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Commentary
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Insulin Resistance, Type 2 Diabetes and Atherosclerosis

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Abstract

Insulin resistance is a hallmark of type 2 diabetes mellitus and is associated with a metabolic and cardiovascular cluster of disorders (dyslipidaemia, hypertension, obesity, glucose intolerance, metabolic syndrome and endothelial dysfunction), each of which is an independent risk factor for Cardiovascular Disease (CVD). Many prospective studies have documented an association between insulin resistance and accelerated CVD in patients with type 2 diabetes. Insulin resistance and lipotoxicity represent the missing links that help to explain the accelerated rate of CVD in type 2 diabetic patients. Accumulation of toxic lipid metabolites in muscle, liver, adipocytes, beta cells and arterial tissues contributes to insulin resistance, beta cell dysfunction and accelerated atherosclerosis, respectively, in type 2 diabetes. Treatment with diet, exercise and drugs mobilizes fat out of tissues, leading to enhanced insulin sensitivity, improved beta cell function and decreased atherogenesis.

Keywords: Glycemic control; Dyslipidemia; Cardiovascular risk; Epidemiology

Introduction

Type 2 diabetes mellitus is a complex disorder complicated by microvascular and macrovascular disease [1]. Hyperglycaemia is the major risk factor for microvascular complications and reduction in HbA1c decreases the incidence of complications are a major cause of morbidity, macrovascular complications represent the primary cause of mortality with heart attacs and stroke accounting for around 80% of all deaths [2-5].

Understanding atherosclerosis in diabetes and instituting therapy guided by emerging evidence should improve outcomes in patients. Clinical manifestations of atherosclerosis occur primarily in 3 vascular beds: coronary arteries, lower extremities, and extracranial carotid arteries. Diabetes increases the incidence and accelerates the clinical course of each vascular bed. The evidence supports aggressive anti-atherosclerotic management strategies upon diagnosis of type 2 diabetes to minimize the risk of cardiovascular morbidity and mortality [6-9]. Risk factors occur simultaneously,, although such interactions are difficult to quantify (Figure 1).

This review will explore the current understanding of atherosclerosis and the existing researches supporting the association between insulin resistance, type 2 diabetes and atherosclerosis as well the atherosclerotic complications of diabetes. We focus on type 2 diabetes, characterized by insulin resistance and inadequate beta cell insulin secretion, because these patients represent more than 90% of those with diabetes and atherosclerosis.

Hyperglycaemia and Cardiovascular Disease

The negative results of the ACCORD, ADVANCE and VADT studies, in which intensified glycaemic control failed to reduce vascular complications, it is reasonable to ask which role hyperglycaemia plays in the development of cardiovascular disease (CVD) [9-12]. Epidemiological analysis of the UKPDS demonstrated that the rising of HbA1c was associated with increased risk of myocardial infarction and stroke [3].

The increased hazard ratio was modest and the reduction in HbA1c following insulin or sulfonylurea therapy did not significantly decrease myocardial infarction or stroke, although long-term follow up did demonstrate a significant reduction in atherosclerotic cardiovascular events.

The results of the Hoorn Study, 8 years of follow-up, 185 subjects died; 98 of cardiovascular causes. Fasting plasma glucose was only predictive in the diabetic range, although the risks started to increase at about 6.1 mmol/l. Post-load glucose and HbA1c values were, even within the non-diabetic range, associated with an increased risk (p for linear trend <0.05). These increased risks were mostly, but not completely, attributable to known cardiovascular risk factors [47].

Insulin and Atherosclerosis

Several *in vivo* and *in vitro* studies have demonstrated that insulin can promote atherogenesis. Insulin promotes *de novo* lipogenesis and increases hepatic VLDL synthesis, via the stimulation of sterol regulatory element- binding protein-1c and by the inhibition of acetyl-CoA carboxylase [16-21].

Insulin administration prevented regression of coronary atherosclerosis, when low-cholesterol diet was instituted. Alloxan-induced diabetic rabbits fed with a high-cholesterol diet have developed marked hypercholesterolaemia, but their aorta remained free of atherosclerotic plaques [22]. Finally, insulin therapy is frequently associated with weight gain. Several studies designed to reduce HbA1c <7.0% with large insulin doses failed to achieve the targeted HbA1c goal and resulted in weight gain. This is of major concern since the current diabetes epidemic is being driven by obesity, a major risk factor for CVD [23-26].

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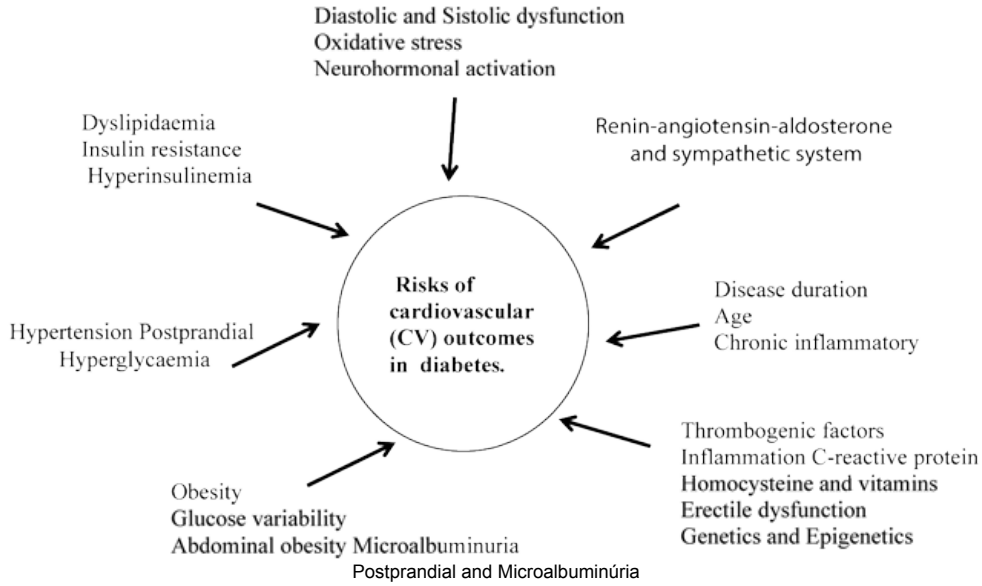

Figure 1: Risks of cardiovascular (CV) outcomes in diabetes.

Studies in man demonstrated that impaired IRS-1 tyrosine phosphorylation/PI-3 kinase activation in lean type 2 diabetic and obese non-diabetic participants causes a profound defect in glucose transport/phosphorylation and glycogen synthesis. Nitric oxide production is impaired because nitric oxide synthase is activated by the same PI-3 kinase pathway, resulting in endothelial dysfunction and accelerated atherosclerosis. This pathogenic sequence establishes the molecular basis linking insulin resistance, inflammation and accelerated atherosclerosis in patients with type 2 diabetes mellitus and may help to explain the missing 30% CVD risk that cannot be explained by circulating cardiovascular risk factors [27-35].

Diabetes and Vascular Smooth Muscle Function

The impact of diabetes mellitus on vascular function is not limited to the endothelium. In patients with type 2 diabetes mellitus, the vasodilator response to exogenous NO donors is diminished. Moreover, vasoconstrictor responsiveness to exogenous vasoconstrictors, such as endothelin-1, is reduced. Dysregulation of vascular smooth muscle function is exacerbated by impairments in sympathetic nervous system function. Diabetes increases PKC activity, NF-κB production, and generation of oxygen-derived free radicals in vascular smooth muscle [36-41].

Epidemiological studies have provided convincing evidence that the risk of CVD is increased by the presence of diabetes and that the increased risk is related to the extent of glycemic control. However, epidemiological studies provide no insight into causality. *In vitro* studies have provided important clues to the mechanism by which hyperglycemia might lead to atherosclerosis.

Diabetes and atherosclerosis are major causes of disability and death in patients with diabetes mellitus. Diabetes mellitus substantially increases the risk of developing coronary, cerebrovascular, and peripheral arterial disease.

Dyslipidaemia

In T2DM, IR increases the mobilization of free fatty acids from adipose tissue. Three mechanisms across which there is increased very low-density lipoproteins hepatic production: an increased lipogenesis, an exacerbation of substrate availability, and decreased apolipoprotein B-100 (ApoB) degradation. The lipid profile marked by low high-density lipoprotein cholesterol (HDL-C), high triglycerides (Tgs), increased ApoB synthesis and small dense LDL particles. This LDL subtype is more inclined to oxidation, playing an important role in atherogenesis. Stronger than LDL cholesterol, a low HDL-C or lonely elevated Tgs, atherogenic dyslipidaemia (Low HDL-C and ApoA, elevation of both fasting and post-prandial Tgs, small dense LDL particles and elevation of ApoB) is in T2DM patients a self-determining predictor of cardiovascular risk. The protective function of HDL may be lost in type 2 diabetics owing to alterations of the protein, resulting in a pro-oxidant, inflammatory phenotype [42-43]. Association exists between elevation of TGs-rich particles and their remnants, low HDL-C and cardiovascular risk,. Cardiovascular event rates were significantly greater in those with dyslipidaemia: LDL-C >2.6 mmol/L, HDL-C ≤ 0.88 mmol/L and TGs ≥ 2.3 mmol/L, as is proved in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study and in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study [42-47].

IR is commonly observed in the metabolic syndrome, in which multiple metabolic risk factors are co-existed including abdominal obesity, hyperglycemia, hyperinsulinemia, dyslipidemia, hypertension, and hyperhomocysteinemia. Patients with the metabolic syndrome are at increased risk of developing coronary heart disease, stroke and T2DM. Future studies to identify molecular basis of impaired insulin signaling in different tissues would lead to the discovery of novel therapeutic strategies for IR-related metabolism syndrome to reduce the risk of cardiovascular disease.

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