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An Overview on Inflammatory Biomarkers for Diabetes Mellitus

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Abstract

Diabetes mellitus is a very complex disease affecting almost every tissue and organ system, with heterogeneous etiology characterized by insulin resistance. Obesity, sedentary lifestyle and unhealthy diet are well-known risk factors for development of type 2 diabetes mellitus (T2DM). Understanding pathological mechanisms is imperative to prevent and treat the disease. Therefore, identification of specific biomarkers for T2DM is of great interest. Biomarkers are the biological molecules which play a vital role in conducting clinical trials, for screening and risk assessment before diagnosis and are helpful for monitoring recurrent diseases. Developing and characterizing an effective biomarker is arduous. To know the root cause and the effect in the pathogenesis of disease are some of the major challenges in the field of biomarkers. Several approaches including proteomics, genomics, metabolomics and transcriptomics are being applied for early detection of T2DM and further devising new therapies to treat it. The emphasis of the present review is to identify non-genetic and genetic biomarkers through the application of novel methodologies that would predict hyperglycemia and incident T2DM.

Keywords: Diabetes Mellitus; Biomarkers; Hyperglycemia; T2DM; Obesity; Insulin.

Introduction

Diabetes mellitus

Diabetes Mellitus (DM) is a complex multi factorial metabolic disorder with disordered metabolism and hyperglycemia prevailing world wide. Some risk factors contributing to DM are smoking, alcohol, obesity, diet, overweight, vascular or cardiovascular disease, level of physical activity, hormones and some medical treatments. Exercise and diet can improve the health habits further reducing the risk of developing diabetes. Type 1 and type 2 are the two most important types of DM (figure 1). Type 1 DM commonly referred as juvenile diabetes and known as insulin dependent diabetes mellitus (IDDM) in which pancreas is unable to produce insulin due to autoimmune β-cell destruction. Type 2 DM, an adult-onset diabetes is known as non insulin dependent diabetes mellitus (NIDDM) in which body tissues and cells are unable to respond properly to the action of insulin [1]. Genetic and metabolic abnormalities are some other abnormalities produced in response to insulin action and secretion. Type 2 DM usually occurs in adulthood and develops more with the age and sometimes it is also observed in children and some adolescents having obesity [2]. Over the past two decades, worldwide prevalence of diabetes mellitus has risen and is considered as one of the most widely occurring human ailments. According to survey led by some health agencies like World Health Organization (WHO) and International Diabetes Federation (IDF), diabetes becomes an epidemic which is not controlled and is sixth leading cause of human mortality and morbidity globally.

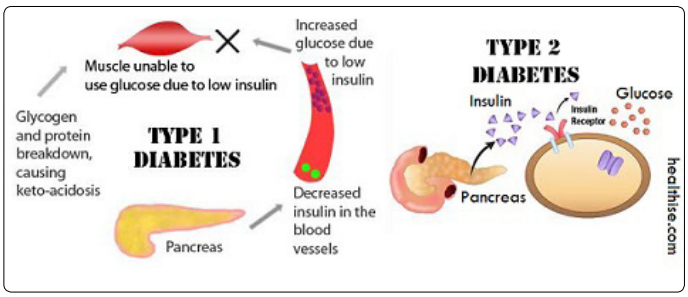

Figure 1. Types of Diabetes Mellitus.

Biomarkers

Biomarker is a substance which is used as an indicator for pathological state of disease and a characteristic that is estimated and evaluated for normal, pathological, and pharmacologic responses to a therapeutic intervention. In 21st century, they have gained tremendous scientific momentum. They are the biological molecule found in blood, other bodily fluids, or tissue which may have any clinical value and can be the component of interest in the practice of medicine and represents a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition. Moreover, it provides high-throughput platforms, adequate analytic performance, carries therapeutic implications and assesses progression thus improving the treatment strategy. Biomarkers may reflect the presence and severity of hyperglycemia (i.e. diabetes itself), or the presence and severity of the vascular complications of diabetes. Biomarkers can play an imperative role in laboratory for drug discovery, diagnosing, classification, and grading the severity of disease in both laboratory and clinical settings. They have a potential for understanding the relationship between disease and health. Some of the diseases are as of protein biomarkers are, for example, cancer, diabetes, and cardiovascular and neurological diseases. The protein biomarkers are very useful for diagnosis and prognosis of the asymptomatic phase before the development of acute and chronic diseases such as diabetes, various forms of cancer, and other syndromes.

Inflammatory biomarkers for diabetes

Biomarkers for monitoring diabetes and associated micro- and macro vascular complications can be broadly classified as follows: genomic (single-nucleotide polymorphisms), transcriptomic (mRNA), proteomic (proteins and glycoproteins), metabolites (lipids, sugars, amino acids), markers of subclinical disease (arterial function, aortic plaque burden) and metabolic end-products (urinary proteins). Further research is needed to identify novel biomarkers for progression monitoring and for incremental improvement in T2DM diagnosis. In each stage of T2DM management, biomarkers play an imperative role. Plasma glucose (A_{1C}) is one of the most common biochemical parameters or biomarkers based on which T2DM diagnosis is done (figure 2). Type 1 diabetes (T1D) is caused by T-cell abnormalities further leading to the destruction of pancreatic islets while in type 2 diabetes, activation of monocytes and inflammation are responsible for insulin resistance resulting in the loss of insulin secretory function by islet cells. Various studies have suggested the co-relation between inflammation and diabetes demonstrating that inflammatory markers can be used to refine T2DM risk prediction. Cytokines are those groups of proteins which act as immune mediators and regulators and are expressed by several cell types. Insulin resistance has been associated with decreased production of anti-inflammatory mediators (IL-4 and IL-10) and abnormal secretion of pro inflammatory cytokines (tumor necrosis factor-α (TNF-α) and Interleukin-6 (IL-6)) (figure 3). IL-1 could promote beta-cell destruction and alter insulin sensitivity. Interleukin-6 (IL-6) is a pleiotropic pro inflammatory cytokine, induces the development of insulin resistance by inducing the expression of SOCS-3 leading to the impairment of phosphorylation of insulin receptor and insulin receptor substrate-1. CRP (C-reactive protein) is sensitive and systemic biomarker for inflammation and is synthesized by liver. Recent reports have suggested that IL-6 and CRP are associated with T2DM.

Figure 2. HbA1c as biomarker for diabetes mellitus.

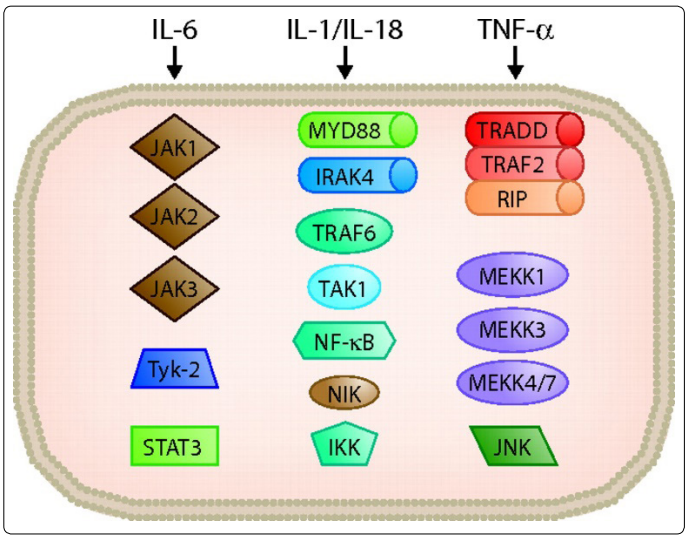

Figure 3. Cytokines as biomarker for diabetes mellitus [3].

Literature Review

Leinonen et al. [4] reported urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG) as a sensitive biomarker in NIDDM patients. They investigated oxidative DNA damage and oxidative stress by urinary 8-OHdG assessments in the urine samples. They further determined increased level of 8-OHdG in NIDDM patients when compared to non-diabetic control

subjects by screening 24 hr urinary excretion [4]. Tso et al. [5] investigated serum adipocyte fatty acid-binding protein (A-FABP) levels to predict the development of T2DM. They reported that serum A-FABP levels were higher in glucose intolerant patients. Lui et al. 2013 systemically reviewed the association of IL-6 and CRP in diabetes mellitus by conducting meta-analysis. They explored numerous electronic databases and a systematic literature search was performed. They further demonstrated that chronic inflammation is a predictor of type 2 diabetes development. Ghosh P et al. [6] established an enzyme linked immune sorbent assay (ELISA) to measure serum/plasma glycated human CD59 and evaluated its potential as a diabetes biomarker. They conducted a clinical trial and found that GCD59 was significantly higher in individuals with than in individual without diabetes [6]. Takada T et al. [7] reported increased level of an up regulated protein known as monomeric α_2-macroglobulin in diabetic patients. They purified the protein through highly efficient strategy from diabetic and control (non-diabetic) serum samples. SDS-PAGE was used to fractionate the extracted sera and further the isolated protein bands were analyzed by mass spectrometry. They concluded that monomeric α_2-macroglobulin can be used as a potential biomarker in many diabetic subjects [7]. Molnos et al. [8] showed pair wise metabolite (valine to phosphatidylcholine acyl-alkyl C32:2) ratio to be associated with an increased risk of type 2 diabetes. They conducted a clinical trial on 130 healthy members and examined the association of metabolite levels on those patients. They observed dynamic changes in metabolite levels after arginine, glucose and glucagon-like peptide-1 (GLP-1) stimulation [8].

Conclusion

Diabetes is a global endemic with rapidly increasing prevalence in both developing and developed countries.T2DM is a chronic, progressive disease that traditionally is characterized by insulin resistance. Currently, the diagnosis and progression of diabetes rely predominately on glycemic indices. Biomarkers play an integral part in conducting clinical trials and treating patients. However, much research, prospectively planned and with clear treatment implications, is needed before wear rive at truly "personalized" diabetes care.

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