Biomarkers of Inflammation for Management of Diabetes

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Contributor: Akira Matsumori

Virus infection, inflammation and genetic factors are important factors in the pathogenesis of diabetes mellitus. The nuclear factor-kappa B (NF-κB) is a family of transcription factors that bind the enhancer of the κ light chain gene of B cell immunoglobulin. NF-κB plays an essential role in the activation and development of B cells, and the activation of NF-κB is critical in the inflammation and development of diabetes mellitus. Recently, immunoglobulin-free light chain (FLC) λ was found to be increased in the sera of patients with diabetes mellitus, and the FLC λ and κ/λ ratios are more specific and sensitive markers for the diagnosis of diabetes relative to glycated hemoglobin A1c. Thus, FLCs may be promising biomarkers of inflammation that could relate to the activation of NF-κB.

Keywords: anti-inflammation ; biomarker ; diabetes ; immunoglobulin ; light chains ; nuclear factor kappa B ; hepatitis C virus ; SARS-CoV-2 ; treatment ; prevention

1. Role of Inflammation in the Pathogenesis of Diabetes Mellitus

1.1. Inflammatory Cytokines

Circulating levels of acute-phase proteins are elevated in diabetes, such as serum amyloid A, C-reactive protein (CRP), fibrinogen, haptoglobin, plasminogen activator inhibitor, sialic acid, interleukin (IL)-1β, IL-1 receptor antagonist (IL-1Ra), IL-6 and tumor necrosis factor (TNF)-α[1][2][3][4]. Elevated circulating CRP, IL-1β, IL-1Ra and IL-6 are predictive markers for the development of type 2 diabetes mellitus (T2DM)[2][5][6][7][8]. The production of TNF-α is increased by adipose tissues during obesity, and insulin sensitivity is improved by a TNF-α antagonist [9]. Macrophages and other immune cells exist in adipose tissues and may release TNF-α, IL-1β, IL-6 and IL-33[9][10][11][12]. It is now well-established that tissue inflammation plays a critical role in insulin resistance[13][14].

Inflammation may play an important role in defective insulin action and insulin secretion. Increased cytokine expressions and immune cell infiltration of pro-inflammatory macrophages are seen in pancreatic islets of patients with T2DM[15][16]. This chronic inflammatory process is associated with fibrosis and amyloid deposits, which are observed in the islets of most patients with T2DM.

1.2. Nuclear Factor-Kappa B (NF-κB)

Nuclear factor-kappa B (NF-κB) is a key molecule in the pathogenesis of diabetes. The NF-κB pathway is activated by genotoxic, oxidative and inflammatory stress, and regulates the expression of cytokines, growth factors and genes that regulate apoptosis, cell-cycle progression and inflammation[17]. Pharmacologic and genetic suppression implicated that NF-κB activation causes insulin resistance and glucose metabolism[18]. Upregulation of NF-κB signaling in hepatocytes results in a T2DM, and innate immune activation and inflammatory response that may underlie T2DM[19][20]. Therefore, NF-κB activation in numerous tissues, including adipose tissue, pancreas and liver, contributes to the pathogenesis of T2DM.

2. Novel Biomarkers of Inflammation: Immunoglobulin-Free Light Chains (FLCs)

2.1. FLCs as Novel Biomarkers of Chronic Inflammation

NF-κB was originally identified as a family of transcription factors that binds the immunoglobulin κ light chain gene enhancer. FLCs are synthesized de novo and secreted into circulation by B cells. FLCs emerge as an excess byproduct of antibody synthesis by B cells; elevated FLCs have been proposed to be a biomarker of B cell activity in many inflammatory and autoimmune conditions. Polyclonal FLCs are a predictor of mortality in the general population,

measured by the sum of κ and λ concentrations. Increased FLCκ, and the higher κ/λ ratio, occurred more in rheumatic disease than in healthy blood donors[21][22][23]. FLCs in inflammatory and autoimmune diseases correlate with disease activity, suggesting their role as potential therapeutic targets in such conditions.

2.2. FLCs as Markers of Heart Failure and Myocarditis

FLCs were increased in a mouse model of heart failure due to viral myocarditis. Recently, additional research was conducted with patients in heart failure, and circulating FLC λ was increased while the κ/λ ratio was decreased in sera from patients with heart failure resulting from myocarditis, as compared to a group of healthy controls. These findings demonstrated that the FLC λ and κ/λ ratio together showed good diagnostic potential for the identification of myocarditis. In addition, the FLC κ/λ ratio could also be used as an independent prognostic factor for overall patient survival[24][25].

2.3. FLCs and COVID-19 and Heart Diseases

The recent review of 316 cases of postmortem examination of COVID-19 patients demonstrated that cardiac abnormalities, either on gross pathology or histology, were identified in almost all cases. Most autopsies demonstrated chronic cardiac pathologies such as hypertrophy (27%), fibrosis (23%), amyloidosis (4%), cardiac dilatation (20%), acute ischemia (8%), intracardiac thrombi (2.5%), pericardial effusion (2.5%), and myocarditis (1.5%). SARS-CoV-2 was detected within the myocardium of 47% of studied hearts[26]. However, the Dallas criteria was satisfied in only five of these cases. In an additional 35 cases, minimal lymphocytic or mononuclear infiltration was reported, and they did not satisfy the Dallas criteria for myocarditis. Lymphocytic infiltration was scarce but could be detected in the pericardium, myocardium, epicardium, or endothelium. Therefore, cellular infiltration may be rare in COVID-19 myocarditis and, therefore, the Dallas criteria may not be accurate in the diagnosis of COVID-19 myocarditis, as it is the same in the case of HCV myocarditis[27][28].

An increase in blood troponin levels in COVID-19 is an indicator of myocardial damage. Several studies have documented a strong association between COVID-19 progression and elevated blood troponin. Reports from China found that elevated circulating cardiac troponin was present in 7–28% of COVID-19 patients, suggesting the existence of myocardial injury or myocarditis[29][30]. In hospitalized patients with COVID-19, mortality in the elevated-blood-troponin group was 51–60%, a range markedly higher than in the 5–9% in the normal-blood-troponin group.

It has been studied how frequently myocardial injury or myocarditis occurs in COVID-19 patients[31][32]. Troponin T was positive in 63% of patients, NT-proBNP was elevated in 68% of patients, and elevated creatine kinase was noted in 43% of patients at admission. NT-proBNP showed a significant correlation with the length of hospital management and the severity of pulmonary CT findings. In addition, the existence of enhanced inflammatory biomarkers such as CRP and ferritin suggested that myocardial injury may be caused by inflammatory myocardial processes. D-dimer was also elevated frequently, suggesting that coagulation abnormality occurs frequently in COVID-19 patients. Thus, COVID-19 has been frequently associated with myocardial injury, suggesting that SARS-CoV-2 causes myocarditis.

It has also been measured FLCs and IL-6 in COVID-19 patients. FLCs and was elevated in 73% and 80% of patients, respectively, and the frequency of the elevated levels was higher than those of troponin T, NT-proBNP, creatine kinase, and IL-6. IL-6 has been frequently measured in COVID-19 patients, but elevated levels of IL-6 were less frequent, as compared to other parameters.

2.4. FLCs as Markers of Atrial Fibrillation

Atrial fibrillation is the most common arrhythmia, which is an important cause of stroke. Diabetes is a risk factor for the development of atrial fibrillation. Diabetes in patients with atrial fibrillation is associated with increased cardiovascular and cerebrovascular mortality. The pathogenesis of diabetes-related atrial fibrillation remains to be clarified, but may be related to structural, electrical, electromechanical, and autonomic remodeling.

Abnormal atrial histology compatible with a diagnosis of myocarditis was uniformly found in patients with lone atrial fibrillation. Patients with atrial fibrillation exhibited a higher concentration of cytokines, higher NF-κB activity and more severe lymphocyte infiltration than those in sinus rhythm. These observations imply local inflammatory responses in the atria in atrial fibrillation[33][34]. The concentrations of circulating FLC κ and λ in patients with lone atrial fibrillation were significantly different from the healthy group. The mechanism by which FLCs cause atrial fibrillation remains to be clarified. However, the inflammation associated with FLCs directly induces atrial fibrillation. Moreover, FLCs might cause a change in membrane fluidity, which, in turn, could alter ion channel function[34].

2.5. FLCs as Biomarkers of Diabetes

Since FLCs could be biomarkers of NF-κB, immune responses and inflammation, FLCs were measured in the patients with T2DM. Circulating levels of FLC λ were higher, and the κ/λ ratio was lower in patients with T2DM than in controls.

A statistical analysis showed that the area under the receiver operating curve (ROC-AUC) of the FLC λ and κ/λ ratio was significantly larger than glycated hemoglobin (HbA1c). The diagnostic ability for distinguishing between T2DM and controls had a sensitivity of 0.96, a specificity of 1, a positive predictive value of 1 and a negative predictive value of 0.96, with an optimal cutoff value of 1.3 for the FLC κ/λ ratio,. The odds ratio was 0.000018. The ROC-AUC, sensitivity, and specificity for HbA1c were 0.95, 0.86 and 0.94, respectively, on the cutoff value of 6.2%.

Since NF-κB activation is a critical mechanism of the inflammatory cascade in developing T2DM as discussed above, it is interesting that FLC λ and the κ/λ ratio are more specific and sensitive markers for the diagnosis for T2DM than HbA1c. Therefore, FLCs represent promising potential biomarkers that may reflect the activation of NFκB.

Recently, FLC λ was higher, and the κ/λ ratio was lower in patients with T1DM, as seen in those with T2DM (unpublished observation). The reason why the specific activation of FLC λ occurred is unknown. B lymphocytes and plasma cells, which produce FLC λ, may be specifically activated in diabetes. Another possibility is that FLC κ and λ are differently regulated because NF-κB may not exercise control of the production of FLC κ and λ in the same manner. NF-κB could be a target for new types of anti-inflammatory therapy for diabetes when FLCs are changed and could be a surrogate endpoint in the management of diabetes.

3. Targeting Inflammation for the Management of Diabetes

Several therapeutic approaches or pharmacologic agents used for diabetes are reported to have anti-inflammatory properties in addition to their major mechanisms of action. Conversely, some anti-inflammatory approaches may affect glucose metabolism and cardiovascular health. It is suggested that targeting the inflammation may differentially affect hyperglycemia and atherothrombosis. Clarifying the underlying pathogenetic mechanisms may contribute to the development of effective new therapies for the optimal management of both metabolic and atherothrombotic disease states.

3.1. Metformin

Cytokines and chemokines play important roles in inflammation, and some of them are therapeutic targets for attenuating chronic inflammatory diseases[35][36][37]. In a large-scale treatment trial of newly diagnosed diabetic patients, metformin decreased the neutrophil-to-lymphocyte ratio, a marker of systemic inflammation. Metformin also inhibited circulating cytokines and chemokines in a non-diabetic heart failure trial. These findings show that metformin has anti-inflammatory effects in both diabetic and non-diabetic patients. Metformin attenuates the production of IL-6 and TNF-α induced by lipopolysaccharide (LPS) and reduces the activation of NF-κB induced by TNF-α. NF-κB inhibition by metformin also reduces IL-1β production [39]. Metformin was shown to inhibit LPS-stimulated chemokine expression by activating AMP-activated protein kinase (AMPK), and to inhibit the phosphorylation of I-κBα and p65 in a macrophage cell line. Metformin also attenuated LPS-stimulated acute lung injury by activating AMPK; reducing inflammatory cytokine, neutrophil, and macrophage infiltration; and reducing myeloperoxidase activity [40]. Metformin therapy reduced acute phase serum amyloid A, a pro-inflammatory adipokine that is upregulated in patients with obesity and insulin resistance. The anti-inflammatory actions of metformin seem to be independent of glycemia and are most prominent in immune cells and vascular tissues[38][39][40].

3.2. Dipeptidyl Peptidase-4 Inhibitors

Dipeptidyl peptidase-4 (DPP-4) is a transmembrane glycoprotein known as CD26, expressed on T lymphocytes, macrophages and endothelial cells, and regulates the actions of chemokines and cytokines involved in T cell activation. DPP-4 inhibitors suppress the actions of NLRP3 inflammasomes, TLR4 and IL-1β in macrophages. Sitagliptin and other DPP-4 inhibitors reduce the expression or activity of TNF-α, jun amino terminal kinase (JNK)1, Toll-like receptor (TLR) 2, TLR4, β subunit of IκB kinase and the chemokine receptor CCR2.

3.3. The Glucagon-Like Peptide 1 Receptor Agonists

The glucagon-like peptide 1 (GLP-1) receptor agonists reduce circulating inflammatory biomarkers even in the absence of substantial weight loss. Markers of inflammation, are reduced including reactive oxygen species, NF-κB activity, the

expression of mRNAs of IL-1β, TNF-α, JNK1, TLR2, TLR4 and SOCS-3 in mononuclear cells, and circulating concentrations of IL-6, monocyte chemoattractant protein-1, matrix metalloproteinase-9, and serum amyloid A[42][43][44][45].

3.4. SGLT2 Inhibitors

SGLT2 inhibitors improve cardiovascular and renal outcomes in large cardiovascular outcome trials in patients with diabetes. SGLT2 inhibitors reduce adipose tissue-mediated inflammation and pro-inflammatory cytokine production[46][47][48]. An SGLT2 inhibitor, canagliflozin, was reported to decrease circulating levels of IL-6, TNF receptor 1, fibronectin 1 and matrix metalloproteinase 7, and contributes to improving molecular processes related to inflammation, extracellular matrix turnover and fibrosis. Empagliflozin may contribute to cardiovascular benefits in heart failure by repleting AMP kinase activation-mediated energy and reducing inflammation[49].

3.5. Anti-IL-1 Agents

Anakinra (recombinant human IL-1 receptor antagonist) improved glycemia, reduced CRP levels and improved β-cell secretory function. The CANTOS study demonstrated that anti–IL-1β antibody (canakinumab) treatment lowered cardiovascular events over placebo. IL-1β antagonism significantly decreased HBA1c in a subanalysis on metabolic endpoints[50][51]. A T2DM meta-analysis, following the CANTOS study, demonstrated a substantial reduction in HbA1c[52][53].

Therapeutic approaches to reduce inflammation may include weight-reducing diets and lifestyles, pharmacologic or surgical approaches to weight management, statin therapy and antidiabetic drugs. Serial measurements of FLCs in these interventions may be helpful in the evaluation of their therapeutic efficacy as anti-inflammatory interventions. The determination of FLCs seems suitable as an initial health screening in the general population. When the abnormalities of FLCs are found, secondary tests such as HbA1c would be performed and followed up for diabetes.

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