The Link between Diabetes and Cardiovascular Disease: The Epidemiological Perspective

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The association between hyperglycemia/diabetes and cardiovascular disease has been known since the first half of the 20th century, and its causes and mechanisms have been examined ever since. During the past two decades, with the development of new epidemiological approaches to chronic disease, factors acting during intrauterine development and early in life were identified that may significantly affect the risk of cardiovascular disease in adulthood. Parallel to this development, evidence emerged from evolving laboratory research that the link between diabetes and cardiovascular disease has multiple pathways which may be represented by different phenotypes or clinical expressions of the disease.

LIFE COURSE EPIDEMIOLOGY

Classically, epidemiological studies hypothesize the association between one or more risk factors (exposures) to a clinical outcome. The Framingham prospective study is a typical example of the conventional epidemiological approach, which analyzes the contribution of individual factors or a combination of factors to the development of cardiovascular disease. In the last decade or so, a new approach to chronic disease epidemiology was adopted and defined as "the study of long-term effects on chronic disease risk of physical and social exposures during gestation, childhood, adolescence, young adulthood and later adult life" [1]. This approach focuses on the biological, behavioral and psychosocial pathways that act during the individual's life to promote chronic disease. Life course epidemiology is based on the modeling of a temporal sequence of exposures before statistical modeling is attempted, in contrast with the conventional grouping of exposures (risk factors) in multivariate analyses that are performed without consideration of the temporal relationship between variables included in the model. The complex interaction between genetic and environmental factors in the development of chronic diseases offers a new opportunity for the application of this concept while studying the link between diabetes and cardiovascular disease.

The "developmental model" described by Barker [2] proposes that nutrition during fetal life, infancy and early childhood changes gene expression and by that determines responses to the later development of chronic disease. Low birth weight in relation to the length of gestation as an expression of decreased intrauterine growth is associated with an increased risk of type 2 diabetes, coronary heart disease and stroke. In the Hertfordshire study, men whose birth weight was 2.5 kg or less, and 8 kg or less at 1 year, had more than twice the risk of dying from coronary heart disease before age 65 years than men whose weight at birth and at 1 year was 4 kg and 12 kg, respectively [3]. In the intrauterine stage of life the fetus is able to adapt to its environment while its developmental plasticity is lost in later stages of the child's life. Developmental plasticity is defined as "the phenomenon by which a single genotype can give rise to a wide range of different physiologic or morphologic states in response to different environmental conditions during development" [4]. As an example of this, adult leg length is a marker of early childhood environmental conditions, since this is the period of fastest leg growth. It has been shown that leg length is inversely and independently related to an increased risk of diabetes in middle-aged white men and women [5]. The developmental origin hypothesis proposes that coronary heart disease, type 2 diabetes, stroke and hypertension originate in developmental plasticity in response to under-nutrition during fetal life and infancy. An undernourished baby will probably develop a "thrifty" way of managing food intake. Insulin resistance, which is associated with low birth weight, could be the result of a continuous response of the fetus to hyperglycemia which was maintained to preserve the brain at the expense of muscle growth [6]. Probably the hyperglycemia and insulin resistance initiate a chain of processes in the diabetic vasculature that facilitate the development of atherosclerosis in the future.

METABOLIC ABNORMALITIES

Hyperglycemia is the primary characteristic of all types of diabetes and leads to organ damage through several mechanisms that are activated by a basic phenomenon: an overproduction of reactive oxygen species (ROS). While in the microvasculature, ROS is the result of intracellular hyperglycemia; in dia-

betic macroangiopaty and in the heart it seems to be related to an increased oxidation from fatty acids partly as a consequence of insulin resistance [7]. Diabetic microangiopathy is the result of sustained exposure to hyperglycemia. From the epidemiological perspective this statement is supported by long-term longitudinal studies [8]. The specific damage to vascular endothelial cells seems to be related to their incapacity to down-regulate uptake of glucose in the case of extracellular hyperglycemia [9].

Insulin resistance, which occurs in most type 2 diabetic patients, is also a major component of the metabolic syndrome. Its independent association with cardiovascular disease was also shown in 147 non-diabetic non-obese volunteers [10]. More recent experimental studies in mice have shown that the loss of insulin signaling in the endothelium leads to vascular dysfunction and atherosclerosis [11]. At present it is clear that the link between insulin resistance/hyperinsulinemia and cardiovascular disease is related to dysglycemia, dyslipidemia, hypertension, endothelial dysfunction and inflammation [12].

A recent study found genetic evidence for a normal weight "metabolically obese" phenotype, which links insulin resistance, hypertension, coronary artery disease and type 2 diabetes [13]. In this study, an analysis of genetic risk scores against disease outcomes by hierarchical clustering identified 11 variants associated with a metabolic profile consistent with a common, subtle form of lipodystrophy. The same risk alleles were associated with lower body mass index and increased visceral to subcutaneous adipose tissue ratio. Clinically, the concept of metabolically obese, normal-weight individuals, who represent one end of the spectrum of people with the insulin resistance syndrome, was described almost 40 years ago and revisited in 1998 [14]. These metabolically obese, normal-weight individuals could account for the higher prevalence of type 2 diabetes, cardiovascular disease and other disorders in people whose body mass index is in the 20–27 kg/m^2 range and who have gained a modest amount of weight in adult life.

Additional biochemical links between diabetes and cardiovascular disease were described. There are epidemiological data supporting the association between leptin, a 167 amino acid polypeptide hormone synthesized and secreted into the circulation primarily by white adipocytes, with an increased risk of myocardial infarction [15] and stroke [16], although the mechanisms of these associations are not yet completely understood.

In addition, a significant association was recently found between a metabolic score composed of plasma levels of three amino acids (tyrosine, phenylalanine and isoleucine) and type 2 diabetes incidence in the Malmö Diet and Cancer Cardiovascular Cohort. During a 12 year follow-up period, individuals in the highest quartile of the amino acids score had a 2.2 times higher risk to develop cardiovascular disease than those in the lowest quartile [17].

Fetuin-A, a protein secreted by the liver, induces insulin resistance, and its circulating levels are elevated in individuals with the metabolic syndrome. In the European Prospective Investigation into Cancer and Nutrition Potsdam Study, fetuin levels were measured in 227 individuals who developed myocardial infarction, 168 who developed stroke, and 2198 individuals who remained free of cardiovascular events during a mean follow-up period of 8.2 years. Individuals in the highest quintile of fetuin levels had a 3.2-fold increased risk of developing myocardial infarction and a 3.8 times increased risk of developing ischemic stroke compared to those in the lowest quintile, after adjusting for known cardiovascular risk factors [18].

People with non-alcoholic fatty liver disease (NAFLD), a manifestation of the metabolic syndrome characterized by insulin resistance, are at increased risk of developing diabetes and cardiovascular disease independently of the already known cardiovascular risk factors. Several epidemiological studies have described the association of NAFLD with an increased prevalence and incidence of cardiovascular disease [19].

Recently identified adipocytokines are visfatin (nicotinamide phosphoribosyltransferase, Nampt) and ghrelin. Visfatin is highly expressed in visceral fat and serum levels of the protein correlate with obesity. Ghrelin, the "hunger hormone," is a peptide produced by ghrelin cells in the gastrointestinal tract which functions as a neuropeptide in the central nervous system and regulates the distribution and rate of use of energy. Although their role in atherosclerosis is still largely unknown, there is epidemiological evidence of their association with carotid atherosclerosis in people with type 2 diabetes. In a cross-sectional study, 122 with type 2 diabetes were age and gender matched with healthy individuals. Mean carotid intima-media thickness was statistically significantly higher in diabetic persons compared to non-diabetic controls. While visfatin levels were significantly higher in diabetic people than in controls the levels of ghrelin were lower in diabetic individuals [20].

In conclusion, it seems evident from all the described metabolic markers linking diabetes and cardiovascular disease that the common denominator is insulin resistance as a result of liver and adipose tissue dysfunction. This association is also implied from the studies of diabetes and cardiovascular disease and prenatal and early life growth. It is also clear that there are multiple metabolic pathways leading to these associations. Some of them have the potential of serving as a basis for planning interventions in order to reduce the burden of cardiovascular disease among diabetic individuals.

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