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Does statin monotherapy address the multiple lipid abnormalities in type 2 diabetes?

James Shepherd *

Department of Biochemistry, Royal Infirmary, Glasgow G4 OSF, Scotland, UK

Abstract

Lipid abnormalities, which are common in type 2 diabetes, predispose to a greatly increased risk of coronary heart disease. This characteristic dyslipidaemia includes decreased concentrations of high-density lipoprotein cholesterol (HDL-C), elevated triglycerides, and a small, dense, atherogenic form of low-density lipoprotein cholesterol (LDL-C). Insulin resistance and obesity, which is commonly present in type 2 diabetes, act in concert to disrupt normal lipoprotein metabolism; reverse cholesterol transport in particular. The proatherogenic changes, which result from this process include enrichment of very-low-density lipoprotein with cholesteryl esters and enrichment of LDL with triglycerides. Results from both the Pravastatin Pooling Project and the Heart Protection Study demonstrate that, although people with diabetes obtain the same relative risk reduction with statin therapy, the absolute benefit derived is much lower than for comparable individuals without diabetes. In order to achieve improved outcomes in diabetes patients, it will be important to address other abnormalities in their lipid profiles, including elevated triglycerides and low HDL-C.

Keywords: Lipoprotein metabolism; Dyslipidaemia; Diabetes; Statin therapy

1. Introduction

Patients with type 2 diabetes have significant metabolic abnormalities, which ultimately predispose them to increased risk of coronary heart disease (CHD). This finding was vividly demonstrated by data in the Third National Health and Nutrition Examination Survey, 1988–1994, in USA. NHANES contained a probability sample of 18,825 US adults aged 20 years or more who were interviewed to ascertain a medical history of diagnosed diabetes, and subsamples of 6587 adults for whom fasting plasma glucose values were obtained, and 2844 adults between 40 and 74 years of age who received an oral glucose tolerance test [1]. Prevalence of type 2 diabetes was high, about 11%, and nearly all (>99%) of these individuals had other comorbid conditions, such as hypertension, obesity or dyslipidaemia [2]. In fact, over two-thirds were dyslipidaemic, implying that at the time, 8% of the US population had both diabetes and dyslipidaemia [2].

2. Characteristics of dyslipidaemia in diabetes

People with diabetes frequently have a characteristic lipid profile, which includes elevated triglycerides and low high-density lipoprotein cholesterol (HDL-C), and to a lesser extent, raised low-density lipoprotein cholesterol (LDL-C). Contrary to popular belief, elevated LDL-C is not a unique marker of diabetic dyslipidaemia: it is also quite common in the general population, occurring in half the US population, half the German population, and more than half the UK population [2–4]. Indeed, this finding was first recognized 30 years ago in the Framingham Study [5] and has been substantiated more recently by the NHANES data [2].

The NHANES data quantify the extent to which risk factors for CHD occur more frequently among people with diabetes compared with the general population. For example: 37% of the general US population are obese compared with 63% of the diabetic population; 27% of the general population are hypertensive compared with 58% of people with diabetes; 16% have elevated triglycerides compared with 37% of people with diabetes; 10% have low HDL-C compared with 24% of people with diabetes; and 43% have raised LDL-C compared with 59% of people with diabetes [2]. In addition to

* Tel.: +44 141 211 4628/9; fax: +44 141 553 1703.
E-mail address: jshepherd@gri-biochem.org.uk.

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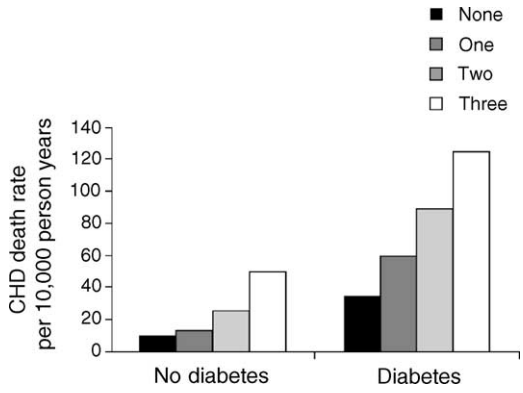

Fig. 1. Coronary heart disease (CHD) risk increases linearly with the number of individual risk factors present, and diabetes accentuates cardiovascular risk for each combination of risk factors. Adapted from MRFIT trial data [7].

being more common in people with type 2 diabetes, these risk factors also tend to occur together within individuals.

3. Consequences of clustering of risk factors in diabetes

Risk factors for CHD, such as hypertension, hypertriglyceridaemia and low HDL-C are additive. Therefore, the risk of cardiovascular disease (CVD) is enhanced with each additional risk factor present (Fig. 1) [6]. Even more striking is the finding that diabetes enhances this risk, approximately doubling the risk of a major cardiovascular event compared with the general population irrespective of the number of risk factors (Fig. 1) [7].

The prominence of this characteristic pattern of raised triglycerides and low HDL-C within the population of people with diabetes reflects the major disruption induced by insulin resistance on lipid metabolism. This pathophysiology is complex and still being clarified. Therefore, it is useful to first review the normal production of triglyceride-rich particles and the role of the liver as the hub of both an endogenous and an exogenous loop of cholesterol metabolism.

4. Normal lipid and lipoprotein metabolism

Following a meal, ingested (exogenous) triglycerides are transported to muscle and adipose tissue by chylomicrons, where they are degraded by the enzyme lipoprotein lipase in capillary endothelium, to free fatty acids (FFAs). Following the degradation of chylomicrons, most of the liberated FFAs enter muscle and adipose tissue, but excess FFAs, as well as cholesterol-rich chylomicron remnants, remain in the plasma, eventually reaching the liver. An additional source of FFAs, which takes on particular importance in type 2 diabetes and will be discussed later, is central abdominal fat. This tissue is highly metabolically active, and releases FFAs into the portal bloodstream in proportion to the volume of fat present.

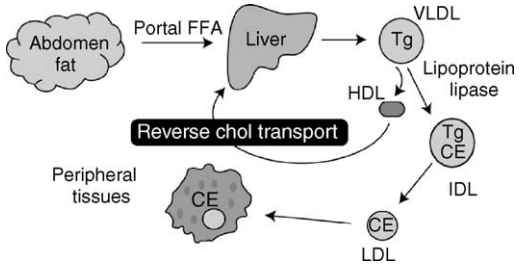

Fig. 2. In normal lipoprotein metabolism, lipoprotein lipase breaks down very low-density lipoprotein (VLDL) to low-density lipoprotein (LDL) particles, which are rapidly cleared by the liver. High-density lipoprotein (HDL) removes excess cholesteryl esters (CE) through the process of reverse cholesterol (chol) transport. IDL, intermediate-density lipoprotein; FFA, free fatty acid; Tg, triglyceride.

On reaching the liver, cholesterol-rich chylomicron remnants, excess FFAs not taken up by peripheral tissues, and FFAs released from abdominal fat stores are extracted, incorporated into very low-density lipoprotein (VLDL) and then secreted back into plasma. These large, triglyceride-rich, VLDL particles are quickly broken down in peripheral tissues by the enzyme lipoprotein lipase, which liberates FFAs for use by peripheral tissues. The VLDLs consequently shrink to become small, intermediate-density lipoproteins (IDLs) and eventually even smaller LDLs, which are rapidly removed from circulation by the liver (Fig. 2). In summary, the role of VLDL is to shuttle FFAs between the liver and the periphery.

During the enzymatic breakdown of VLDL by lipoprotein lipase in peripheral tissues, excess cholesteryl esters are generated [8]. Small HDL particles, which have previously been secreted by the liver as relatively cholesterol-poor lipoproteins, play a critical role at this stage by accepting the transfer of excess cholesteryl esters. These enlarged HDL particles return to the liver with their cholesterol load: a process known as reverse cholesterol transport. In fact, the cardioprotective effects of HDL are largely attributed to this ability to facilitate cholesterol transport away from peripheral tissues.

5. FFAs, insulin and lipid metabolism

When FFAs are secreted from central adipose tissue, they exert two primary regulatory effects on entering the portal circulation. One effect is to trigger insulin secretion from the pancreas, the other is to down-regulate further release of FFAs from central abdominal fat and to accelerate FFA extraction by the liver (Fig. 3).

Consequently, less triglyceride is packaged into VLDL, and both VLDL and triglyceride concentrations fall. As insulin passes through the portal blood, a large portion is extracted by hepatocytes before entering the systemic circulation. Another effect of insulin is to activate the enzyme lipoprotein lipase, which breaks down VLDL and ensures a very rapid clearance from the blood. Lipoprotein lipase is more active in women than in men, which partially accounts for their normally decreased risk of cardiovascular events