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Diabetes Mellitus and Inflammation

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Abstract Type 2 diabetes mellitus (T2DM) is increasingly common worldwide. Related complications account for increased morbidity and mortality, and enormous healthcare spending. Knowledge of the pathophysiological derangements involved in the occurrence of diabetes and related complications is critical for successful prevention and control solutions. Epidemiologic studies have established an association between inflammatory biomarkers and the occurrence of T2DM and complications. Adipose tissue appears to be a major site of production of those inflammatory biomarkers, as a result of the cross-talk between adipose cells, macrophages, and other immune cells that infiltrate the expanding adipose tissue. The triggering mechanisms of the inflammation in T2DM are still ill-understood. Inflammatory response likely contributes to T2DM occurrence by causing insulin resistance, and is in turn intensified in the presence of hyperglycemia to promote long-term complications of diabetes. Targeting inflammatory pathways could possibly be a component of the strategies to prevent and control diabetes and related complications.

Keywords Diabetes mellitus · Inflammation · Biomarkers · Adipocytes · Cytokines · Adipokines · Interleukin

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Introduction

Diabetes mellitus and type 2 diabetes (T2DM) in particular is becoming increasingly important worldwide, assuming epidemic proportions in many populations and settings [1]. The increasing diabetes figures have been largely attributed to the environmental changes that promote the adoption of unhealthy behaviors and development of obesity and overweight around the world. Excess weight is a strong antecedent of T2DM, and both are associated with adverse cardiovascular risk profile. Inflammatory pathways have been suggested as the underlying unifying pathogenic mediators for excess weight, diabetes mellitus, and cardiovascular diseases [2]. Indeed, subclinical chronic inflammation is a common feature in the natural course of diabetes and levels of inflammatory biomarkers, many of which are secreted by adipocytes, correlate with prevalent and incident diabetes, as well as major complications and cardiovascular diseases in particular.

This review will summarize recent evidence linking low-grade chronic inflammation with the occurrence of type 2 diabetes mellitus and related complications. Type 1 diabetes is not discussed owing to differences in risk factors' profile and pathophysiology between type 1 and type 2 diabetes. Our current understanding is that type 1 diabetes is predominantly an autoimmune disease in

which the pancreatic insulin-producing beta-cells are selectively destroyed by the immune system, with the triggering factors being still ill-understood. Contrarily, type 2 diabetes occurs as a combination of varying degrees of insulin secretion defects and impaired insulin action. For a recent review on inflammation and type 1 diabetes, the reader may refer to Bending et al. [3]. In the current review, therefore, unless a distinction cannot be made in the cited study, the focus is on type 2 diabetes.

Historical Perspectives

From a historical standpoint, it is over a century ago that observations suggesting possible connections between inflammation and diabetes were made. It was, for instance, found by Ebstein in 1876 (cited by Shoelson [4]), and Williamson 25 years later [5] that administration of high doses of sodium salicylate decreased the glycosuria in individuals likely with type 2 diabetes in those days [4]. These observations, however, did not attract much attention until the second half of the 20th century when similar observations were reported in insulin-treated diabetic patients receiving high dose salicylate for arthritis [6]. Subsequently, studies on the role of inflammation in insulin resistance revealed that the hypoglycemic action of salicylates was related to the inhibition of the serine kinase IκB kinase-β (IKKβ) [2, 7], which are now known to interfere with the post-receptor action of insulin.

The earliest strong evidence in support of the role of inflammation in the disease process beyond that of a simple marker comes from the work of Hotamisiligil et al. [8]. They showed that tumor necrosis factor α (TNF-α), a proinflammatory cytokine, was produced by adipose cell, and could induce insulin resistance in animal model. Furthermore, TNF-α blockade improved insulin resistance, suggesting that similar mechanisms could operate in humans [8]. Over the last few decades, many studies have established a positive correlation between type 2 diabetes occurrence and nonoptimal levels of markers and mediators of inflammation [9]. Many lines of evidence suggest that chronic activation of proinflammatory pathways in target cells of insulin action may contribute to obesity, insulin resistance, and related disorders including type 2 diabetes [2]. The characterization of possible pathways linking inflammation to diabetes mellitus has generated interest in targeting inflammation to improve prevention and control of diabetes and related complications [10]. However, some of the suggested interventions targeting inflammation remain very hypothetical, and many other have not passed the test of clinical trials. Others have tested if measuring inflammation markers could improve risk stratification for diabetes or related complications, again with mixed findings [11, 12].

Organs Involved in Chronic Inflammation Related to Diabetes

While the inflammatory process in obesity and diabetes is systemic, some organs appear to be more involved than others.

Adipose Tissue

Adipose tissue is a major source of inflammatory makers but also a target of the inflammatory process in diabetes. Adipose tissue comprises the white adipose tissue (WAT), which is the most common type, and brown adipose tissue, which seems to be less involved in the inflammatory process. WAT is further distinguished in term of subcutaneous and visceral (or abdominal) fat tissues, with distinct physiologies and roles in the pathologic processes [13]. Abdominal WAT appears to play a major role in the inflammation process. WAT is the site for production of cytokines and many other bioactive substances involved in the inflammatory pathways. These include TNF-α, interleukin (IL) 1, IL-6, IL-10, leptin, adiponectin, monocyte chemoattractant protein, resistin, angiotensinogen, visfatin, retinol-binding protein-4, serum amyloid protein, and many others [2].

Hematopoietic System/Immune Cells

Adipose tissue expansion in obesity is characterized by increasing infiltration by macrophages and immune cells. These infiltrating cells contribute to localized and systemic chronic low-grade inflammation. Hypoxia, adipocyte cell death, and increased secretion of chemokines and adipokines have been suggested as some of the mechanisms that initiate the infiltration of adipose tissue by immune cells. Both the adaptive and innate immunity are involved in adipose tissue inflammation, with the phenotype switching of macrophages from predominantly anti-inflammatory M2-type macrophage population to include increased proportions of proinflammatory M1-type macrophages, being a determining event [14]. Current knowledge supports that T-cells phenotype changes and recruitment of B cells and T cells precedes adipose tissue infiltration by macrophages. Ultimately, infiltrated cells produce cytokines and chemokines that serve as pathologic link between obesity and insulin resistance, and down the line diabetes occurrence [14, 15].

Pancreas

Several lines of evidence support the involvement of the islet inflammatory process in the pathophysiological derangements in type 2 diabetes [16]. This process appears to be highly dependent on interleukin 1 (IL-1), which has made some to suggest the concept of an auto-inflammatory nature for type 2 diabetes, similar to what is observed in type 1 diabetes [17]. But whether islet inflammation in type 2 is an

auto-immune process [17], is induced by the glucotoxicity that characterized diabetes [16], is triggered by circulating adipokines or other factors [16, 18] is still unclear.

Other Organs

The inflammatory state has also been reported in different other organs involved in the control of metabolic homeostasis including the liver [19], the hypothalamus [20], and possibly skeletal muscle [21].

Triggers of Chronic Inflammation in Obesity and Diabetes

The triggering factors of the inflammatory process in obesity and diabetes are still ill-understood, but some hypotheses suggested below have been proposed.

Obesity

Chronic inflammation in TD2 is thought to occur in response to hypoxia, the altered lipolysis and remodeling/necrosis of the expanding adipose tissue compartment, subsequent to the growing fat mass in overweight and obesity [22]. Direct and indirect evidences, both in animals and humans, indicate that adipose tissue becomes hypoxic as the fat mass expands. This expansion that is not paralleled by the development of the capillary network [23], causes the adipocytes, which are already larger than the diffusion distance of the oxygen, to become too distant from the vasculature [24]. The consideration that the ensuing hypoxia is the trigger of the inflammatory response related to obesity relates to the direct effects of low oxygen pressure [24]. It has been postulated that hypoxia response could actually be a feedback mechanism in the protection of the body against obesity [25], while recent suggestion that human's adipose tissues exhibit hyperoxia rather than hypoxia [26] indicates that a possible role of hypoxia is far from definitive. It has been suggested that free fatty acid and potentially several other metabolites produced by fat tissue such as acyl-CoAs, ceramide, and diacylglycerol can act as signaling molecules that will activate the inflammatory cascade associated with insulin resistance [27]. Infiltration of adipose tissue by inflammatory cells and macrophages in particular is a determining factor in the low-grade inflammation associated with obesity and diabetes. One of the currently accepted theories holds that the balance of adipokines secreted by the enlarging fat tissues could be a stimulating factor for the colonization of fat tissue by inflammatory cells [28].

Diet

Dietary pattern can contribute to systemic inflammation via several mechanisms. High-fat diet for instance can induce changes in the gut microbiota, by favoring the development of gram negative bacteria, which will trigger systemic inflammation via increased production of lipopolysaccharide (LPS) and/or induction of periodontitis [29]. It has also been suggested that high-fat diet could enhance the translocation of live gram-negative bacteria from the gut to the adipose tissue [30]. Nutrients such as saturated fatty acid have pro-inflammatory properties [31], whereas others like ω-3 fatty acid can be anti-inflammatory [32].

Periodontal Diseases/Oral Health

Existing evidence supports a 2-way relationship between diabetes mellitus and periodontal disease [33]. Periodontitis has been conceptualized as a 'low grade infection' capable of developing a 'low-grade systemic inflammation' that may ultimately affect the general systemic health. Several proinflammatory mediators are expressed in periodontitis, as a result of the activation of the host immune-inflammatory mechanisms. Furthermore, the periodontopathogenic microflora produce toxin, including the potent LPS, which may trigger systemic inflammatory response. In general, however, the weight of evidence relating oral health to diabetes occurrence remains very weak [34, 35].

Gut Microbiota

The gut microflora has complex and bidirectional relationship with host metabolism and immune function. Host health and diet influence the composition of the gut flora, and conversely, different flora compositions influence host metabolism [36, 37]. It has been postulated that products from the microbiome could interact with the immune system to induce a tissue metabolic infection, which is the molecular origin of the low-grade inflammation that characterizes the onset of obesity and diabetes [38•]. LPS, a highly inflammatory component of the cell-wall of the gram negative bacteria, has been suggested as a causal link between gut microflora and systemic low-grade inflammation leading to obesity and diabetes mellitus [38•].

Exposure to Air Pollutants

Long-term exposure to fine particles (particles <2.5 μm in aerodynamic diameter ($PM_{2.5}$) or traffic-related air pollutant has been associated with increased risk of diabetes occurrence, and increased mortality in people with diabetes compared with nondiabetic subjects [39, 40]. Inflammation attributable to oxidative stress has been suggested as one of the underlying mechanisms [39, 41]. Other potential mechanisms include $PM_{2.5}$ mediated alterations in glucose homeostasis, endoplasmic reticulum stress in the liver and

lung, mitochondrial dysfunction and brown adipose tissue dysfunction, activation of toll-like receptors, and nucleotide oligomerization domain receptors [41].

Vitamin D Deficiency

It has been suggested that vitamin D deficiency plays a key role in insulin resistance leading to diabetes mellitus [42, 43]. Inherited gene polymorphisms have been mostly proposed as the mechanisms linking vitamin D deficiency with diabetes occurrence. However, several lines of evidence support the anti-inflammatory role of vitamin D and its regulatory effects on the immune system. A possible loss or attenuation of those functions in the presence of vitamin D deficiency may explain the development of insulin resistance and type 2 diabetes mellitus [42, 43, 44•, 45].

The Vagus Nerve and the Inflammatory Reflex

The vagus nerve is a key component of the neuro-reflex mechanism 'the inflammatory reflex' that controls inflammatory response during pathogen invasion and tissue injury. Emerging evidence suggests that possible dysregulation of the vagus nerve signaling might contribute to the pathogenesis of obesity and related metabolic abnormalities such as diabetes mellitus [46].

Genetics Factors

Single nucleotide polymorphisms have been reported to occur in the upstream regulatory regions of several pro- and anti-inflammatory marker genes that influence the levels of production of those markers/mediators [47, 48]. These single nucleotide polymorphisms may affect the intensity of the inflammation, as well as the outcome of inflammatory stress [47]. However, whether the allele that increases expression of such genes is increased in frequency in type 2 diabetes has not been conclusively demonstrated. Indeed, preliminary attempts to demonstrate such a connection at the genetic level found no evidence in support of an association [49]. One large-scale association analysis has provided findings that suggest an over-representation of genetic variants of inflammatory pathways in type 2 diabetes [50], likely the role of the predisposition of inflammation in the susceptibility to diabetes. DNA methylation profiling studies of type 2 diabetes have recently uncovered hypomethylation across over 200 gene promoters in human islet cells [51], raising the possibility that epigenetic mechanisms may be involved in the occurrence of diabetes, some of which could potential involve inflammatory pathways [52, 53].

Inflammatory Markers in Diabetes (Table 1)

White Cell Count

White cell count is the most fundamental measure of inflammation in clinical settings. Even within what is considered to be the normal range, higher total white blood cell counts have been reported to be associated with type 2 diabetes occurrence [54••]. This association appeared to be driven primarily by the granulocytes subpopulations and to a lesser extent the lymphocytes subpopulation, but not the monocytes subfractions [54••]. The lack of an association between monocyte counts, the precursor of macrophages, which are determining cells in the inflammation associated with obesity and diabetes, has been explained by the fact that the primary destination of monocytes is not the blood stream, and therefore, peripheral count may not reflect monocytes population in tissues where many are attracted to differentiate to macrophages [54••].

Adipokines

Adipose tissue secretes several hundred of bioactive factors termed adipokines, many of which are involved in the inflammatory process [55]. A dysregulation of these adipokines is observed under conditions of both excessive and lack of adipose tissue. While many of the adipocytes-derived inflammatory proteins are also secreted by immune cells which infiltrate the adipose tissue in obesity, some others proteins are produced exclusively by adipocytes. Leptin and adiponectin appear to be the adipokines exclusively produced by the adipocytes, and for which more evidence of an association with inflammation and diabetes has been demonstrated. Leptin, the protein product of the obesity (*ob*) gene, has been shown to be related with several metabolic, inflammatory and hemostatic factors, and serum leptin levels are directly proportional to the total fat mass. The expression of the *ob* gene is regulated by different factors including food intake, insulin levels, and steroid hormones. The production of leptin increases during inflammatory conditions [56], and leptin can modulate the innate and adaptive immune responses, including the promotion of T cell responses, activation of monocytes and neutrophils, and the induction of pro-inflammatory mediators [57, 58]. Prospective cohort studies support the association of high serum leptin levels with incident diabetes [59, 60].

Adiponectin is a protein abundantly produced by white adipose tissue, and plasma circulating levels are in the order of 5–30 mg/L. Adiponectin exerts its biological effect by binding on specific receptors found on many cells, and myocytes and liver cells in particular. Plasma adiponectin concentrations are inversely correlated with fasting insulin levels, and positively correlated with insulin sensitivity, consistent with the suggested role of adiponectin as insulin

Table 1 Selection of key inflammation biomarkers involved in obesity related disorders

Cytokines and adipokines	Cell source	Role in obesity pathogenesis
Leptin (adipokine)	Adipocytes	Regulates food intake and energy balance.
	Gastric mucosa cells	Increase release in parallel with weight gain.
		Activates anorexigenic pathways in the hypothalamic arcuate nucleus and other brain regions.
		Acts through leptin receptors on vagus nerve afferents and on brain neurons and via intracellular JAK2-STAT3-mediated signaling.
		Positive regulator of glucose homeostasis and insulin sensitivity in muscle and liver.
		Leptin resistance in obesity associated with intracellular SOCS-3 mediated suppression of STAT3 phosphorylation.
		Hyperleptinemia has proinflammatory effect in obesity.
TNF (pro-inflammatory cytokine)	Macrophages	Major contributor to local and systemic insulin resistance.
	Other immunes cells	Increased expression in adipose tissue.
	Adipocytes	Simulates resistin expression in human macrophages and suppresses adiponectin expression in human adipocytes.
		Implicated in the pathogenesis of fatty liver disease.
IL-6 (pro-inflammatory cytokine)	Macrophages	Mediates local and systemic insulin resistance.
	Other immunes cells	Suppresses adiponectin expression in human adipocytes.
	Adipocytes	Implicated in pathogenesis of fatty liver disease.
		Inducer of acute-phase protein, including C-reactive protein in lever, which is linked to an increased risk of cardiovascular disease.
		Increased expression in adipose tissue and increased circulating levels in obesity.
CCL2 (chemokine)	Macrophages	Mediates macrophage and other immune cell infiltration into adipose tissue.
	Other immunes cells	Linked to insulin resistance and hepatosteatosis in rodents.
	Adipocytes	Increased levels in obesity.
Resistin (adipokine)	Macrophages (humans)	Induces insulin resistance in mice, and might have a similar role in humans.
	Adipocytes (mice)	Simulates TNF and IL-6 production.
		Increased circulating and adipose tissue levels in rodent models of obesity.
Adiponectin (adipokine)	Adipocytes	Anti-inflammatory and insulin-sensitizing functions.
		Suppresses macrophage activation and proinflammatory cytokine release.
		Inversely correlated with insulin resistance, type 2 diabetes mellitus, fatty liver disease, and atherosclerosis.
		Decreased circulating levels in adiposity.

Adapted with permission from Pavlov VA, Tracey KJ. The vagus nerve and the inflammatory reflex-linking immunity and metabolism. Nat Rev Endocrinol. 2012;8:743–54 [46]

sensitizer. Pro-inflammatory markers such as TNF-α and IL-6 inhibit adipose tissue adiponectin m-RNA expression and adiponectin secretion [61]. On the other hand, adiponectin impairs the production of proinflammatory cytokines such as TNF-α and interferon-gamma in macrophages and reduce their phagocytic capacity while promoting the production of anti-inflammatory markers such as IL-10, IL-1 receptor agonist by monocytes, and derived cells [62]. Low levels of adiponectin are associated with incident T2DM [9].

Chemotactic Proteins

Chemotactic proteins secreted by adipocytes and immune cells are involved in the inflammatory process related to obesity and diabetes mellitus. Of these chemotactic proteins,

those of the chemokine family have been the most investigated. Chemokines are small proteins secreted by adipocytes and other cell residing in the adipose tissue, and that further attract various immune cells into the adipose tissue [63]. Several chemokines including CCL2 (MPC-1), CCL5 (RANTES), and CXCL8 (IL-8) have been found to be related to diabetes [63]. Other chemoattractants not of the chemokines family such as chimerin have increasingly been shown to have pro- or anti-inflammatory properties, which may explain some of the connection between obesity and diabetes mellitus [64, 65].

Other Cytokines

Other cytokines secreted by adipocytes and immune cells are also involved in the inflammatory process related to diabetes. TNF-α, IL-6, and IL-10 appear to be some of the most investigated. TNF-α is a cytokine originally known for its important proinflammatory properties, but it also exerts effects on glucose and lipid metabolism [66]. At low concentrations, TNF-α acts locally as a regulator of immune inflammatory response (autocrine and paracrine effects). At high concentrations, TNF-α enters the circulation and acts as an endocrine factor, associated with insulin resistance [67–69]. TNF-α causes an increase in release of fatty acids by adipocytes, resulting in increased levels of free fatty acids, which can deteriorate insulin signaling [70]. TNF-α inhibits insulin signal transduction and may also decrease insulin secretion [71].

IL-6 is a cytokine secreted to about 30 % by adipose tissue, mainly visceral adipose tissue. The secretion of IL-6 by certain cells such as macrophages is induced by other cytokines such as TNF and IL-1 and inhibited by IL-4 and IL-10. Plasma concentrations of IL-6 are statistically higher in obese and insulin resistant subjects [72]. A high plasma concentration of IL-6 is also predictive of type 2 diabetes occurrence [73]. However, the effect of IL-6 on glucose metabolism is still disputed [74]. There has been suggestion of an interaction between TNF-α and IL-6, whereby TNF-α stimulates the IL-6 transcription gene, and induces the production of its receptor [48].

Unlike TNF-α and IL-6 that are proinflammatory, IL-10 is an anti-inflammatory cytokine, which exerts insulin sensitizing effects. IL-10 has a pivotal role in the inhibition of the production of proinflammatory cytokines like TNF-α and IL-6. Decreased production of IL-10 has been linked with the inflammatory response in diabetes mellitus, likely through decreasing activity of insulin receptors' tyrosine kinase [48]. IL-10 is mainly produced by type 2 macrophages and lymphocytes. Members of the IL-1 superfamily including IL-1α, IL-1β, and IL-1 receptor agonist (IL-1Ra) have increasingly been reported to play a role in energy metabolism and glucose homeostasis. IL-1 affects glucose metabolism among others by impairing insulin signaling, modulating insulin secretion, and amplifying insulin dependent glucose uptake [74]. Studies have linked IL-1 members with type 2 diabetes occurrence [75].

Acute Phase Reactants

Acute phase reactants are nonspecific components of the normal response to acute stress, which is usually of short duration. High levels, but within normal range of several acute phase reactants including C-reactive protein (CRP), fibrinogen, orosomucoid, sialic acid, and serum albumin (low levels) have been linked with type diabetes occurrence, with, however, no evidence for a convincing causal relationship [76]. CRP is probably the most investigated acute phase reactants in relation with diabetes risk [76]. CRP is secreted by the liver, a secretion induced by proinflammatory cytokines including IL-6 and IL-1. There has been suggestion that CRP may play a substantial role in the onset of the insulin resistance by altering signaling pathways of insulin [77].

Links Between Inflammation and Diabetes at the Cellular Level

Insulin exerts its action by binding to a specific receptor (insulin receptor), which, after undergoing activation and autophosphorylation, triggers the phosphorylation of several intracellular docking proteins including insulin receptor substrates 1 and 2 (IRS-1 and IRS-2), Scr homology collagen, and associated protein substrate. IRS proteins are the major and most investigated proteins involved in insulin signaling process. IRS actives several pathways (including the phosphatidylinositol-3 kinase (PI3-K pathway)) involved in the regulation of key cellular events including glucose uptake and metabolism, protein synthesis, gene expression, cell survival, growth, development, and differentiation [78]. Downstream proteins on the PI3-K pathways include several serine/threonine kinases, such as protein kinase C, glycogen synthase kinase-3, and protein kinase B (PKB also known as Akt).

Insulin resistance, a major pathophysiological derangement in obesity and type 2 diabetes mellitus, arises when the target tissues of insulin action such as the liver, muscle, and adipose tissue are unable to respond appropriately to insulin. The precise mechanisms involved in insulin resistance are still ill-understood but could include among other factors the increasing levels of free fatty acid, oxidative stress, altered gene expression, mitochondrial dysfunction, and subclinical chronic inflammation. As reviewed above, low-grade inflammation operates in target tissues of insulin action in the state of obesity and related conditions such as diabetes

mellitus and has led to the suggestion of an existing cross-talk between inflammation and insulin resistance, although the exact mechanisms involved have not been fully elucidated. Inflammatory response is a well-coordinated process, which is an integral part of the body defense mechanisms against noxious stimuli, infection, injuries etc. [79]. The inflammatory response is imitated by the binding of the inducers (bacterial products for instance) to their receptors, leading to the activation of biological responses by inflammatory cells like macrophages and mast cells [79]. Several cell receptors have been identified as the sensors of the inflammation inducers, including the toll-like receptors (TLRs), the receptors of the advanced glycation end-products (RAGE), and the intracellular nucleotide oligomerization domain (NOD). Postreceptor response to the inflammatory signal involves the activation of several pathways including the activation of the c-Jun NH(2)-terminal kinase (JNK) and the inhibitor of κappa-B kinase (IKK). JNK and IKK can also regulate downstream transcriptional processes through transcription factors activated proteins and nuclear factor κB (NF-κB), therefore, amplifying the expression of proinflammatory mediators. Indeed, at the cellular and molecular level, NF-κB has a pivotal role in controlling the synthesis of several key proteins involved in the activation and maintenance of the inflamed state.

The currently widely accepted theory linking chronic inflammation to obesity and diabetes mellitus holds that many of the triggers of chronic inflammation described above (or some still to be discovered) operate via activation of TLRs and TLR4 and TLR2 in particular [80••], therefore, activating the JNK/IKK NF-κB pathways and the inflammatory cascade. Both JNK and IKK are thought to be the mediator of insulin resistance induced by inflammation and exert their action by phosphorylating the serine residues on IRS proteins, therefore, blocking the phosphorylation of IRS on tyrosine residues subsequent to activation by insulin receptor [8]; the resulting consequence being the inhibition of the action of insulin [81]. Furthermore, phosphorylation on serine/threonine residues also increases IRS degradation contributing to insulin resistance [81, 82].

Another molecular link between inflammation and defective insulin action is provided by the suppressors of cytokine signaling (SOCS) 1 and 3, which are induced by cytokines and IL-6 in particular, and lead to ubiquitinylation and degradation of IRS protein [83]. SOCS-3 expression is strikingly enhanced in insulin-sensitive tissues from patients with type 2 diabetes and insulin resistance [83]. Experimental studies also support the role of NOD1 and NOD2 in glucose intolerance and diabetes induced by high fat diet in animal models [30]. A possible role of inflammasomes as a link between obesity-induced inflammation and diseases occurrence has been suggested, a role that has yet to be clarified [80••].

Inflammation Control and Diabetes

An improved understanding of the mechanisms linking inflammation to diabetes mellitus and related complications has stimulated interest in targeting inflammatory pathways as part of the strategy to prevent or control diabetes mellitus and its complications [2, 84]. New lines of interventions continue to emerge; some are being abandoned, while others have been tested either in experimental studies or clinical trials, often with mixed results [10]. Nonpharmacological interventions such as those implemented in diabetes prevention trials lower levels of inflammatory markers [85]. Some glucose control agents like glitazones or insulin at high dose reduce markers of inflammation, independently of the glucose lowering effects [2, 10]. Statins, which are commonly used in people with diabetes, have also been shown to lower inflammatory biomarkers [86], without sizable effect on insulin resistance. Lifestyle changes likely affect inflammation through weight changes whereas the effect of glitazones and statins appear to be related to specific anti-inflammatory properties, which likely contribute to the clinical benefits of those compounds.

Other strategies have been tested, without necessarily reaching the stage of clinical application. Salicylates (aspirin) which are nonsteroidal anti-inflammatory drugs, have been known for over a century now to improve metabolic control in diabetes, but at a dose not applicable in routine clinical care without facing serious adverse effects [2]. The nonacetylated form of salicylates, which are relatively safer, have been shown in small clinical trials to improve metabolic control in people with type 2 diabetes [87, 88], suggesting possible utility for diabetes prevention and control, a possibility currently under investigation in much larger trials [10]. Trials with different IL-1 receptor antagonists in type 2 diabetes have resulted in only small improvements in glycemic control. Definitive conclusions on the possible clinical utility of IL-1 control in prevention diabetes may arise from the large ongoing Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) phase III clinical trial [89]. Likewise, TNF-α blockade has shown only limited clinical utility in the context of insulin resistance associated or not with type 2 diabetes [90, 91]. 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 few others [45]. Similarly, available trials have shown no convincing benefits of vitamin D supplementation on plasma glucose levels and insulin resistance [92, 93•]. Improving gut microbiota through dietary intervention or probiotics has been considered as a possible emerging strategy for preventing the development and progression of diabetes mellitus [94]. However, reliable scientific evidence to support the hypothesis in human subjects is still lacking. The potential for targeting cholinergic pathways [46], immune modulation [95], or other mediators of inflammation

such as JNK and TLRs [84] have also been discussed in details.

Conclusions

The increasing global population of people with type 2 diabetes has been largely attributed to obesity resulting from the adoption of unhealthy habits worldwide. Available evidence supports the role of low-grade chronic inflammation as a possible connection between obesity and type 2 diabetes via inflammation-induced insulin resistance essentially. Obesity is characterized by low-grade inflammation operating in the adipose tissue and other target organs of insulin action, and has led to the suggestion of a possible cross-talk between inflammation and insulin resistance, through mechanisms that are still poorly characterized. There are also suggestions that some antecedents of diabetes not involving obesity on the causal pathways such as air pollution may induce diabetes via inflammatory pathways. The improved understanding of the mechanisms linking inflammation to diabetes mellitus has stimulated interest in targeting inflammatory pathways to improve diabetes prevention and care. However, interventions specifically targeting inflammation are still to make their way into routine practice as part of the strategy to prevent and control diabetes. There has also been growing interest in measuring inflammation markers to improve risk stratification for diabetes or related complications. Our work and those from other investigators suggest that inflammatory markers add little to risk stratification once classical risk factors for diabetes or cardiovascular diseases have been accounted for [11, 12, 96]. Therefore, for the time being, measuring inflammatory marker for diabetes or cardiovascular risk stratification may not be cost-effective.

Conflict of Interest Eric Lontchi-Yimagou declares that he has no conflict of interest.

Eugene Sobngwi declares that he has no conflict of interest.

Tandi E Matsha declares that she has no conflict of interest.

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- • Of importance
- •• Of major importance

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