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Mini Review

New Biomarkers for the Prevention and Treatment of Diabetes

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ABSTRACT

Virus infection, inflammation and genetic factors play important roles in the pathogenesis of diabetes mellitus. The role of chronic inflammation in the pathogenesis of diabetes mellitus and associated complications is increasingly recognized. In all classes of immunoglobulin, the light chains comprise 1 of 2 subtypes, known as kappa and lambda. Immunoglobulin light chains are synthesized in excess during the generation and assembly of complete immunoglobulins, and can be found in the circulation under normal physiological conditions, whereas during inflammatory conditions, greatly enhanced concentrations are found in various body fluids. Nuclei factor kappa B (NF-kB), originally identified as a family of transcription factors that bind the enhancer of the immunoglobulin kappa light chain gene of B cells, plays critical roles in the development, survival, and activation of B cells, and its activation is a critical mechanism of the inflammatory cascade in the development of diabetes. Recently, we found that circulating immunoglobulin Free Light Chain (FLC) lambda is increased in patients with diabetes mellitus, and FLC lambda and kappa/lambda ratio have been shown to be more specific and sensitive diagnostic markers for diabetes mellitus than hemoglobin A1c. Therefore, FLCs may represent promising potential biomarkers of inflammation which may reflect activation of NF-kB. We suggest that NF-kB could represent a target for new types of anti-inflammatory prevention and treatment for diabetes when FLCs are elevated, and FLCs could be a surrogate endpoint of the preventions and treatment of diabetes mellitus.

Keywords: Diabetes; Immunology; Inflammation; Immunoglobulin; Light chains

INTRODUCTION

Diabetes mellitus is a metabolic disorder which is characterized by hyperglycemia and glucose intolerance due to insulin deficiency, impaired action of insulin action or, both. Type 1 diabetes mellitus (T1DM) is caused by autoimmune destruction of pancreatic islet beta-cells leading to loss of insulin production. Type 2 diabetes mellitus (T2DM) is more common in older people with overweight. There is evidence that virus infection, inflammation and genetic factors play important roles in the pathogenesis of T1DM and T2 DM [1-3].

LITERATURE REVIEW

Role of inflammation in the pathogenesis of diabetes mellitus

The human enteroviruses are common picornaviruses often implicated as triggers of human T1DM. Among them, coxsackieviruses B have been reported to be most commonly associated with T1DM [1,2]. Hepatitis C virus infection, and the presence of insulin resistance and the new onset of T2DM have been reported [4-6]. The molecular mechanism remains to be clarified, but oxidative stress, cytokines, inhibition of insulin signaling, and reduced expression of glucose transporters may be part of the mechanism [4]. These viral infections may induce inflammation and immune activation, and may develop diabetes. T1DM is believed to be an autoimmune disorder and it is characterized by the destruction of pancreatic β cells by the immune system, which leads to lifelong dependency on exogenous insulin. Although T cells are considered to be

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responsible for β-cell destruction in T1DM, increasing evidence suggests that B cells may play an important role in the pathogenesis of the disease [7]. T1DM and T2DM are characterized by chronic inflammation; both diseases involve pancreatic islet inflammation, while systemic low-grade inflammation is a feature of obesity and T2DM. Long-term activation of the immune system impairs insulin secretion and action, and inflammation also contributes to vascular complications of diabetes [8]. Inflammatory response may contribute to T2DM occurrence by causing insulin resistance, and induce hyperglycemia to promote long-term complications of diabetes [9]. The role of chronic inflammation in the pathogenesis of T2DM and associated complications is increasingly recognized, as evidenced by the commonly elevated levels of serum interleukin(IL)-1 beta (IL-1β), IL-6, and C-reactive protein in patients with T2DM [10]. Therapeutic interventions to counteract metabolic inflammation can improve insulin secretion, action and glucose control and may prevent long-term complications [11]. Nuclear factor kappa B (NF-kB) consists of a family of transcription factors, which regulate the inflammatory response of vascular cells, by transcription of various cytokines which causes an increased adhesion of monocytes, neutrophils, and macrophages, resulting in cell damage [3]. NF-kB is activated by TNFα and IL-1 next to hyperglycemia, the advanced glycation end-products, angiotensin-II, oxidized lipids, and insulin. Once activated, NF-kB translocate from the cytoplasm to the nucleus to activate gene transcription. NF-kB-regulated genes are adhesion molecules, IL-1, IL-6, IL-8 and other molecules which may play important roles in inflammation [3].

Immunoglobulin free light chains as new biomarkers of diabetes

In all classes of immunoglobulin, the light chains comprise 1 of 2 subtypes, known as kappa and lambda. Immunoglobulin light chains are synthesized in excess during the generation and assembly of complete immunoglobulins and can be found in the circulation under normal physiological conditions, whereas during inflammatory conditions, greatly enhanced concentrations are found in various body fluids [12]. B cells play multiple functions. Following differentiation into plasma cells, they secrete antibodies into the body fluids. Autoantibodies can contribute to the pathogenesis of autoimmune diseases in multiple ways [13]. We found that circulating immunoglobulin free light chains (FLCs) were increased in mice with heart failure due to viral myocarditis [12]. More recently, we found that circulating FLC lambda is increased and kappa/lambda ratio was lower in the sera from patients with heart failure with myocarditis than in healthy controls, and FLC lambda and kappa/lambda ratio had good diagnostic ability for identification of heart failure with myocarditis. Further, FLC kappa/lambda ratio was an independent prognostic factor for overall survival [14]. We also found that FLCs are increased in patients with atrial fibrillation which is an important risk factor of stroke suggesting that atrial fibrillation is an inflammatory disease [15]. As FLCs could be biomarkers of activation of NF-kB, inflammation, and immune responses, we recently measured FLCs in the patients with T2DM. The concentration of circulating FLC lambda was higher, and the kappa/lambda ratio was lower in patients with T2DM than in healthy volunteers [16]. The area under the receiver operating curve (ROC-AUC) of the FLC lambda and kappa/lambda ratio was larger than that of hemoglobin A1c. Thus, sensitivity, and specificity for the diagnosis of T2DM of FLC lambda and kappa/lambda ratio were larger than HbA1c [16]. As a critical mechanism of the inflammatory cascade in developing T2DM is NF-kB activation [17], it is highly interesting that the results of this study indicate FLC lambda and kappa/lambda ratio are more specific and sensitive diagnostic for T2DM than HbA1c. They therefore represent promising potential biomarkers of inflammation which may reflect activation of NF-kB. Recently, we also found that FLC lambda was higher and kappa/lambda ratio was lower in patients with T1DM as seen in those with T2DM (unpublished observation). Although why specific activation of FLC lambda expression would occur in this situation is as yet unknown, but it may suggest that the clones of B lymphocytes and plasma cells which produce FLC lambda may specifically be activated in diabetes [16]. It is also possible that FLC kappa and lambda are differently regulated because NF-kB may not exercise control of the production of FLC kappa and FLC lambda in the same manner [16]. We suggest that NF-kB could represent a target for new types of anti-inflammatory treatment for diabetes when FLCs are elevated with FLCs could be surrogate endpoint of the treatment of diabetes.

Therapeutic interventions using new biomarkers of diabetes

Agents with anti-inflammatory actions can have beneficial effects to improving insulin sensitivity. Pharmacological inhibition of proinflammatory pathways that drive insulin resistance may be promising for therapeutic intervention [18]. As discussed above, NF-kB pathway is one of the key mediators of inflammation, and this pathway is activated by genotoxic, oxidative and inflammatory stress, and regulates expression of cytokines, growth factors, thus the inhibition of NF-kB may lead to delayed onset of diabetes. One of the examples is metformin. Metformin is commonly used as an anti-diabetic medication in T2DM throughout the world. Although metformin has the pleiotropic effects, it been shown to inhibit the expression of NF-kB gene, and suppress inflammatory responses [19]. Thus, anti-diabetic effects of metformin could be explained by its anti-inflammatory effect. We suggest that NF-kB could represent a target for new types of anti-inflammatory treatment for diabetes when FLCs are elevated, and FLCs could be a surrogate endpoint of the prevention and treatment of diabetes mellitus.

CONCLUSION

Circulating FLCs are specific and sensitive diagnostic markers for diabetes mellitus. They may represent promising potential biomarkers of inflammation which may reflect activation of NF-kB. NF-kB could represent a target for new types of anti-inflammatory prevention and treatment for diabetes when FLCs are elevated, and FLCs could be a surrogate endpoint of the treatment of diabetes.

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REFERENCES

1. Sakurami T, Nabeya N, Nagaoka K, Matsumori A, Kuno S, Honda A. Antibodies to coxsackie B viruses and HLA in Japanese with juvenile-onset type 1 (insulin-dependent) diabetes mellitus. Diabetologia. 1982; 22(5):375-377.
2. Tracy S, Drescher KM, Jackson JD, Kim K, Kono K. Enteroviruses, type 1 diabetes and hygiene: A complex. Rev Med Virol. 2010; 20(2): 106–116.
3. Van den Oever IAM, Raterman HG, Nurmohamed MT, Simsek S. Endothelial dysfunction, inflammation and apoptosis in diabetes mellitus. Mediators Inflamm. 2010;792393:15.
4. Haykal M, Matsumori A, Saleh A, Fayez M, Negm H, Shalaby M, et.al. Diagnosis and treatment of HCV heart diseases. Expert Rev Cardiovasc Ther. 2021.
5. Shintani Y, Fujie H, Miyoshi H, Tsutsumi T, Tsukamoto K, Kimura S, et.al. Hepatitis C virus infection and diabetes: direct involvement of the virus in the development of insulin resistance. Gastroenterology. 2004;126(3):840-8.
6. Vanni E, Abate ML, Gentilcore E, Hickman I, Gambino R, Cassader M, et.al. Sites and mechanisms of insulin resistance in nonobese, non-diabetic patients with chronic hepatitis C. Hepatology. 2009;50(3): 697-706.
7. Smith MJ, SimmonsKM, Cambier JC. B cells in type 1 diabetes mellitus and diabetic. Kidney disease. Nat Rev Nephrol. 2017;13:712–720.
8. Donath MY, Dibarello CA, Mandrup-Poulsen T. Targetting innate immune mediators in type 1 and type 2 diabetes. Nat Rev Immunol. 2019;19:734-746
9. Lontchi-Yimagou E, Sobngwi E, Matsha TE, Kengne AP. Diabetes mellitus and inflammation. Interdiscip Review Curr Diab Rep. 2013;13:435-444.
10. Navarro-Gonzalez JF, Mora-Fernandez C, Muros de Fuentes M, Garcia-Perez J. Inflammatory molecules and pathways in the pathogenesis of diabetic nephropathy. Nat Rev Nephrol. 2011;7:327–340.
11. Donath MY, Daniel T, Meier DT, Böni-Schnetzler M. Inflammation in the pathophysiology and therapy of cardiometabolic disease. Endocr Rev. 2019;40:1080-1091.
12. Matsumori A, Shimada M, Jie X, Higuchi H, Kormelink G, Regegeld FA. Effects of free immunoglobulin light chains on viral myocarditis. Circ Res. 2010;106:1533-1540.
13. Hofmann K, Clauder A-K, Manz RA. Targeting B cells and plasma cells in autoimmune diseases. Front Immunol. 2018;9:835.
14. Matsumori A, Shimada T, Nakatani E, Shimada M, Tracy S, Chapman NM, et.al. Immunoglobulin free light chains as an inflammatory biomarker of heart failure with myocarditis. Clin Immunol. 2020;217:108555.
15. Matsumori A, Shimada T, Shimada M, Otani H, Drayson MT, Mason JW. Immunoglobulin free light chains as inflammatory biomarkers of atrial fibrillation. Circ Arrhythm Electrophysiol. 2020;13:e009017.
16. Matsumori A, Shimada T, Shimada M, Drayson MT. Immunoglobulin free light chains: An inflammatory biomarker of diabetes. Inflamm Res. 2020;69:715-718.
17. Zhang Y-Y, Tan R-Z Zhang X-Q, Yu Y, Yu C. Calycosin ameliorates diabetes induced renal inflammation via the NF-κB pathway In vitro and in vivo. Med Sci Monit. 2019;25:1671-1678.
18. Olefsky JM, Glass CK. Macrophages, inflammation and insulin resistance. Annu Rev Physiol. 2010;72:219–246.
19. Sultuybek GK, Soydas T, Yenmis G. NF-kB as the mediator of metformin's effect on aging and ageing-related diseases. Clin Exp Pharmacol Physiol. 2019;46:413-422.