Biomarkers in Type 2 Diabetes

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Abstract
Biomarkers are measurable substances in an organism indicative of disease such as Type 2 diabetes. Biomarkers are utilized to obtain necessary information about a certain disease such as Type 2 diabetes. Type 2 diabetes is estimated to be the 7th leading cause of mortality by 2030, according to the World Health Organization. Comprehending the number of biomarkers that affect Type 2 diabetes will be the focus of this review. Obtaining different classes of biomarkers related to Type 2 diabetes could enable researchers to identify and characterize levels of Type 2 diabetes inception. Thus, they represent a logical way to improve diagnosis, track progression and activity, guide molecularly targeted therapy and monitor therapeutic response to Type 2 diabetes. Furthermore, great effort has been put into the identification of novel biomarkers. A comprehensive overview associated with Type 2 diabetes will be presented.

Introduction

Type 2 diabetes is a critical problem worldwide affecting about 8% of the population [1]. Type 2 diabetes is the inability of the pancreatic beta-cells to secrete insulin which captures glucose from the blood to supply the organs with glucose that transform eventually to ATP or energy via glycolysis thereby utilized in the body.

Biomarkers nowadays are crucial for determining the health status of an individual. Whether it be HbA1c for blood glucose determination over a period of three months or simply adiponectin levels that have anti-inflammatory properties decreasing the risk of type 2 diabetes-biomarkers can lead the way to comprehend and overcome not only metabolic diseases but other types of diseases as well.

Methodology

The methods used in the studies provided utilized PubMed and Google Scholar as search engines for articles that are related to type 2 diabetes, biomarkers, gene-nutrient interaction (genomics), transcriptomics, proteomics, metabolomics, markers of subclinical disease and metabolic end products.

Results

Studies using biomarkers have demonstrated on how type 2 diabetes can be regulated. It also manifested substantial differences in those derived by comparison with other methods of dietary or non-dietary assessment. Nutrient biomarkers have been minimal, as uncommon yet essential biomarkers and their relation to type 2 diabetes have been highlighted.

Discussion

There are numerous types of biomarkers for type 2 diabetes. Ranging all the way from metabolomic to genetic, biomarkers can be interpreted in a multiple fashion, depending on the studies conducted and individuals involved. In this segment, certain studies will be provided to support the findings available.

Firstly, type 2 diabetes can cause cardiac arrhythmias. Ventricular arrhythmia, to be specific, is known to be associated with increased risk of cardiovascular death. Study by Caveney et al. showed that ventricular ectopy as a biomarker for ventricular arrhythmia and that suppression of this would lead to reduced mortality [2].

Pulse wave analysis can also assess endothelial function. This endothelial function can be a critical early target for preventing atherosclerosis and cardiovascular disease. As type 2 diabetes is indeed related to or affected by cardiovascular issues, managing endothelial function then becomes an important role in preventing type 2 diabetes [3]. Pulse wave analysis is a biomarker for vascular dysfunction. It becomes abnormal in the development of hypertension, diabetes, kidney disease and connective tissue disorders. Several intervention studies in healthy individuals and in patients with type 2 diabetes or Metabolic syndrome has reported a significant change in pulse wave velocity as a biomarker of arterial stiffness or vascular dysfunction. Supplementation of omega 3-fatty acids and serum lycopene concentrations have been shown to decrease and inversely associated with pulse wave velocity, respectively [4].

Skin autofluorescence is also a biomarker in type 2 diabetes. It is a marker of long term accumulation of AGEs (advanced glycation end products) which are the accumulation of glucose in proteins or lipids. Concerning accumulation of AGEs in skin tissues, Basu et al. hypothesized that individual variations in oxidative stress may modulate susceptibility to the complications of diabetes. This explains differing susceptibilities among individuals with similar glycemic exposure over many years to the development of complications. It also suggests that a given degree of chronic hyperglycemia

may have different consequences depending on oxidative stress and or antioxidant defences [4]. In a study by Meerwaldt et al., autofluorescence values increased with age, micro albuminuria, dialysis treatment and diabetes duration. Autofluorescence was strongly linked to cardiovascular heart disease (CHD). Multivariate analysis showed that autofluorescence was more strongly associated with CHD and mortality compared with A1C, triglycerides and low density lipoprotein [5].

Another biomarker for type 2 diabetes is serum gamma-glutamyl transferase (GGT). GGT is an enzyme that catalyzes transfer of gamma-glutamyl functional groups for molecules such as glutathione to an acceptor that may be an amino acid, peptide or water. GGT can also exert pro-oxidant role with regulatory effects at various levels in cellular signal transduction and cellular pathophysiology. Positive associations have been reported between GGT and incidence of type 2 diabetes [6]. Study by Meisinger et al. also showed the increased risk of type 2 diabetes with increasing levels of serum GGT [7]. Photometric method was used in this study to determine serum GGT content.

Furthermore, Ferritin is also a biomarker in type 2 diabetes. Based on results studied by Momeni et al., serum ferritin decreased after decline of patient's blood sugar, so it can be used as one of the diabetes control indices for diabetic patients. Their study initially was conducted to evaluate the relationship between two acute phase reactants—C-reactive protein and ferritin. The study also showed that in diabetic patients, improvement of diabetic control indices, the amount of serum CRP was not changed, however, serum ferritin level has a relationship with hyperglycemia and its level decreased with lowering of serum blood glucose [1].

Pancreatic polypeptide, another biomarker of type 2 diabetes, is a possible marker of beta cell failure in diabetes. Pancreatic polypeptide, a 36 amino acid peptide hormone, is synthesized in pancreatic islets of Langerhans and acts as a regulator of pancreatic and gastrointestinal functions. It was found that increased levels of secreted pancreatic hormone are found in beta-cell failure. Therefore, finding increased pancreatic polypeptide would indicate beta-cell failure thereby showing type 2 diabetes [8].

Next, Creatine-kinase-MB (CK-MB), a unique enzyme, serves to be an additional biomarker in type 2 diabetes. It is an isoenzyme that measures blood levels of CK-MB of enzyme phosphocreatinine kinase. It is said to be related to heart disease. Study by Hong et al. found less diabetes in CK-MB elevated groups [6].

In addition, atrial natriuretic peptide (ANP) has also been reported to be a biomarker of type 2 diabetes. Its mechanism of action is unknown; however experimental data suggest that low levels of ANP promote development of insulin resistance. B type natriuretic peptide is associated with myocardial infarction, and increased death, as stated in one study by de Lemos et al [9].

Fructosamine is also a biomarker of Type 2 diabetes. It is a compound that results from glycation reactions between sugar and a primary amine followed by isomerization. It has been known to replace HbA1c when it is not available. Fructosamine is a ketamine rearrangement formed by interaction of glucose with e-amino group on lysine residues of albumin. Fructosamine tests help a person with diabetes monitor his or her blood glucose level. In a study by Averna

et al., 142 diabetic patients were investigated. Fructosamine Levels were found to be higher in patients on insulin treatment than on hypoglycemic agents. Mean values of Fructosamine were higher in poorly controlled patients. Fructosamine however correlated better with glycemia in patients with recent variations in metabolic state than HbA1c [10].

1, 5-anhydroglucitol (1, 5-AG) and glycated albumin are also biomarkers implicated in type 2 diabetes. 1, 5-AG is a naturally occurring monosaccharide. Blood concentrations of 1, 5-AG decrease during hyperglycemia above 180 mg/dl and return to normal levels approximately 2 weeks in absence of hyperglycemia. Glycated Albumin (GA) on the other hand, is a glucose bonded to albumin. Albumin is a high molecular weight protein with 66.7 kDa, composed of a single polypeptide chain which contains 585 amino acids, 17 disulfide bridges and 3 homologous domains that are connected in a helical structure. Albumin structure makes it easier to perform its physiological functions, such as maintain pH and blood osmotic pressure. Also, albumin acts as a powerful antioxidant, and as the main transporter of metabolic products, ions, nutrients, drugs, hormones and fatty acids. GA is also used as an alternative test to HbA1c. GA is more reliable in evaluating glycemic variability. Compared to Fructosamine, it is more advantageous since it not influenced by other serum proteins. Glycation from GA is the spontaneous reaction in which a reducing sugar is added to a free amino group, typically lysine or arginine present within proteins, also called Maillard reaction. It involves the formation of an unstable and reversible product known as Schiff base, formed by bonding of a carbonyl group of an acyclic carbohydrate with the N-terminal amino acid [11].

Amylin is similar to insulin, another hormone produced by the pancreas. This hormone regulates the rate which the food suggests. It is also known for blocking glucagon secretion. Glucagon is a pancreatic hormone that raises blood glucose level by stimulating liver to release stored glucose. This then proves how glucagon can be blocked by amylin, thereby preventing spikes of blood glucose after a meal. It is also known to slow digestion and enhance satiety thereafter preventing one from overeating or gaining weight which is also a hallmark that implicates type 2 diabetes [12]. Contradictingly, in vitro and in vivo studies however have been shown that amylin has an effect on insulin secretion as Well as insulin sensitivity. Current data shows a damaging role of intermediate sized toxic amyloid particles to the beta cell resulting in a beta cell defect contributing to the relative deficiency or loss of insulin secretion. Within the islet itself, there is an intense redox stress which may be associated with unfolding of amylin's native secondary structure compounding its amyloid genic properties [13].

In addition, adiponectin is also a biomarker of type 2 diabetes. Hypoadiponectinemia can cause reduction of fatty acid oxidation, decreased glucose uptake in skeletal cells, and increased gluconeogenesis in hepatic cells. On the other hand, decrease of fatty oxidation increases free fatty acid which increases insulin resistance and then decreases glucose uptake, which ultimately causes increased plasma glucose and type 2 diabetes. Study by Yamamoto et al. found that adiponectin levels have anti-inflammatory and insulin-sensitizing properties. Prospective studies consistently shown lower risk of type 2 diabetes among Those with higher circulating adiponectin levels [14].

Increased C-reactive protein (CRP) is a sign of uncontrolled diabetes. Study by Rodriguez- Moran et al. showed that hyperglycemia is a related factor to the increase of serum CRP in noncontrolled type 2 diabetic subjects [15].

Conclusion

Indirect nutrient and biomarker interaction have been exposed in this study. Since biomarkers have great implications in metabolic diseases such as type 2 diabetes, knowing and highlighting each one of them has proven to be critical. Biomolecules discussed in this report underscores the validity of biomarkers and thereby show a promising phenomenon for the future of biomarkers.

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