per week, *without* weight loss (PMID 18043308) is associated with improvements in metabolic and inflammatory profiles. Kadoglou and colleagues not only found that exercise was associated with CRP decrements, but also led to increases in the anti-inflammatory cytokine IL-10. Roberts and colleagues found that just a 3-week regimen of a low-fat, high-fiber diet alongside daily aerobic exercise in men with T2DM resulted in significant improvements ( $P<0.05$ ) in body mass index, insulin resistance, CRP, prostaglandin factor 2 $\alpha$  (PGF2 $\alpha$ ), intercellular adhesion molecule-1 (ICAM-1), and E-selectin (the latter induced by

IL-1 and TNF- $\alpha$ ) (PMID 16616795) (Table 2, previous page).

Unfortunately, in patients with T2DM, weight loss is difficult to achieve and sustain. However, the odds that a patient will actually attempt weight loss are raised 3-fold when it is suggested by a health care provider. In addition to exercise, some studies have suggested a role for dietary supplements (such as  $\alpha$ -lipoic acid, vitamin D, L-arginine, flaxseed, and omega-3 fish oil) in anti-inflammatory lifestyle modification regimens for patients with T2DM. The Look AHEAD (Action for Health in Diabetes) study, a major clinical trial evaluating the cardiometabolic outcomes of intensive lifestyle modification in overweight patients with T2DM, found that after a 1-year period of marine omega-3 fatty acid supplements weight was reduced and was associated with improved lipid profiles (PMID 19841042). Whether use of these agents helped with weight loss or had a role in improving the lipid profile associated with weight loss is uncertain. These and other complementary supplements are becoming increasingly popular; however, most are not FDA-approved and require additional study in large clinical trials

### Potential New Treatments

In patients with diabetes, it is well established that use of high-dose salicylates (~7g/day; ASA) is associated with a significant reduction in inflammation and improvements in glycemic control (PMID 12021247). The potential to use high-dose ASA in clinical practice is severely diminished due to the high risk of side effects such as gastrointestinal bleeding and tinnitus. Salsalate, a pro-drug of salicylic acid, is a nonsteroidal anti-inflammatory (NSAID) found to improve insulin resistance and glycemic control in subjects with and without diabetes. Its proposed mechanism of action is via inhibition of IKK $\beta$ /NF- $\kappa$ B; however, due to its weak inhibition of the cyclooxygenase enzymes COX-1/COX-2 and its sparing effects on the gastric mucosa compared with other NSAIDs, salsalate does not alter bleeding time, causes less gastrointestinal bleeding, and does not suppress renal prostaglandin. A preliminary report of the

*Continued*

ongoing NIH-sponsored TINSAL-T2D (Targeting Inflammation Using Salsalate in Type 2 Diabetes) study reported that standard (3.0 g/day) and high (4.5 g/day) doses of salsalate improved insulin sensitivity and reduced fasting and postchallenge glucose levels after just 2 weeks of treatment ([PMID 19337387](#)).

On the horizon are a few additional novel approaches for reducing the underlying chronic inflammatory state in diabetes (Table 3). Studies suggest an auto-crine role for IL-1 $\beta$  in damage to rodent and human islets ([PMID 16249450](#)). Anakinra, a recombinant IL-1-receptor antagonist (IL-1Ra), would act to competitively bind to the IL-1 receptor without subsequent activation of the NF- $\kappa$ B signaling pathway. IL-1Ra, in turn, acts to dampen the systemic inflammatory response induced by IL-1 $\beta$ . Lisofylline is another agent under investigation. Developed as an anti-infective for cancer patients, lisofylline is a synthetic anti-inflammatory shown to protect

pancreatic islets from IL-1 $\beta$ -induced inhibitory effects on insulin release and in turn prevent type 1 diabetes mellitus in mouse models. Although the exact mechanism of action is unknown, increasing evidence suggests that lisofylline also blocks the IL-12 and STAT4 pro-inflammatory pathways and improves cellular mitochondrial function ([PMID 12717280](#)).

### Conclusion

Reductions in inflammation for patients with T2DM have been associated with improvements in glycemic control, blood pressure, and lipid profiles; in turn, this may lower the risk of microvascular and macrovascular complications. Use of antidiabetic agents in combination with therapeutic interventions that have anti-inflammatory properties represents a physiologic and potentially optimal regimen for patient management. Multicenter randomized trials are needed to determine the beneficial effects of different anti-

inflammatory interventions in improving glycemic control, as well as preventing long-term complications of T2DM.

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### Suggested Reading

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Duncan BB, Schmidt MI, Pankow JS, et al. Low-grade systemic inflammation and the development of type 2 diabetes: the Atherosclerosis Risk in Communities Study. *Diabetes.* 2003;52:1799-1805.

Goldfine AB, Fonseca V, Jablonski KA, et al; TINSAL-T2D (Targeting Inflammation Using Salsalate in Type 2 Diabetes) Study Team. The effects of salsalate on glycemic control in patients with type 2 diabetes: a randomized trial. *Ann Intern Med.* 2010;152:346-357.

**Table 3. Ongoing clinical trials of two potential new antidiabetic agents with inflammation targets**

<b>Salsalate</b> (an anti-inflammatory pro-drug of salicylate prescribed for many years for arthritis; method of action not fully elucidated)						
<b>Trial name</b>	<b>Phase</b>	<b>Participants</b>	<b>Regimen</b>	<b>Primary outcome</b>	<b>Status</b>	<b>Anticipated end date</b>
Targeting Inflammation Using Salsalate in Type 2 Diabetes (TINSAL-T2D)	II/III	T2DM, 18-75 years	Salsalate 3.0 g/d vs 3.5 g/d vs 4.0 g/d vs placebo	Change in A1C from baseline to week 14 (stage 1) or week 26 (stage 2)	Study ongoing, enrollment complete	December 2010
<b>Anakinra</b> (synthetic SC medication with anti-inflammatory effects used in the treatment of rheumatoid arthritis; blocks the effects of IL-1)						
<b>Trial name</b>	<b>Phase</b>	<b>Participants</b>	<b>Regimen</b>	<b>Primary outcome</b>	<b>Status</b>	<b>Anticipated end date</b>
An Exploratory, Open Label Study of Anti-inflammatory Therapy With Anakinra in Children With Newly Diagnosed Type 1 Diabetes Mellitus	I/II	T1DM, 6-18 years	Anakinra q day for 28 days	Change in EGR2 expression in PBMCs	Completed	July 2009
A Randomised Clinical Trial of the Effect of Interleukin-1 Receptor Antagonism on the Insulin Production in Patients With New Onset Type 1 Diabetes	II/III	T1DM, 18-35 years	Anakinra 100 mg SC q day vs saline for 2 years	Change in 2-hr C-peptide response at 1, 3, 6, and 9 months	Enrollment ongoing	September 2011
Effect of Interleukin-1 Receptor (IL-1 Rc) Antagonist on Insulin Sensitivity in Obese, Insulin Resistant Individuals	II	T2DM	Anakinra 150 mg SC q day for 4 weeks	Assess effect of IL-1 Rc antagonist on insulin sensitivity per euglycemic hyperinsulinemic clamp	Not yet recruiting	March 2010

EGR2, early growth response protein 2; IL-1, interleukin-1; PBMC, peripheral blood mononuclear cell; SC, subcutaneous; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

From [www.clinicaltrials.gov](http://www.clinicaltrials.gov).