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Inflammation and Diabetes

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Abstract

An effort has been made in this review to outline the origin of diabetes as a serious disease. A large number of studies are going on in order to understand the cause of this disease, both environmental as well as genetic factors have been found to be involved. We have tried to throw some light on inflammation in diabetes with special emphasis on interleukins and adipocytokines. Recently the involvements of cytokines and adipocytokines have been extensively studied and have been found to play an extremely important role in the manifestation of diabetes and its associated complications.

Keywords: Inflammatory cytokines; Type 2 diabetes; Interleukins; Adipocytokines; Tumor necrosis factor- α

Introduction

It has been postulated that type 2 diabetes mellitus (T2DM) is a manifestation of the inflammatory host response. Increased inflammatory activity plays a critical role in the development of atherogenesis and rupture of atherosclerotic plaques. Inflammation is an initial step of many diseases. Cytokines are a group of small soluble or cell-membrane bound proteins or low molecular glycoprotein messenger molecules with high potential secreted by WBCs and various other cells in the body in response to a number of stimuli in the regulation of inflammatory responses.

The balance of proinlammatory and anti-inflammatory cytokines is essential for normal cellular function. Some polymorphic cytokine genes have been shown to be associated with variation in cytokine production in T2DM because it is caused due to dysfunction of pancreatic β-cells. Due to destruction and inflammation in β-cells, level of cytokines is slightly disturbed. It has already reported that cytokines, chemokines and interleukins are involved in T2DM to cause inflammatory and immune responses mediating the pathogenesis of T2DM. Mediators of inflammation such as Tumor Necrosis Factor–α (TNF- α), Interleukin (IL) -1β, IL-1Ra, IL-6, IL-18, IL-10 and certain chemokines have been proposed to be involved in the events causing Diabetes [1].

Interleukin-6 which is known to be the main stimulator of the production of most acute phase proteins was shown to increase the risk of diabetes. Other cytokines such as IL-1β or TNF-α are also central mediators of inflammatory reactions. IL-18 is a potent pro-inflammatory cytokine which plays a role in plaque destabilization and prediction of cardiovascular disease (CVD) death in patients with cardio artery diseases (CAD).

Tumor Necrosis Factor Alpha (TNF-α), IL-1β and IL-1Ra

Pro-inflammatory cytokines Tumor Necrosis Factor-α (TNF-α) and IL-1 could significantly contribute to the pathogenesis of T2DM. Tumor necrosis factor alpha (TNF-α) is a proinflammatory cytokine that impairs insulin action and alters lipid metabolism. It was suggested that the -238G>A and -308G>A polymorphisms of TNF-α alter circulating free fatty acids and insulin resistance in obese subjects with T2DM [2]. Vascular endothelial growth factor (VEGF) is a potent multifunctional cytokine which plays a key role in the pathogenesis of diabetic microvascular complications [3]. IL-1β and IL-1Ra shows similar association in chronic inflammatory diseases as well as in T2DM. TNF-α decreases tyrosine kinase activity of the insulin resistant rodents and humans, suggesting that it is a possible mediator of insulin resistance and diabetes [4-5].

IL-1β and IL-1Ra genotypes of the IL-1 cluster genes are associated with diabetic nephropathy in Korean patients with T2DM [6]. The -308A allele of the promoter polymorphism (G-308A) of the TNF-α gene is a predictor for the conversion from Glucose tolerance to T2DM. Furthermore, this polymorphism seems to have a gene-gene interaction with the C-174C genotype of the IL-6 gene [7]. Studies have provided increasing evidence that hepatocytes growth factor (HGF) has a pathophysiological role in the development of the diabetic complications. Serum HGF concentration may be a new marker of atherosclerotic complications in T2DM patients [8].

Macrophages and T-lymphocytes are the first cells to appear in pancreatic islets in the development of autoimmune diabetes. It has been suggested that cytokines released by monocytes/macrophages including IL-1β and TNF-α could have initial role in islet β-cell damage. T2DM and atherosclerotic cardiovascular disease share many antecedent factors that frequently coexist, which has given rise to the concept of a common basis [9-10]. The cluster of risk factors, such as uric acid and dyslipidemia are strongly related to fasting insulin concentration of inflammatory markers in people with and without T2DM. Inflammatory processes play a part in the cause of atherosclerotic CVD [11]. The members of the IL-1 cytokine superfamily IL-1α and IL-1β are strong inducers of inflammation. IL-1

receptor antagonist (IL-1Ra) acts in an antagonistic manner and serves as a natural compensatory mechanism for the IL-1 induced disease process [12]. In healthy individuals, IL-1Ra is detectable in plasma, in contrast to usually undetectable levels of IL-1. White adipose tissue is an important source of IL-1Ra. IL-1Ra levels are increased in human obesity and may contribute to the development of insulin resistance [13].

Interleukin-6

Interleukin-6 is a pro-inflammatory cytokine secreted by immune cells, adipose tissue, muscles, and is able to accelerate or inhibit the inflammatory processes [14-15]. It is also involved in immunoregulatory actions and affects glucose homeostasis and metabolism directly and indirectly by action on skeletal muscle cells, adipocytes, hepatocytes, β-Cells of pancreas and neuroendocrine cells. High circulating IL-6 levels have been associated with insulin resistance and greater risk of T2DM [16]. It has been reported that the common C-174G polymorphism in the promoter of the human IL-6 gene regulates its transcription in vitro with the G allele, showing increased transcriptional activity both under basal condition and in response to inflammatory stimuli such as lipopolysaccharides or IL-1 [17].

There is a significant correlation between adipose IL6 mRNA expression and insulin resistance [18]. Several prospective studies have associated increased plasma IL-6 levels with a higher risk of T2DM and suggest that IL6 is a candidate gene for T2DM [19-20].

Interleukin-18

Interleukin-18 is a unique member of the Interleukin-1 family. Although closely related to IL-1β in structure and in the requirement of caspase-1 to cleave its precursor form into an active cytokine, the IL-18 precursor is present in monocytes and macrophages of healthy humans and mice, whereas the IL-1β precursor is absent in these same cells [21]. Insulin-producing islet β-cells secrete IL-18 and supernatants from stimulated islets induce IFN-γ in T cells in IL-18 dependent manner [22]. In humans, the gene for IL-18 maps to chromosome 9, where a diabetes susceptibility locus, Idd2, resides [23]. From previous studies, IL-18 levels have been associated with adiposity and insulin resistance in obese premenopausal women. IL-18 concentration is increased by acute hyperglycemia in humans [24]. In T2DM the level of IL-18 is elevated in case of diabetic children [25].

Interleukin-10

Interleukin-10 is also involved in obesity and has a role in the regulation of immune system. Low levels of IL-10 production are associated with hyperglycemia and T2DM [26]. It has been reported that the presence of an A at position -1082 is correlated with low IL-10 production after stimulation of T-cells in vitro, while G at the same position has been associated with high IL-10 synthesis [27]. It has been demonstrated that the A/G mutation at position -1082 in the promoter region of the IL-10 gene is probably associated with the incidence of developing diabetes mellitus [28]. IL-10 stimulates antibody production by B-lymphocytes and promotes their proliferation and differentiation [29]. The predominance of the high IL-10 genotype in T2DM is probably protective against the development of inflammation, encouraging humoral immunity responses, delaying the initiation of cytotoxic inflammatory reactions that mediate β-cell destruction in pancreatic islets and driving their manifestations in older age.

Adiponectin

Adiponectin is a serum protein produced and secreted exclusively by adipose tissues. Adiponectin also known as adipocyte complement-related protein of 30 KDa (Acrp30), is a hormone of adipocyte origin that is involved in the homeostatic control of circulating glucose and lipid level [30-31]. Adiponectin is a 147 amino acid protein that is similar in sequence and structure to the C1q complement factor. Unlike insulin and leptin, adiponectin levels in plasma remain constant throughout the day and are not acutely affected by food intake. Resistin is another hormone secreted by adipocytes that acts on skeletal muscle myocytes, hepatocytes and adipocytes themselves, where it is suggested to reduce insulin sensitivity leading to T2DM (Figure 1). Leptin is the protein product of ob gene in mice and is involved in appetite control. Visfatin is considered a new member of the adipokine family. It is highly expressed in visceral fat and whose level correlates with obesity. The action and identity of diabetes susceptibility genes represent an important area for consideration of disease mechanism.

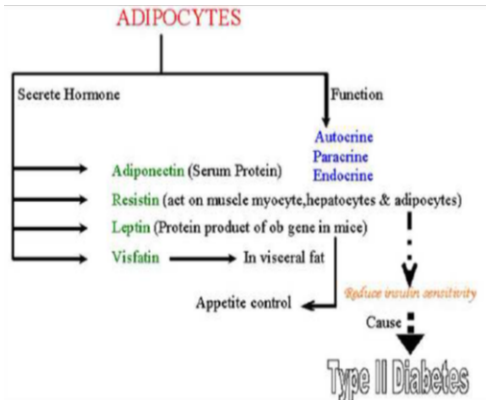

Figure 1: Adipocytokines classification and functions leading to type 2 diabetes.

Conclusion

In this review we have discussed the type 2 diabetes and its relation with inflammation. Different environmental stresses, population differences in activity and different diets clearly cause some genes to manifest as a disease phenotype. The spectacular rise in rates of diabetes among different populations as they adapt modern diet and life style dramatically demonstrates the key role of environment, insulin regulation and metabolic pathway. Many susceptibility genes inhibit different pathways in the complex physiologic network that cause T2DM. Our increased understanding of such phenomenon will open new doors to understanding how common variants can alter disease susceptibility and will be essential in understanding the physiological importance of the genetic associations related to inflammation and T2DM.

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References

1. Banerjee M, Saxena M (2014) Genetic polymorphisms of cytokine genes in type 2 diabetes mellitus. World J Diabetes 5: 493-504.
2. Fontaine-Bisson B, Wolever TM, Chiasson JL, Rabasa-Lhoret R, Maheux P, et al. (2007) Tumor necrosis factor alpha -238G>A genotype alters postprandial plasma levels of free fatty acids in obese individuals with type 2 diabetes mellitus. Metabolism 56: 649-655.
3. Buraczynska M, Ksiazek P, Baranowicz-Gaszczyk I, Jozwiak L (2007) Association of the VEGF gene polymorphism with diabetic retinopathy in type 2 diabetes patients. Nephrol Dial Transplant 22: 827-832.
4. Hotamisligil GS, Murray DL, Choy LN, Spiegelman BM (1994) Tumor necrosis factor alpha inhibits signaling from the insulin receptor. Proc Natl Acad Sci U S A 91: 4854-4858.
5. Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, et al. (2000) Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 20: 1595-1599.
6. Lee SH, Ihm CG, Sohn SD, Lee TW, Kim MJ, et al. (2004) Polymorphisms in interleukin-1 beta and Interleukin-1 receptor antagonist genes are associated with kidney failure in Korean patients with type 2 diabetes mellitus. Am J Nephrol 24: 410-414.
7. Kubaszek A, Pihlajamäki J, Komarovski V, Lindi V, Lindström J, et al. (2003) Promoter polymorphisms of the TNF-alpha (G-308A) and IL-6 (C-174G) genes predict the conversion from impaired glucose tolerance to type 2 diabetes: the Finnish Diabetes Prevention Study. Diabetes 52: 1872-1876.
8. Satani K, Konya H, Hamaguchi T, Umehara A, Katsuno T, et al. (2006) Clinical significance of circulating hepatocyte growth factor, a new risk marker of carotid atherosclerosis in patients with Type 2 diabetes. Diabet Med 23: 617-622.
9. Jarrett RJ, Keen H, McCartney P (1984) The Whitehall Study: ten year follow-up report on men with impaired glucose tolerance with reference to worsening to diabetes and predictors of death. Diabet Med 1: 279-283.
10. Stern MP, Gonzalez C, Mitchell BD, Villalpando E, Haffner SM, et al. (1992) Genetic and environmental determinants of type II diabetes in Mexico City and San Antonio. Diabetes 41: 484-492.
11. Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V (2000) Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? Atherosclerosis 148: 209-214.
12. Banerjee M, Saxena M (2012) Interleukin-1 (IL-1) family of cytokines: role in type 2 diabetes. Clin Chim Acta 413: 1163-1170.
13. Schmidt MI, Duncan BB, Sharrett AR, Lindberg G, Savage PJ, et al. (1999) Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities study): a cohort study. Lancet 353: 1649-1652.
14. Fried SK, Ricci MR, Russell CD, Laferrère B (2000) Regulation of leptin production in humans. J Nutr 130: 3127S-3131S.
15. Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, et al. (1997) Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. J Clin Endocrinol Metab 82: 4196-4200.
16. Qi L, van Dam RM, Meigs JB, Manson JE, Hunter D, et al. (2006) Genetic variation in IL6 gene and type 2 diabetes: tagging-SNP haplotype analysis in large-scale case-control study and meta-analysis. Hum Mol Genet 15: 1914-1920.
17. Fishman D, Faulds G, Jeffery R, Mohamed-Ali V, Yudkin JS, et al. (1998) The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. J Clin Invest 102: 1369-1376.
18. Cardellini M, Perego L, D'Adamo M, Marini MA, Procopio C, et al. (2005) C-174G polymorphism in the promoter of the interleukin-6 gene is associated with insulin resistance. Diabetes Care 28: 2007-2012.
19. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM (2001) C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 286: 327-334.
20. Spranger J, Kroke A, Möhlig M, Bergmann MM, Ristow M, et al. (2003) Adiponectin and protection against type 2 diabetes mellitus. Lancet 361: 226-228.
21. Lewis EC, Dinarello CA (2006) Responses of IL-18- and IL-18 receptor-deficient pancreatic islets with convergence of positive and negative signals for the IL-18 receptor. Proc Natl Acad Sci U S A 103: 16852-16857.
22. Frigerio S, Holländer GA, Zumsteg U (2002) Functional IL-18 Is produced by primary pancreatic mouse islets and NIT-1 beta cells and participates in the progression towards destructive insulitis. Horm Res 57: 94-104.
23. Sarvetnick N (1997) IFN-gamma, IGIF, and IDDM. J Clin Invest 99: 371-372.
24. Hung J, McQuillan BM, Chapman CM, Thompson PL, Beilby JP (2005) Elevated interleukin-18 levels are associated with the metabolic syndrome independent of obesity and insulin resistance. Arterioscler Thromb Vasc Biol 25: 1268-1273.
25. Blazhev A, Nicolff G, Petrova Ch, Jordanova-Laleva P (2006) Serum levels of interleukin 12 and interleukin 18 in diabetic children. Diabetologia Croatica 35: 1-6.
26. Kristiansen OP, Mandrup-Poulsen T (2005) Interleukin-6 and diabetes: the good, the bad, or the indifferent? Diabetes 54 Suppl 2: S114-124.
27. Turner DM, Williams DM, Sankaran D, Lazarus M, Sinnott PJ, et al. (1997) An investigation of polymorphism in the interleukin-10 gene promoter. Eur J Immunogenet 24: 1-8.
28. Tsiavou A, Hatziagelaki E, Chaidaroglou A, Manginas A, Koniavitou K, et al. (2004) TNF-alpha, TGF-beta1, IL-10, IL-6, gene polymorphisms in latent autoimmune diabetes of adults (LADA) and type 2 diabetes mellitus. J Clin Immunol 24: 591-599.
29. Sankaran D, Asderakis A, Ashraf S, Roberts IS, Short CD, et al. (1999) Cytokine gene polymorphisms predict acute graft rejection following renal transplantation. Kidney Int 56: 281-288.
30. Saxena M, Srivastava N, Banerjee M (2012) Genetic association of adiponectin gene polymorphisms (+45T/G and +10211T/G) with type 2 diabetes in North Indians. Diabetes Metab Syndr 6: 65-69.
31. Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF (1995) A novel serum protein similar to C1q, produced exclusively in adipocytes. J Biol Chem 270: 26746-26749.