



# Coronary artery disease and diabetes

**Sabino Iliceto**

**Department of Cardiovascular and Neurological Sciences, University of Cagliari, Italy**

Correspondence: Professor Sabino Iliceto, Department of Cardiovascular and Neurological Sciences, University of Cagliari, Italy. Tel: +39 070 609 2421/2236 fax: +39 070 662 747  
e-mail: iliccard@pacs.unica.it/segrcard@pacs.unica.it

The present status of our knowledge of the relationship between the heart and diabetes is characterized by two conflicting situations: the first is the increasing awareness that diabetes is a primary risk factor and that cardiovascular disease is the leading cause of death in diabetic patients; the second is that our strategies to counteract this risk have been less effective in diabetic patients than in nondiabetics.

## Increased cardiovascular morbidity and mortality

The presence of diabetes mellitus increases mortality for any cause, in particular cardiovascular mortality two- to fourfold. Furthermore, mortality is dramatically increased in the presence of clinical features such as diabetic nephropathy. Although part of this increase can be explained by interaction with other risk factors and by the clustering of diabetes with other risk elements in the so-called 'metabolic syndrome', increased cardiovascular mortality and morbidity are conferred by the presence of diabetes per se.

Atherosclerotic plaques tend to develop earlier and be more advanced and more diffuse in diabetic patients. Unfortunately, our reperfusion strategies have proven less efficacious in diabetic patients. In particular, PTCA (with or without stenting) seems to have a catastrophic outcome in these patients, who are affected by a high incidence of reocclusion. Due to silent ischemia, this diagnosis is often achieved later in this patient population.

Furthermore, a complex of different adverse characteristics of diabetes, including endothelial dysfunction and a prothrombotic state, augments the probability of plaque 'instability' and occlusion. Diabetes renders patients

peculiarly prone to heart failure, resulting from both diffuse coronary heart disease and direct microvascular and myocardial damage. Heart failure is the main cause of death during acute myocardial infarction, the global risk of failure being almost three times higher in the presence of diabetes.

The above situation is rendered more dramatic by the growing incidence of both type 1 and type 2 diabetes and its incidence is expected to double in the next decade.

Although therapeutic improvements and public health policies for risk factor control have brought about a dramatic reduction in cardiovascular mortality among the general population, this success has not been extended to diabetic patients. In fact, death for any cause including cardiovascular mortality in diabetic patients has only marginally diminished in recent decades.

Theoretically, prevention of cardiovascular complications of diabetes consists of: (1) counteraction of metabolic derangement and (2) reduction of other risk factors known to interact with diabetes. Of course, for each of these aspects it is crucial to know when, how, and to what extent to act. Unfortunately, there is a lack of clinical trials specifically designed to address most of these issues.

## Trial outcomes

The impact of therapeutic strategies to reduce cardiovascular events in patients with coronary artery disease and diabetes has been the focus of increasing interest in recent years. The results of trials have sometimes been either difficult to interpret or have failed to shed any light on the issue.

Among trials testing the effects of strict vs. conventional metabolic control, only the DIGAMI (Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction) trial provided clear evidence of positive results in cardiovascular prevention at 1 year.

Conversely, disappointing results of the UKPDS (United Kingdom Prospective Diabetes Study) may have been due to a wide overlap between different subgroups, with potential dilution of differences between beneficial and harmful interventions.

With regard to type 1 diabetes, again an inadequate design compromised the possibility of demonstrating the efficacy of strict metabolic control in reducing long-term mortality in the DCCT (Diabetes Control and Complications Trial), apart from a weak positive trend.

If DIGAMI and possibly the DCCT seem to cautiously suggest the efficacy of insulin in cardiovascular prevention, the effects of other classical pharmacological therapies are much less clear and have been questioned by many experts, while a number of new promising metabolic remedies still lack adequate clinical testing.

In this issue of *Heart and Metabolism* a variety of basic and clinical aspects of diabetes are discussed. One of the crucial aspects in diabetic patients is the fact that diabetes not only affects the coronary (macro- and micro-) circulation, but also myocyte function. As outlined by Gary Lopaschuk in his article, energy metabolism is altered. In particular, glucose uptake and oxidation decrease, while fatty acid oxidation increases. As a consequence, myocardial contractility decreases.

The risk of developing significant coronary artery disease is also high in diabetic patients because of their increased frequency of dyslipidemia, which is linked to central obesity and

insulin resistance. In her review, Michaela Diamant argues that patients with diabetes can be considered 'postprandial' throughout the entire day, long-lastingly exposing the arteries to potentially atherogenic triglyceride-enriched particles. Even if patients with type 2 diabetes do not have particularly elevated LDL cholesterol levels, intensive LDL lowering therapy may be effective in reducing ischemic events.

Fisman and colleagues in their article deal with the important problem of therapeutic strategy in patients with diabetes and coronary artery disease. Apart from the positive effects, these authors discuss the potential negative effects of insulin, of biguanides, and of some sulfonylureas.

In their article Freeman and Langer describe the potential of imaging modalities aimed to assess cardiac sympathetic autonomic dysfunction. Myocardial  $^{123}\text{I}$ -labeled metaiodobenzylguanidine uptake is useful in predicting autonomic function in patients with diabetes mellitus.

A recently presented trial, outlined in this issue by Hanna Szwed, demonstrated the therapeutic value of a metabolic agent in patients with stable angina pectoris. There was a significant improvement in all exercise and clinical parameters. Also in the subgroup of patients with diabetes a consistent improvement in exercise parameters was present but, because of the relatively small number of patients, did not reach statistical significance.

Patients with diabetes submitted to PTCA are at risk of restenosis: a case report of a patient with myocardial infarction submitted to thrombolytic therapy and, thereafter, because of recurrent chest pain, treated with PTCA is presented by Jonathan Hill, emphasizing the importance of glycemic control and the metabolic implication of acute ischemia in this type of patient.

# Myocardial metabolism and function in diabetes

Gary D. Lopaschuk  
 Cardiovascular Research Group, Faculty of Medicine,  
 University of Alberta, Edmonton, Alberta, Canada

Correspondence: Professor Gary D. Lopaschuk, Cardiovascular Research Group,  
 Faculty of Medicine and Oral Health Sciences, University of Alberta, 423 Heritage Medical  
 Research Centre, Edmonton, Alberta, Canada.

Tel: +1 780 492 2170, fax: +1 780 492 9753, e-mail gary.lopaschuk@ualberta.ca

## Introduction

Alterations in energy metabolism in the diabetic can have profound effects on cardiac function, both in the presence and absence of coronary artery disease. It has been well documented that abnormalities in cardiac function (termed 'diabetic cardiomyopathies') can occur in the diabetic in the absence of ischemic heart disease.<sup>1-5</sup> Diabetes-induced alterations in myocardial fatty acid and glucose metabolism are an important contributing factor to these cardiomyopathies.<sup>6</sup> These changes in energy metabolism can also contribute to the complications and severity of ischemic heart disease in the diabetic. Diabetics have a significantly greater incidence and severity of angina, acute myocardial infarctions, congestive heart failure, and other manifestations of atherosclerosis than do nondiabetics.<sup>1,7-9</sup> While an increased incidence and severity of coronary artery disease are major contributors to the high prevalence of heart disease in the diabetic compared with the nondiabetic population, it is also clear that changes within the myocytes themselves contribute to the severity of ischemic injury.

One of the prominent cellular changes that occurs in the heart of a diabetic is an alteration in the control of energy metabolism. In particular, glucose uptake and oxidation decrease, while fatty acid oxidation increases.<sup>6</sup> These high fatty acid oxidation rates and low glucose metabolism rates can decrease contractile function and cardiac efficiency in the heart.<sup>10</sup> The inability to use glucose also contributes to the severity of an ischemic insult, and can impair functional recovery during and following ischemia.<sup>10</sup> Both heart failure following an acute myocardial infarction and diabetic cardiomyopathies have been correlated with the acute metabolic status of the patient.<sup>9,11-14</sup> Furthermore, cardiomyopathies

in the absence of ischemic heart disease can be improved by correction of hyperglycemia.<sup>11</sup> As a result, diabetes-induced changes in energy metabolism have the potential to significantly impact cardiac function both in the presence and absence of ischemia.

## Control of energy metabolism in the normal and diabetic heart

Glucose is the principal carbohydrate metabolized by the heart. Glucose is taken up by the cardiomyocytes in an insulin-dependent manner, and is then predominantly metabolized through glycolysis to form pyruvate.<sup>15</sup> Pyruvate generated from glycolysis, and to a lesser extent from lactate, is further metabolized within the mitochondria to produce the majority of carbohydrate-derived ATP (*Figure 1*). The conversion of pyruvate in the mitochondria to acetyl-CoA is catalyzed by pyruvate dehydrogenase (PDH). This acetyl-CoA undergoes further mitochondrial metabolism, culminating in the synthesis of ATP by the process of oxidative phosphorylation.

Fatty acids are the other major source of acetyl-CoA for the TCA cycle, and the oxidative production of myocardial ATP. Fatty acids seem to be the 'preferred' substrate of the myocardium, contributing approximately 60–70% of the heart's energy requirements when supplied at physiologic levels.<sup>15</sup> However, fatty acids are not as efficient as glucose as a source of energy (with respect to oxygen consumption), and require approximately 10% more oxygen to produce the equivalent amount of ATP.

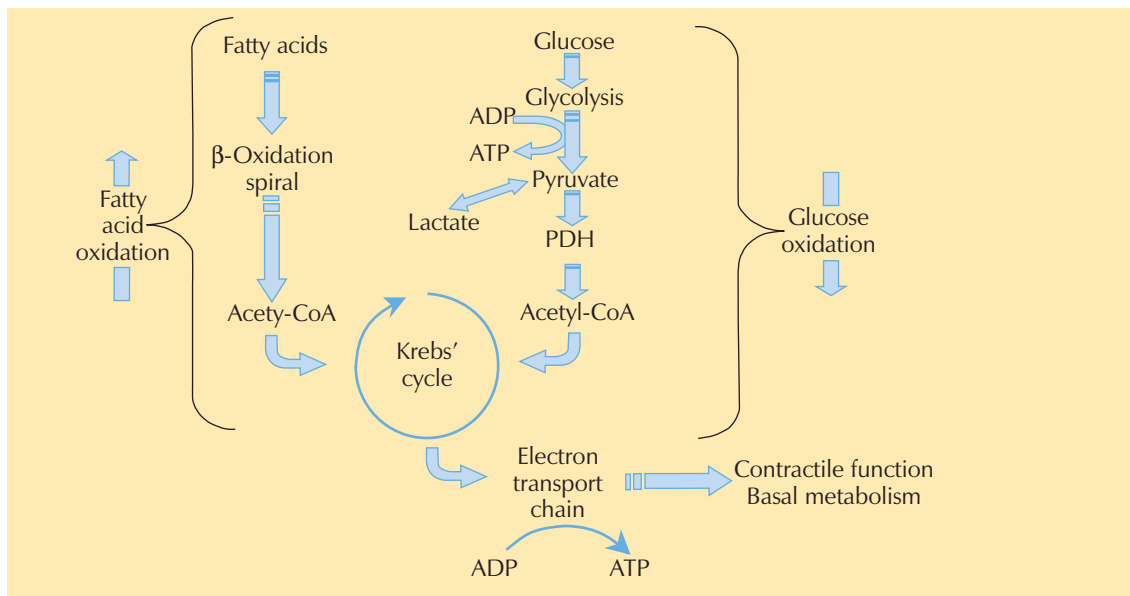


Figure 1. Effect of diabetes on energy metabolism in the heart.

**Diabetes-induced alterations in glucose metabolism**

Myocardial glucose transport, glycolysis, and glucose oxidation are all decreased in diabetes (Figure 1). Accompanying the decrease in glucose transport is a decrease in the rate of glycolysis in the diabetic heart.<sup>6</sup> The rate of glucose oxidation is also significantly reduced in the diabetic heart.<sup>16,17</sup> This is due to a marked decrease in PDH activity, the rate-limiting enzyme for glucose oxidation. High circulating free fatty acid levels and myocardial fatty acid oxidation are the key factors responsible for the decreased myocardial PDH activity in diabetes. Numerous studies have now demonstrated that low PDH activity (and therefore low glucose oxidation rates) are detrimental to heart function in both the presence and absence of ischemia (see references 6, 10 and 18 for reviews). In support of this, therapeutic strategies that increase PDH and glucose oxidation have been to improve cardiac function in the diabetic heart, both in the absence and presence of ischemia.<sup>6,10,18</sup> This can be achieved by either directly stimulating PDH, or by directly inhibiting fatty acid oxidation.

**Diabetes-induced alterations in fatty acid metabolism**

While fatty acid oxidation normally provides 60–70% of the energy requirements of the heart, in uncontrolled diabetes fatty acid oxidation can provide between 90 and 100% of the heart's energy requirements (Figure 2).<sup>6,10</sup> While decreased glucose uptake due to insulin deficiency can partly explain the decrease in glucose metabolism, high levels of circulating fatty acids and alterations in the control of fatty acid oxidation appear to be primarily responsible for this switch. Plasma free fatty acid levels are elevated in patients with either noninsulin-dependent or insulin-dependent diabetes. In diabetics, in whom plasma levels of both free fatty acids and triacylglycerol-rich lipoproteins are increased, fatty acid inhibition of both glycolysis and glucose oxidation in the heart is especially prominent. Although high levels of circulating fatty acids contribute to low rates of glucose metabolism, alterations in the control of fatty acid oxidation also occur within the myocardium of diabetics. One site that appears to be particularly important is the control of fatty acid uptake by the mitochondria.<sup>6,18</sup>

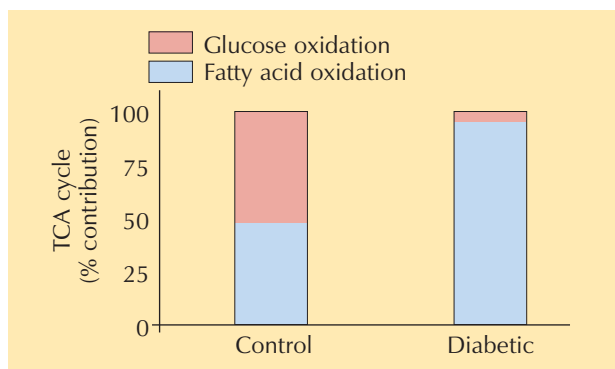


Figure 2. Contribution of fatty acid oxidation and glucose oxidation to mitochondrial TCA cycle activity in the diabetic rat heart. Isolated working hearts from control and 6-week streptozotocin diabetic rats were perfused with 5 mM [ $U$ - $^{14}$ ]glucose, 1.2 mM [9,10- $^3$ H]palmitate, and 100  $\mu$ U/ml insulin, palmitate and glucose oxidation measured, and the contribution of palmitate and glucose to TCA cycle activity determined, as described in reference 19.

### Energy metabolism during and following cardiac ischemia in the diabetic

During a mild ischemic episode, fatty acid oxidation and glucose oxidation both decrease, with glycolysis becoming the dominant source of energy production.<sup>15</sup> A large increase in the amount of glycolysis relative to glucose oxidation occurs, resulting in the anaerobic hydrolysis of ATP and the production of excess cytosolic protons. This uncoupling of glycolysis from glucose oxidation is a major source of proton production in the myocardium during ischemia. Since coronary flow is diminished at this time, excess protons accumulate, resulting in intracellular acidosis. These protons exchange for other cations, and can lead to an increase in intracellular calcium overload. The need to use ATP to reestablish  $H^+$ ,  $Na^+$ , and  $Ca^{2+}$  homeostasis can lead to a decrease in cardiac efficiency. As a result, low glucose oxidation rates contribute to a decrease in cardiac efficiency during ischemia.<sup>19</sup>

During reperfusion following an episode of ischemia, a rapid recovery of mitochondrial energy production must occur if contractile

function is to recover. During this period, fatty acid oxidation quickly recovers and becomes the predominant source of myocardial ATP production, providing 80–90% of the heart's energy requirements.<sup>19</sup> High rates of fatty acid oxidation during reperfusion of ischemic hearts markedly decrease glucose oxidation rates, contributing to contractile dysfunction during reperfusion.<sup>19</sup> In the diabetic, the problems associated with low glucose oxidation both during and following ischemia are exacerbated. While serum fatty acid concentrations in normal individuals range from 0.2 to 0.5 mM, during an acute myocardial infarction serum fatty acids can increase above 1 mM.<sup>6</sup> In diabetics, serum fatty acids can be elevated even in the absence of an acute myocardial infarction, and can rise during ischemia to very high levels. A number of experimental studies have examined the involvement of fatty acids during ischemia, and possible mechanisms by which fatty acids contribute to injury (see references 6, 10 and 18 for reviews). Fatty acid inhibition of glucose oxidation (via PDH inhibition) appears to be one contributing factor to ischemic injury. Fatty acids also promote and accelerate arrhythmias, decrease mechanical function, and impair membrane integrity and suborganelle performance.

### Pharmacological modification of cardiac energy metabolism in the diabetic

Interventions aimed at decreasing proton production by increasing glucose oxidation have the potential to improve cardiac efficiency.<sup>19</sup> Recent experimental and clinical studies have shown that stimulating glucose oxidation can improve both cardiac function and cardiac efficiency.<sup>6,10</sup> Experimental studies have shown that direct stimulation of glucose oxidation can improve cardiac function in hearts from diabetic animals, and decrease the adverse effects of ischemia.<sup>20</sup> Stimulation of glucose oxidation can either be by direct stimulation of glucose oxidation, or indirectly by inhibiting fatty acid oxidation. For instance, direct stimulation of glucose oxidation with the PDH acti-

vator dichloroacetate improves cardiac function in the nonischemic heart,<sup>20</sup> and improves functional recovery and cardiac efficiency in the reperfused ischemic heart.<sup>19</sup> Overcoming fatty acid inhibition of PDH with L-carnitine is another effective approach to benefiting cardiac function in the nonischemic and ischemic heart.<sup>21</sup>

Another effective approach to increasing glucose oxidation in the heart is by inhibiting fatty acid oxidation. This can either be achieved by inhibiting fatty acid uptake into the mitochondria, or by inhibiting fatty acid  $\beta$ -oxidation within the mitochondria. Agents that block mitochondrial fatty acid uptake (such as etomoxir, methylpalmoxirate, and oxfenicine) have been shown in experimental studies to improve heart function and decrease ischemic injury in animal models of diabetes.<sup>10</sup> Direct inhibition of fatty acid  $\beta$ -oxidation within the mitochondria can also benefit the diabetic heart. Pharmacological agents that inhibit fatty acid oxidation and stimulate glucose oxidation are now being used clinically to treat ischemic heart disease. Trimetazidine, the first 3-KAT inhibitor which stimulates glucose oxidation in the heart secondary to an inhibition of fatty acid oxidation,<sup>22</sup> is licensed worldwide for the treatment of ischemic heart disease.<sup>23</sup> Whether a similar approach may be efficacious in diabetics with ischemic heart disease is presently being evaluated. Clinical studies in Poland coordinated by Dr Hanna Szwed have shown that trimetazidine can reduce the symptoms, severity, and frequency of angina attacks in diabetic patients with angina pectoris.<sup>24</sup> Further studies are necessary to evaluate whether diabetic cardiomyopathic changes can also be decreased with the use of this therapy.

## Summary

**Increased fatty acid oxidation and decreased glucose metabolism contribute to the development of diabetic cardiomyopathies, and can decrease the ability of the heart to withstand an ischemic insult. Optimizing energy metabolism is now recognized as an effective clinical approach to treating ischemic heart disease. This metabolic approach may also have clinical potential in treating the diabetic patient. ■**

## REFERENCES

1. Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: the Framingham study. *Circulation*. 1979;59:8–13.
2. Factor SM, Minase T, Sonnenblick EH. Clinical and morphological factors of human hypertensive-diabetic cardiomyopathies. *Am Heart J*. 1980;99:446–458.
3. Mustonen JN, Uusitupa MU, Tahvanainen K, et al. Impaired left ventricular systolic function during exercise in middle-aged insulin-dependent and noninsulin-dependent diabetic subjects without clinically evident cardiovascular disease. *Am J Cardiol*. 1988;62:1273–1279.
4. Gwilt DJ, Petri M, Lewis PW, Natrass M, Pentecost BL. Myocardial infarct size and mortality in diabetic patients. *Br Heart J*. 1985;54:466–472.
5. Jaffe AS, Spadaro JJ, Schechtman K, Roberts R, Geltman EM, Sobel BE. Increased congestive heart failure after myocardial infarction of modest extent in patients with diabetes mellitus. *Am Heart J*. 1984;108:31–37.
6. Lopaschuk GD. Abnormal mechanical function in diabetes: relationship to altered myocardial carbohydrate/lipid metabolism. *Coron Artery Dis*. 1996;7:116–123.
7. Bradley RF, Bryfogle JW. Survival of diabetic patients after myocardial infarction. *Am J Med*. 1956;30:207–216.
8. Ulvenstam G, Aberg A, Bergstrand R, et al. Long-term prognosis after myocardial infarction in men with diabetes. *Diabetes*. 1985;34:787–792.
9. Kesler I. Mortality experience in diabetic patients: a twenty-six year follow-up study. *Am J Med*. 1971;51:715–724.
10. Lopaschuk GD, Belke DD, Gamble J, Itoi T, Schönekeess BO. Regulation of fatty acid oxidation in the mammalian heart in health and disease. *Biochim Biophys Acta*. 1994;1213:263–276.
11. Bellodi G, Manicardi V, Malavasi V, et al. Hyperglycemia and prognosis of acute myocardial infarction in patients without diabetes mellitus. *Am J Cardiol*. 1989;64:885–888.

12. Oswald B, Corcovan S, Yudkin JS. Prevalence and risks of hyperglycemia and undiagnosed diabetes in patients with acute myocardial infarction. *Lancet*. 1984;1:1264–1267.
13. Oswald GA, Smith CCT, Betteridge DJ, Yudkin JS. Determinants and importance of stress hyperglycaemia in non-diabetic patients with myocardial infarction. *Br Med J*. 1986;293:917–922.
14. Partamian JO, Bradley RF. Acute myocardial infarction in 258 cases of diabetes. *N Engl J Med*. 1965;273:455.
15. Neely JR, Morgan HE. Relationship between carbohydrate metabolism and energy balance of heart muscle. *Ann Rev Physiol*. 1974;36:413–459.
16. Garland PB, Randle PJ. Regulation of glucose uptake by muscle. X. Effects of alloxan diabetes, starvation, hypophysectomy and adrenalectomy, and of fatty acids, ketone bodies and pyruvate on the glycerol output and concentrations of free fatty acids, long-chain fatty acyl coenzyme A, glycerol phosphate and citrate cycle intermediates in rat hearts and diaphragm muscles. *Biochem J*. 1970;93:678.
17. Wall SR, Lopaschuk GD. Glucose oxidation rates in fatty acid-perfused isolated working hearts from diabetic rat. *Biochim Biophys Acta*. 1989;1006:97–103.
18. Stanley WC, Lopaschuk GD, Kivilo KM. Alterations in myocardial energy metabolism in streptozotocin diabetes. In: McNeill JH, ed. *Experimental Models of Diabetes*. Boca Raton, FL: CRC Press; 1999:19–38.
19. Liu B, Clanachan AS, Schulz R, Lopaschuk GD. Cardiac efficiency is improved after ischemia by altering both the source and fate of protons. *Circ Res*. 1996;79:940–948.
20. Nicholl T, Lopaschuk GD, McNeill JH. Effects of free fatty acids and dichloroacetate on isolated working diabetic rat heart. *Am J Physiol*. 1991;261:1053–1059.
21. Broderick TL, Quinney HA, Lopaschuk GD. L-carnitine increases glucose metabolism and mechanical function following ischemia in diabetic rat heart. *Cardiovasc Res*. 1995;29:373–378.
22. Kantor P, Lucien A, Kozak R, Lopaschuk GD. The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. *Circ Res*. 2000;86:580–588.
23. McLellan KJ, Plsoker GL. Trimetazidine: a review of its use in stable angina pectoris and other coronary conditions. *Drugs*. 1999;58:143–157.
24. Szwed H, Sadowski Z, Pachoski R et al. The anti-ischemic effects and tolerability of trimetazidine in coronary diabetic patients. A substudy from Trimpol-1. *Cardiovasc Drugs Ther*. 1999;13:217–222.

# Treatment targets in type 2 diabetes: non-HDL rather than LDL cholesterol?

Michaela Diamant

Diabetes Center/Department of Endocrinology, Vrije Universiteit Medical Center, Amsterdam, The Netherlands

Correspondence: Dr M. Diamant, Diabetes Center/Department of Endocrinology, Vrije Universiteit Medical Center, De Boelelaan 1117, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands. Tel: +31 20 4444444, fax: +31 20 4440502, e-mail: m.diamant@azvu.nl

The major cause of mortality in type 2 diabetes mellitus is coronary heart disease (CHD). Type 2 diabetic patients have a two- to fourfold increased relative risk of CHD in comparison with age-matched nondiabetic subjects.<sup>1,2</sup> The simultaneous presence of multiple 'classic' risk factors in patients with type 2 diabetes only partly accounts for the excessive risk of developing CHD in this population.<sup>1,2</sup> Although hyperglycemia is strongly associated with microvascular complications (retinopathy and nephropathy), the relation with macrovascular disease in type 2 diabetes is less certain. In particular, data from the largest and longest trial ever conducted in type 2 diabetes, the United Kingdom Prospective Diabetes Study (UKPDS), showed a nonsignificant 16% decrease in CHD risk at 10 years' follow-up in a comparison of intensified vs. conventional glycaemic control (ie, averaged glycosylated hemoglobin 7.0% vs. 7.9%).<sup>3</sup> The UKPDS did not investigate the effect of lipid-lowering on micro- and macrovascular endpoints, but in a separate analysis, low-density lipoprotein (LDL) cholesterol was identified as the major risk factor for macrovascular disease in the UKPDS population.<sup>4</sup> This finding may provide one of the possible explanations for the weak relation between glycaemic control and CHD risk in the UKPDS, as previous studies showed that LDL is barely affected by glycemia.<sup>5,6</sup>

Patients with type 2 diabetes have an increased frequency of dyslipidemia, which is invariably linked to the presence of insulin resistance and central obesity.<sup>7-10</sup> Elevated concentrations of triglyceride-rich lipoproteins, especially very-low-density lipoprotein (VLDL), and decreased levels of high-density lipoprotein (HDL), measured as HDL cholesterol, are the most characteristic lipoprotein

abnormalities in type 2 diabetes.<sup>8,10</sup> Most patients with type 2 diabetes have concentrations of LDL cholesterol which are similar to those of nondiabetic subjects;<sup>10</sup> however, in type 2 diabetes there are important qualitative changes in LDL, including the preponderance of smaller and denser particles, and modifications through glycation and oxidation which increase their atherogenicity.<sup>7,10</sup>

Recently, studies investigating derangements of postprandial lipid metabolism in type 2 diabetes and their atherogenic potential,<sup>11-13</sup> have revived interest in the concept that atherosclerosis may be a postprandial phenomenon, which was formulated by Zilversmit more than 20 years ago.<sup>14</sup> Indeed, evidence from clinical studies suggests that postprandial lipemia, characterized by a long residence time of triglyceride-rich remnants in the circulation and subsequent decrease in HDL levels, is an independent risk factor for CHD.<sup>11,15</sup> In view of their lipid profile, patients with type 2 diabetes may be regarded as permanently postprandial.

This review elaborates upon the lipoprotein abnormalities in type 2 diabetes and the underlying mechanisms, all of which are strongly associated with insulin resistance. In view of the interrelationship of the lipoprotein abnormalities and their atherogenic potential, it is suggested that both fasting and postprandial levels of triglyceride-rich lipoproteins (collectively termed non-HDL cholesterol), rather than LDL cholesterol, may be a more appropriate therapeutic target in type 2 diabetes.

## Physiology of lipoprotein metabolism

In order to enable understanding of the lipoprotein abnormalities in type 2 diabetes, the

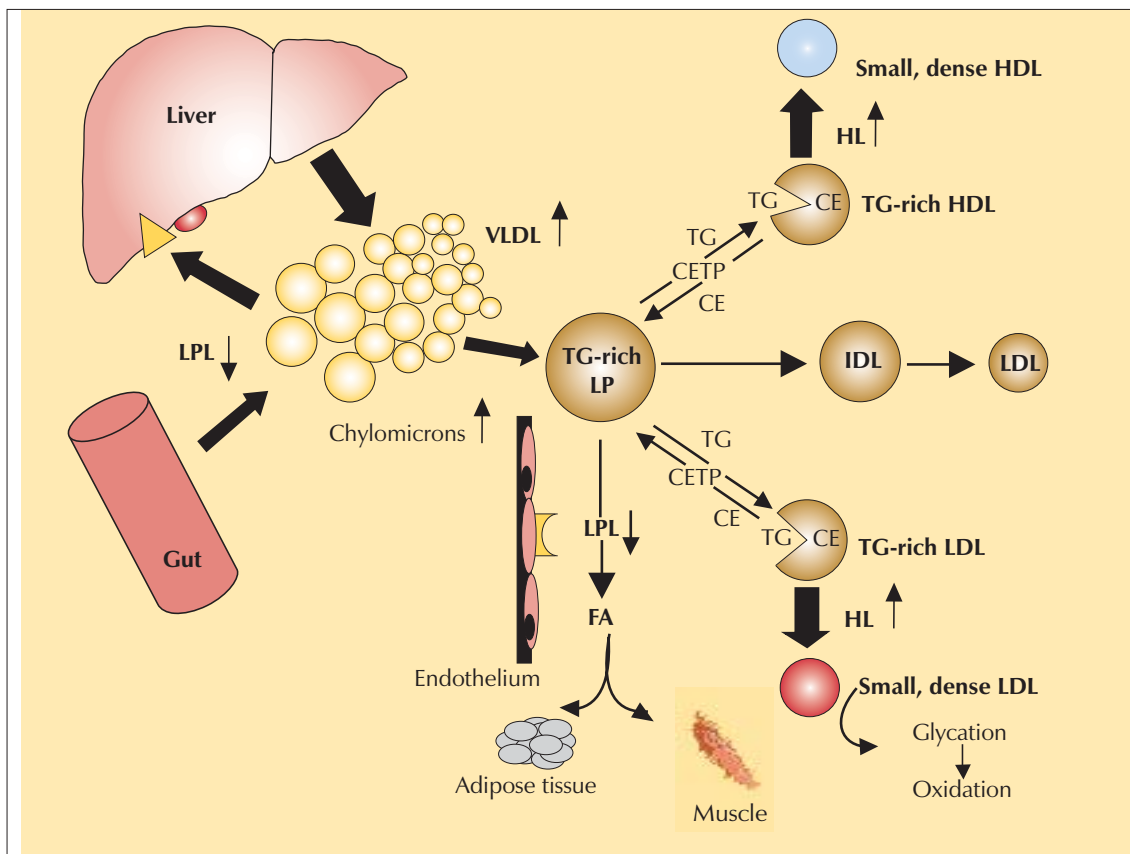


Figure 1. Schematic overview of lipoprotein metabolic pathways in type 2 diabetes. Increased endogenous very-low-density lipoprotein (VLDL) production, elevated postprandial triglyceride (TG) concentrations, and impaired endothelial lipoprotein lipase (LPL) activity lead to raised plasma concentrations of TG-rich lipoproteins (LP). High TG-rich lipoprotein concentrations increase the transfer of TG to low-density lipoprotein (LDL) and high-density lipoprotein (HDL), and simultaneous transfer of cholesteryl esters (CE) from LDL and HDL to TG-rich lipoproteins, mediated by cholesteryl ester transfer protein (CETP). Hydrolysis of core TG by hepatic lipase (HL) produces small, dense (lipid-poor and protein-enriched) LDL that are modified (eg. by oxidation or glycation). Similarly, small, dense HDL particles are produced that have a higher catabolic rate and may be dysfunctional with regard to reverse cholesterol transport. IDL, intermediate-density lipoprotein; FA, fatty acids. Adapted from ref. 8.

physiology of the lipoprotein metabolic cascades is summarized below.

Lipoprotein metabolism can be divided into two major pathways, the apolipoprotein (apo) B-lipoprotein and HDL pathways.<sup>16,17</sup> The apo B-lipoprotein pathway consists of a cascade of lipoproteins containing either the apo B-48 or the apo B-100 isoform of the B apolipoprotein secreted from the intestine or liver, respectively. The triglyceride-rich apo B-48-containing chylomicrons transport dietary lipids from the intestine to the liver and peripheral tissues. The catabolism of the triglyceride-rich chylomicrons is initiated by the endothelial

enzyme, lipoprotein lipase (LPL), which hydrolyzes the triglyceride core of the chylomicrons and releases fatty acids for energy production in muscle and for storage in adipose tissue (Figure 1). The chylomicron remnants are taken up by the liver by the LDL-receptor-related protein and LDL receptors, which have a high affinity for apo E.<sup>18</sup>

In a parallel cascade, the liver assembles triglyceride-rich VLDL-containing apo B-100, which, similarly to chylomicrons, undergoes hydrolysis by LPL and is remodeled to intermediate-density lipoprotein (IDL) and partly further to LDL (Figure 1). The latter step involves another enzyme,

hepatic lipase (HL). VLDL remnants and IDL-containing apo E are removed by hepatic LDL receptors and LDL-receptor-related protein receptors.<sup>18,19</sup> LDL contains only apo B-100 and is metabolized by two pathways: it may be taken up into the liver by an LDL-receptor-mediated mechanism, but it also may become modified or oxidized and removed by the scavenger receptor-A or CD36 scavenger receptors on macrophages.<sup>18,20</sup>

In the HDL pathway, HDL is synthesized as nascent HDL particles from both the liver and intestine as well as by transfer of lipids and apolipoproteins during the metabolism of triglyceride-rich chylomicrons and VLDL. A major function of HDL is the transport of excess cellular cholesterol from peripheral cells to the liver, a process called reverse cholesterol transport (RCT).<sup>21–23</sup> RCT is initiated by the removal of nonesterified or free cholesterol from cells mediated by the ATP-binding cassette transporter ABCA1 (formerly ABC1).<sup>24</sup> In plasma, free cholesterol on nascent HDL is converted to cholesteryl ester (CE) by lecithin cholesterol acyltransferase.<sup>21,23</sup> The CE synthesized on HDL can be transferred to apo B-containing lipoproteins by the cholesteryl ester transfer protein (CETP) in exchange for triglycerides (*Figure 1*).<sup>23</sup> Hepatocytes remove CE from HDL and apo B-containing lipoproteins either by direct uptake of the whole lipoprotein particle (mediated by LDL- and LDL-receptor-related protein receptors) or by selective removal of CE from the particle (mediated by the scavenger receptor BI).<sup>25</sup>

### Lipoprotein metabolism in type 2 diabetes: the impact of insulin resistance

In type 2 diabetes, insulin resistance and visceral obesity have a major impact on the regulatory processes of both the apo B-lipoprotein and the HDL pathways. Many steps in the lipoprotein metabolic cascades are insulin-sensitive.<sup>7,8</sup>

### Apo B-lipoprotein pathway in type 2 diabetes

The insulin-resistant state impairs the normal suppression of free fatty acid (FFA) release from the abundantly present adipose tissue. This increased flux of FFA to the liver is a major stimulus for overproduction of VLDL.<sup>7,10</sup> Postprandially, independent of the FFA flux, hepatic VLDL production is not normally suppressed, resulting in competition for LPL with exogenous triglycerides carried on chylomicrons.<sup>26</sup> LPL activity is lower in type 2 diabetics than in nondiabetic subjects and increases with improved glycemic control.<sup>8</sup> Thus, the raised concentration of triglyceride-rich lipoproteins in type 2 diabetes is due to hepatic overproduction of VLDL and impaired clearance of apo B-containing remnant particles (*Figure 1*).

The prolonged circulating time of high triglyceride-rich lipoprotein particles allows longer exposure to CETP, which facilitates transfer of cholesterol from LDL and HDL to VLDL and chylomicrons in exchange for triglycerides.<sup>5</sup> The enhanced transfer of triglycerides to LDL renders them better substrates for HL. HL hydrolyzes triglycerides from the core of LDL and turns them into smaller and denser LDL particles. The same holds true for modification of HDL (see below). Small, dense LDL particles and triglyceride-rich lipoproteins readily enter the artery wall and show substantial intimal retention, an important step in the development of atherosclerosis.<sup>27,28</sup> Retained lipoprotein particles may then undergo enzymatic or oxidative modifications.<sup>28</sup> These qualitative changes may increase the atherogenicity of LDL particles in type 2 diabetes.<sup>8,10</sup> Epidemiological studies have shown a relation between small-sized LDL particles and the risk of myocardial infarction in nondiabetic populations.<sup>29,30</sup> In type 2 diabetes, small LDL particles from patients were associated with reduced endothelium-dependent arterial dilation, which is a surrogate marker for cardiovascular risk.<sup>31</sup> It should be noted, however, that prospective studies evaluating the role of small, dense LDL particles in atherogenesis in type 2 diabetes are still

awaited.

An inverse relationship exists between hypertriglyceridemia and the number of small, dense LDL particles.<sup>32,33</sup> Indeed, lowering triglyceride levels in type 2 diabetes using fibrates was shown to increase LDL particle size.<sup>34</sup>

### HDL pathway in type 2 diabetes

The above-described changes in apo B-lipoprotein metabolism in type 2 diabetes strongly affect the HDL pathway and consequently its antiatherogenic potential. In type 2 diabetes, analogous to LDL, triglyceride-enriched HDL is readily modified into small, dense HDL, which has an increased metabolic rate and helps to explain the low HDL concentration. Also, modified HDL in type 2 diabetes has been associated with CHD because its compositional changes may lead to impaired RCT.<sup>35,36</sup> It has been suggested that other abnormalities in the RCT cascade may contribute to the development of CHD in type 2 diabetes. Both increased and decreased CETP activity have been described in type 2 diabetes.<sup>37,38</sup> Although as yet this controversy has not been conclusively settled, population studies indicate that with regard to the development of atherosclerosis, plasma HDL rather than CETP levels may be of more importance.

### Postprandial lipid abnormalities in type 2 diabetes

In healthy subjects, the duration of the postprandial state depends on the composition of the meal: after a meal consisting mainly of carbohydrates, a return to the basal state occurs within 2–3 h, after a mixed meal it takes 3–5 h, and after a fat-rich meal the return to baseline may take as long as 8–10 h.<sup>39</sup> Since most individuals eat intermittently throughout daylight hours, they are postprandial for about 18 h of each 24-h day.<sup>40</sup>

In view of their abnormal lipoprotein profile, type 2 diabetic patients may be regarded as postprandial throughout 24 h. Follow-

ing a fat-enriched meal, the rise in triglyceride-rich lipoprotein concentrations is greater in type 2 diabetic patients than in nondiabetic subjects, and the fasting level of triglyceride-rich lipoproteins is positively correlated with the area under the curve for plasma triglyceride levels after the meal (Figure 2).<sup>41</sup> This postprandial lipemia is due to an impaired suppression of hepatic VLDL synthesis after meals and the competition of chylomicrons and their remnants with endogenous VLDL particles for common removal pathways through LPL (Figure 1). These mechanisms, which are linked to insulin resistance, collectively result in prolonged exposure of arteries to potentially atherogenic triglyceride-enriched particles. Also, postprandial lipid disturbances have been associated with alterations in coagulation mechanisms that predispose them to arterial thrombosis.<sup>42,43</sup> Recent studies have demonstrated impaired endothelium-dependent vasodilation following a fatty meal both in healthy subjects and in type 2 diabetic patients.<sup>44,45</sup> In addition, an association was found between postprandial levels of triglyceride-rich remnants and the severity of

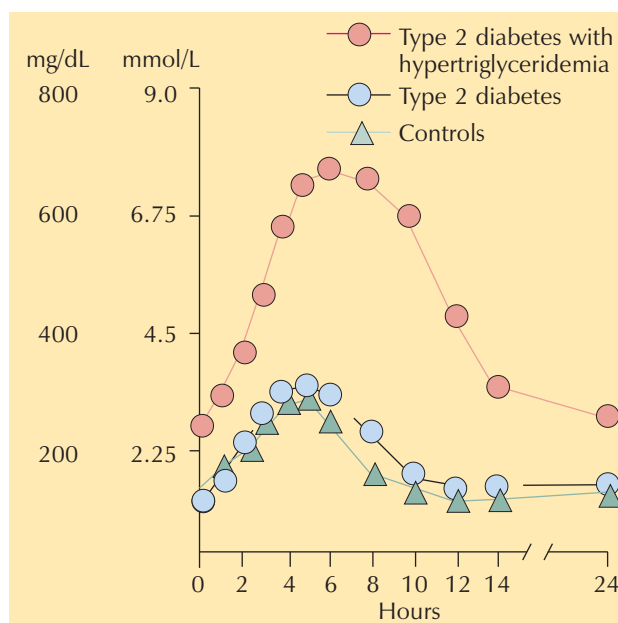


Figure 2. Postprandial changes in triglyceride levels in patients with type 2 diabetes mellitus: relation to fasting triglyceride level. Adapted from ref. 41

coronary artery disease in type 2 diabetic patients.<sup>13</sup> The true atherogenic potential of postprandial dyslipidemia in type 2 diabetes, however, still has to be demonstrated in outcome studies.

**Atherogenicity of diabetic dyslipidemia: the case for non-HDL particles**

There have been frequent attempts to determine which of the dyslipidemic alterations in type 2 diabetes is the most atherogenic, and to assign an independent risk status to changes in the individual lipoproteins.

Based on a large body of evidence, current clinical guidelines have identified LDL as the major atherogenic lipoprotein and the primary target of lipid-lowering therapy.<sup>46</sup> As stated before, patients with type 2 diabetes do not have marked elevations of LDL cholesterol; however, the importance of LDL as a risk factor for CHD in diabetic patients has been demonstrated in subgroup analyses of the major secondary prevention trials, such as the Scandinavian Simvastatin Survival Study, the Cholesterol and Recurrent Events trial, and the Long-term Intervention with Pravastatin in Ischemic Disease trial.<sup>47-49</sup> In all these trials intensive LDL-lowering therapy reduced recurrent CHD events in type 2 diabetic patients.

In view of the close association between the lipoprotein abnormalities in type 2 diabetes, mere estimates of LDL cholesterol levels may underestimate the total atherogenic risk potential associated with the total apo B-containing lipoprotein fractions and low (modified) HDL. And, although no prospective trials have been conducted on the effects of lipid-lowering agents on subsequent CHD specifically in diabetic populations, several prospective studies in type 2 diabetics have convincingly shown a strong association between the different lipoprotein abnormalities and CHD in these patients. Thus, triglyceride levels were positively associated with increased risk for CHD in populations with type 2 diabetes.<sup>50-52</sup> In a 7-year prospective study in type 2 diabetics, low HDL, HDL<sub>2</sub> cholesterol, and high levels of total and VLDL triglycerides and VLDL cholesterol were all found to be powerful risk

indicators for CHD events.<sup>52</sup> In the UKPDS, beside LDL cholesterol, decreased HDL cholesterol was identified as an indicator of CHD.<sup>4</sup>

Thus, it appears that in type 2 diabetes all major lipoprotein abnormalities, including elevated triglyceride-rich lipoproteins, low (modified) HDL cholesterol, and small, dense (modified) LDL particles, constitute the atherogenic phenotype independent of LDL cholesterol levels.<sup>53,54</sup> In patients with type 2 diabetes, all these derangements are present in the fasting and, even more so, in the postprandial state. In view of their atherogenic properties, therapeutic interventions in patients with type 2 diabetes should be aimed at lowering fasting and postprandial levels of triglyceride-rich lipoproteins, also termed non-HDL particles.<sup>53</sup> Table 1 lists the lipoprotein abnormalities in type 2 diabetes and their proposed atherogenic potential, which needs to be confirmed in prospective studies.

At present, several trials are underway that investigate the effects of different lipid-lowering strategies on CHD morbidity and mortality in type 2 diabetic populations or populations containing significant numbers of type 2 diabetic patients. These trials and their potential clinical impact have been reviewed only recently.<sup>55</sup> The results of these trials are awaited with great excitement since they will provide the evidence base for specific recom-

Table 1. Lipoprotein particles in type 2 diabetes and their atherogenic potential.

Lipoprotein particle	Atherogenic potential
<i>Non-HDL cholesterol</i>	
LDL cholesterol	+
– Small, dense LDL	++
– Modified LDL	++
VLDL/IDL triglycerides	++
Postprandial triglyceride-rich remnants	+ / + + (?)
<i>HDL cholesterol</i>	
HDL cholesterol	--
– Modified HDL	+ / (?)

mendations for the place of lipid-modifying therapy in these high-risk patients. ■

### Acknowledgment

The author thanks Robert J. Heine for his helpful comments and criticism of the manuscript.

### REFERENCES

1. Bierman EL. Atherogenesis in diabetes. *Arterioscler Thromb*. 1992;12:647–656.
2. Stamler J, Vaccaro O, Neaton JD, Wenworth D. Diabetes, other risk factors and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care*. 1993;16:434–444.
3. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837–853.
4. Turner RC, Millns H, Neil HAW, et al, for the UK Prospective Diabetes Study Group. Risk factors for coronary artery disease in non-insulin-dependent diabetes mellitus (UKPDS 23) *Br J Med*. 1998;316:823–828.
5. Bagdade JD, Buchanan WE, Kuusi T, Taskinen MR. Persistent abnormalities in lipoprotein composition in non-insulin-dependent diabetes after intensive insulin therapy. *Arteriosclerosis*. 1990;10:232–239.
6. Manzato E, Zambon A, Lapolla A, et al. Lipoprotein abnormalities in well-treated type 2 diabetic patients. *Diabetes Care*. 1993;16:469–475.
7. Taskinen MR. Hyperlipidaemia in diabetes. *Baillière's Clin Endocrinol Metab*. 1990;4:743–776.
8. Syväne M, Taskinen MR. Lipids and lipoproteins as coronary risk factors in non-insulin dependent diabetes mellitus. *Lancet*. 1997;350(suppl 1):20–23.
9. Garg A. Dyslipoproteinemia and diabetes. *Endocrinol Metab Clin North Am*. 1998;27:613–625.
10. Betteridge DJ. Diabetic dyslipidaemias. *Acta Diabetol*. 1999;36:S25–S29.
11. Ebenbichler CF, Kirchmair R, Egger C, Patsch JR. Postprandial state and atherosclerosis. *Curr Opin Lipidol*. 1995;6:286–290.
12. De Man FH, Castro Cabezas M, Van Barlingen HH, Erkelens DW, De Bruin TW. Triglyceride-rich lipoproteins in non-insulin-dependent diabetes mellitus: postprandial metabolism and relation to premature atherosclerosis. *Eur J Clin Invest*. 1996;26:89–108.
13. Mero N, Malmström R, Steiner G, Taskinen MR, Syväne M. Postprandial metabolism of apolipoprotein B-48- and B-100-containing particles in type 2 diabetes mellitus: relations to angiographically verified severity of coronary artery disease. *Atherosclerosis*. 2000;150:167–177.
14. Zilversmit DB. Atherogenesis: a postprandial phenomenon. *Circulation*. 1979;60:473–485.
15. Patsch J, Miesenböck G, Hopferwieser T, et al. Relation of triglyceride metabolism and coronary artery disease: studies in the postprandial state. *Arterioscler Thromb*. 1992;12:1336–1345.
16. Brewer HB Jr, Santamarina-Fojo S, Hoeg JM. Disorders of lipoprotein metabolism. In: DeGroot LJ, Besser M, Jameson JL, et al, eds. *Endocrinology*. Philadelphia, PA: WB Saunders; 1995:2731–2753.
17. Brewer HB Jr. Hypertriglyceridemia: changes in the plasma lipoproteins associated with an increased risk of cardiovascular disease. *Am J Cardiol*. 1999;83:3F–12F.
18. Krieger M, Herz J. Structures and functions of multiligand lipoprotein receptors: macrophage scavenger receptor-related protein (LRP). *Annu Rev Biochem*. 1994;63:601–637.
19. Goldstein JL, Brown MS, Anderson RG, Russell DW, Schneider WJ. Receptor-mediated endocytosis: concepts emerging from the LDL-receptor system. *Annu Rev Cell Biol*. 1985;1:1–39.
20. Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witztum JL. Beyond cholesterol. Modifications of low-density lipoprotein that increase its atherogenicity. *N Engl J Med*. 1989;320:915–924.
21. Glosmet JA. The plasma lecithin:cholesterol acyl transferase reaction. *J Lipid Res*. 1968;9:155–167.
22. Fielding CJ, Fielding PE. Molecular physiology of reverse cholesterol transport. *J Lipid Res*. 1995;36:211–228.
23. Bruce C, Tall AR. Cholesteryl ester transfer proteins, reverse cholesterol transport, and atherosclerosis. *Curr Opin Lipidol*. 1995;6:306–311.
24. Oram JF, Vaughan AM. ABCA1-mediated transport of cellular cholesterol and phospholipids to HDL apolipoproteins. *Curr Opin Lipidol*. 2000;11:253–260.
25. Acton S, Rigotty A, Landschulz KT, Xu S, Hobbs HH, Krieger M. Identification of scavenger receptor SR-B1 as a high density lipoprotein receptor. *Science*. 1996;271:518–520.
26. Malmström R, Packard CJ, Caslake M, et al. Defective regulation of triglyceride metabolism by insulin in the liver in NIDDM. *Diabetologia*. 1997;40:454–462.
27. Mamo J, Proctor S, Smith D. Retention of chylomicron remnants by arterial tissue: importance of an efficient clearance mechanism from plasma. *Atherosclerosis*. 1998;141(suppl 1):S63–S69.
28. Tabas I. Nonoxidative modifications of lipoproteins in atherogenesis. *Annu Rev Nutr*. 1999;19:123–139.
29. Stampfer MJ, Krauss RM, Ma J, et al. A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. *JAMA*. 1996;276:882–889.
30. Lamarche B, Tchernof A, Mauriege P, et al. Fasting insulin and apolipoprotein B levels

- and low-density lipoprotein particle size as risk factors for ischemic heart disease. *JAMA*. 1998;279:1955–1961.
31. Tan KC, Ai VHG, Chow WS, Chau MT, Leong L, Lam KS. Influence of low density lipoprotein (LDL) subfraction profile and LDL oxidation on endothelium-dependent and independent vasodilation in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 1999;84:3212–3216.
  32. Scheffer PG, Bakker SJL, Heine RJ, Teerlink T. Measurement of LDL particle size by high performance gel-filtration chromatography. *Clin Chem*. 1997;43:1904–1912.
  33. Steiner G, Tkác I, Uffelmann KD, Lewis GF. Important contribution of lipoprotein particle number to plasma triglyceride concentration in type 2 diabetes. *Atherosclerosis*. 1998;137:211–214.
  34. Lahdenperä S, Tilly-Kiesi M, Vuorinen-Markkola H, Kuusi T, Taskinen MR. Effects of gemfibrozil on LDL particle size, density distribution and composition in patients with type 2 diabetes. *Diabetes Care*. 1993;16:584–592.
  35. Syväne M, Ahola M, Lahdenperä S, et al. High density lipoprotein subfractions in non-insulin-dependent diabetes mellitus and coronary artery disease. *J Lipid Res*. 1995;36:573–582.
  36. Syväne M, Castro G, Dengremont C, et al. Cholesterol efflux from Fu5AH hepatoma cells induced by plasma of subjects with or without coronary artery disease and non-insulin-dependent diabetes: importance of LpA-I:A-II particles and phospholipid transfer. *Atherosclerosis*. 1996;127:245–253.
  37. Jones RJ, Owens D, Brennan C, Collins PB, Johnson AH, Tomkin GH. Increased esterification of cholesterol and transfer of cholesteryl ester to apoB-containing lipoproteins in type 2 diabetes: relationship to serum lipoproteins A-I and A-II. *Atherosclerosis*. 1996;119:151–157.
  38. Quintão ECR, Medina WL, Passarelli M. Reverse cholesterol transport in diabetes mellitus. *Diabetes Metab Res Rev*. 2000;16:237–250.
  39. Schrezenmeir J, Keppler I, Fenselau S, et al. The phenomenon of a high triglyceride response to an oral lipid load in healthy subjects and its link to the metabolic syndrome. *Ann N Y Acad Sci*. 1993;683:302–314.
  40. Kreisberg R. Diabetic dyslipidemia. *Am J Cardiol*. 1998;82:67U–73U.
  41. Lewis GF, O'Meara NM, Soltys PA, et al. Fasting hypertriglyceridemia in noninsulin-dependent diabetes mellitus is an important predictor of postprandial lipid and lipoprotein abnormalities. *J Clin Endocrinol Metab*. 1991;72:934–944.
  42. Silveira A, Karpe F, Johnsson H, Bauer KA, Hamsten A. In vivo demonstration in humans that large postprandial triglyceride-rich lipoproteins activate coagulation factor VII through the intrinsic coagulation pathway. *Arterioscler Thromb Vasc Biol*. 1996;16:1333–1339.
  43. Georgopoulos A, Bantle JP, Noutsou M, Swaim WR, Parker SJ. Differences in the metabolism of postprandial lipoproteins after a high-monounsaturated-fat versus a high-carbohydrate diet in patients with type 1 diabetes mellitus. *Arterioscler Thromb Vasc Biol*. 1998;18:773–782.
  44. Vogel RA, Corretti MC, Plotnick GD. Effect of a single high-fat meal on endothelial function in healthy subjects. *Am J Cardiol*. 1997;79:350–354.
  45. Shige H, Ishikawa T, Suzukawa M, et al. Endothelium-dependent flow-mediated vasodilation in the postprandial state in type 2 diabetes mellitus. *Am J Cardiol*. 1999;84:1272–1274.
  46. Anonymous. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA*. 1993;269:3015–3023.
  47. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial Investigators. *N Engl J Med*. 1996;335:1001–1009.
  48. The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349–1357.
  49. Haffner SM, Alexander CM, Cook TJ, et al. Reduced coronary events in simvastatin-treated patients with coronary artery disease and diabetes or impaired fasting glucose levels: subgroup analyses in the Scandinavian Simvastatin Survival Study. *Arch Intern Med*. 1999;159:2661–2667.
  50. Fontbonne A, Eschwège E, Cambien F, et al. Hypertriglyceridemia as a risk factor of coronary heart disease mortality in subjects with impaired glucose tolerance or diabetes. *Diabetologia*. 1989;32:300–304.
  51. Lehto S, Rönnema T, Haffner SM, Pyörälä K, Kallio V, Laakso M. Dyslipidemia and hyperglycemia predict coronary heart disease events in middle-aged patients with NIDDM. *Diabetes*. 1997;46:1354–1359.
  52. Laakso M, Lehto S, Penttilä I, Pyörälä K. Lipids and lipoproteins predicting coronary heart disease mortality and morbidity in patients with non-insulin dependent diabetes. *Circulation*. 1993;88:1421–1430.
  53. Garg A. Treatment of diabetic dyslipidemia. *Am J Cardiol*. 1998;81:47B–51B.
  54. Grundy SM. Hypertriglyceridemia, insulin resistance, and the metabolic syndrome. *Am J Cardiol*. 1999;83:25F–29F.
  55. Betteridge DJ, Colhoun H, Armitage J. Status report of lipid-lowering trials in diabetes. *Curr Opin Lipidol*. 2000;11:621–626.

# Antihyperglycemic treatment in Type 2 diabetics with coronary artery disease: facts and questions

Enrique Z. Fisman, Alexander Tenenbaum, Michael Motro  
Cardiac Rehabilitation Institute, Chaim Sheba Medical Center<sup>1</sup>, Tel-Aviv University,  
Tel-Aviv, Israel

Correspondence: Dr Enrique Z. Fisman, Cardiac Rehabilitation Institute, Chaim Sheba Medical Center, 52621 Tel-Hashomer, Israel. Tel: +972 3 5302578, fax: +972 3 5303084, email: (zfisman@yahoo.com)

**As we enter the 21st century our pharmacological armamentarium is increasingly complex, offering a wide array of drugs, both as monotherapy or in combination. It is therefore frequently difficult to determine the best therapeutic option for a given patient. A common problem arises when a drug is known to give a prompt and beneficial effect in the short term, but data regarding long-term outcome are either lacking or insufficient.**

This problem deserves particular attention in type 2 diabetics with coronary artery disease (CAD). Type 2 diabetes accounts for about 90% of the total diabetic population, and CAD is the most common cause of morbidity and mortality. Cardiovascular deaths are increased up to fourfold in diabetics compared with their nondiabetic counterparts.<sup>1</sup> Since these patients will receive antidiabetic therapy indefinitely, any undesirable cardiovascular side effects from well-known and widely used oral antidiabetic drugs should be analyzed in depth. In patients with type 2 diabetes, the University Group Diabetes Program (UGDP) reported in 1970 a higher frequency of major cardiovascular events in patients treated with sulfonylureas.<sup>2</sup> Awareness of this issue has increased during recent years following the detection of harmful influences of sulfonylureas on the ischemic myocardial cell.<sup>3,4</sup> On the other hand, cardiovascular derangement associated with the use of metformin has also been reported during both short-<sup>5,6</sup> and long-term follow-up.<sup>7</sup>

When oral antidiabetic monotherapy does not achieve the glycemic goal, combination treatment is implemented. A sulfonylurea —

usually glibenclamide (known also as glyburide in the USA) — plus metformin constitute the most widely used antihyperglycemic combination in clinical practice.<sup>8</sup> However, the safety of this therapeutic regimen in long-term treatment is questionable.<sup>9</sup> The use of insulin in type 2 diabetes is also controversial. Nonetheless, after 15 or 20 years of disease, the majority of patients receive insulin.<sup>10</sup> The issue whether the adverse cardiovascular effects of each of these medications may be additive and detrimental for the coronary patient is of paramount importance but has not yet been addressed.

This paper aims to review briefly the cardiovascular effects of the most commonly used antidiabetic drugs, in an attempt to improve knowledge and awareness regarding their potential risks when treating patients with CAD.

## Insulin

Insulin is not considered a first-line therapy in type 2 diabetes, except in particular cases such as in women with gestational diabetes (in whom all oral agents are contraindicated) or in patients with markedly elevated fasting glucose levels (>280 mg/dL).<sup>11</sup>

In the setting of coronary diabetes, the possible iatrogenic effects of exogenous insulin have aroused some concern, since hyperinsulinemia has been suspected to be the main culprit behind the excessive cardiovascular morbidity among diabetic patients. Hyperinsulinemia precedes the onset of diabetes and is frequently associated with dyslipidemia, obesity, and hypertension.<sup>12</sup> Moreover, it promotes arterial smooth muscle proliferation and synthesis of connective tissue in the arterial wall. These facts prompt a disturbing question: does insulin decrease cardiovascular complica-

<sup>1</sup> Affiliated to the Sackler Faculty of Medicine.

tions by reducing plasma glucose, or does it facilitate atherogenesis? Most studies of insulin therapy in type 2 diabetes have been performed within an academic framework employing strict research protocols.<sup>11</sup> Among them, the UGDP was a randomized long-term trial comparing cardiovascular outcome in relation to variable doses of insulin therapy. Its final conclusions were that there was no proof that insulin reduced the risk of cardiovascular death, irrespective of dose. Conversely, there was no evidence that higher insulin doses were associated with increased cardiovascular risk.<sup>13</sup> Recent findings from the United Kingdom Diabetes Prospective Study (UKPDS) are consistent with these observations.<sup>14</sup>

## Biguanides

Metformin is the only drug belonging to the biguanide class currently available in most parts of the world. It reduces blood glucose levels through suppression of gluconeogenesis, stimulation of peripheral glucose uptake by tissue (mainly skeletal muscles) in the presence of insulin, and decreased absorption of glucose from the gastrointestinal tract. It has no direct effects on  $\beta$ -cells, does not produce hypoglycemia, reduces glycohemoglobin, may reduce body weight, and improves both blood lipid profile and fibrinolytic activity. In contrast to other antidiabetic medications, metformin does not cause weight gain.

Despite these beneficial effects, metformin presents disadvantages that may influence the cardiovascular system. Gastrointestinal disturbances such as diarrhea are frequent, and the intestinal absorption of group B vitamins and folate is impaired during chronic therapy.<sup>15</sup> This deficiency may lead to increased plasma homocysteine levels which, in turn, accelerate the progression of vascular disease due to adverse effects on platelets, clotting factors, and endothelium.<sup>16</sup> The existence of a graded association between homocysteine levels and overall mortality in patients with CAD is well established.<sup>16</sup>

In addition, metformin may lead to lethal lactic acidosis, especially in patients with clinical conditions that predispose to this compli-

cation, such as heart failure or recent myocardial infarction.<sup>6</sup> It should be remembered that another drug of the biguanide group, phenformin, was withdrawn in many countries during the 1970s due to its link with lactic acidosis. A possible association of phenformin with increased cardiovascular mortality has also been suggested.<sup>17</sup>

Finally, metformin undergoes renal excretion, presenting undesirable pharmacologic interactions with several widely used cardiovascular drugs. The coadministration of nifedipine or furosemide leads to increased metformin plasma levels. Furthermore, digoxin, quinidine, and triamterene — which are eliminated by renal tubular secretion — may interact with metformin by competing for proximal renal tubular transport systems.<sup>18</sup>

Metformin was introduced in the USA in 1995, and serious controversies regarding cardiovascular safety followed its approval for use.<sup>5</sup> We have found increased mortality in CAD patients receiving metformin after a 5-year follow-up.<sup>7</sup> However, it should be stressed that this finding be treated with caution since it arose from a nonrandomized study in which information on drug doses and severity and duration of diabetes was incomplete or unavailable.

## Sulfonylureas

Today, sulfonylureas represent a mainstay of therapy in patients with type 2 diabetes; their hypoglycemic potency is directly related to baseline plasma glucose values.<sup>19</sup> At the cellular level, they exert their action by closing the ATP-dependent potassium channels; this feature is responsible for both the insulinotropic effect and the adverse effects on the heart.<sup>3,4</sup> In this context, it should be stressed that cardiac and vascular sulfonylurea receptors are structurally different from their pancreatic analog.<sup>4</sup> In fact, sulfonylureas have been reported to reduce resting myocardial blood flow,<sup>20</sup> to impair the recovery of contractile function after experimental ischemia,<sup>21</sup> to increase the ultimate infarct size,<sup>22</sup> to elicit proarrhythmic effects,<sup>23</sup> to abolish ischemic preconditioning in animal models,<sup>24</sup> and to

increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction.<sup>25</sup> Prevention of myocardial preconditioning by glibenclamide has also been demonstrated in clinical trials.<sup>26</sup>

It is important to stress that not all the undesirable effects on cardiovascular outcome reported for the first-generation sulfonylureas such as tolbutamide<sup>2</sup> can be automatically extrapolated to the more modern second-generation compounds such as glibenclamide, which is short-acting and possesses antiarrhythmic properties.<sup>3</sup> In our experience, cardiovascular mortality rates in CAD patients on sulfonylureas (mainly glibenclamide) were lower than those on combined sulfonylurea-metformin therapy, and similar to the rates in patients on diet alone.<sup>7</sup> Another second-generation sulfonylurea, glimepiride, is more pancreas-specific and does not show interaction with cardiovascular ATP-dependent potassium channels.<sup>3</sup>

### $\alpha$ -Glucosidase inhibitors

The primary mechanism of action of novel antidiabetic drugs such as acarbose and miglitol is grounded on competitive inhibition of enzymes of the  $\alpha$ -glucosidase group (such as maltase and glucoamylase). Thus, by delaying digestion of carbohydrates, these compounds shift their absorption to more distal parts of the small intestine and colon, and defer gastrointestinal absorption of glucose. Their hypoglycemic potency is less than that of biguanides and sulfonylureas,<sup>11</sup> and, unlike the latter, they do not cause hypoglycemia. The effects of these agents on morbidity and mortality rates for diabetic micro- and macrovascular complications has not been studied.<sup>27</sup>

### Glitazones

This group includes antidiabetic medications such as troglitazone, pioglitazone, and rosiglitazone, the chemical structure and mechanism of action of which are different from those of biguanides and sulfonylureas.

These recently developed drugs are insulin sensitizers, and they bind to a novel receptor called peroxisome proliferator-activated receptor (PPAR)- $\gamma$ , leading to increased glucose transporter expression. Sensitivity to insulin — especially in muscle — is improved, and an additional major effect is the inhibition of hepatic gluconeogenesis.<sup>28</sup> However, troglitazone monotherapy is only modestly effective in reducing glucose and glycohemoglobin levels. Plasma triglycerides are reduced by 10–20%, and HDL cholesterol levels increase by 5–10%, since troglitazone also stimulates the isoform PPAR- $\alpha$  that regulates lipid metabolism. These favorable effects are counterbalanced by a 10–15% increase in LDL cholesterol.<sup>11</sup> Troglitazone was recently withdrawn from clinical use in the US due to hepatotoxicity. Pioglitazone and rosiglitazone, however, do not affect PPAR- $\alpha$ . Edema has been reported in 5% of patients, and these drugs are contraindicated in diabetics with NYHA class III or IV cardiac status.<sup>11</sup>

### Meglitinides

Meglitinides are benzoic acid derivatives that stimulate insulin secretion. The first, repaglinide, was introduced in the USA in 1998. Like sulfonylureas, it works by closing the ATP-dependent potassium channels. However, its mechanism of action seems to be more complex since possibly three repaglinide receptor binding sites have been found on the  $\beta$ -cells.<sup>29</sup> When used as monotherapy, it reduces both fasting plasma glucose and glycohemoglobin, and has no significant effects on lipid profile. The cardiovascular safety of the drug is still uncertain. Increased morbidity, particularly acute ischemic events, was observed after 1 year compared with glibenclamide. Nevertheless, patients on repaglinide appeared to have had more severe CAD

at baseline than those in the glibenclamide group, and when adjustments were made the relative risk declined.<sup>30</sup>

### Combined antihyperglycemic treatment

Combined therapy is based on the premise that pharmacological agents acting via different mechanisms and presenting differing side effects permit the design of individualized antidiabetic regimens. This approach reflects the plausibility that monotherapy with any currently available medication is likely to fail over time in some patients, and this type of pharmacological diabetes management is widely used. Recent findings from the UKPDS showed that after 3 years, approximately 50% of patients could attain satisfactory glucose levels with monotherapy; by 9 years this had declined to only 25%.<sup>31</sup> Long-term problem-oriented prospective studies that focus specifically on the outcome of coronary diabetics on combined therapy are lacking. Data from an observational study performed at our laboratory indicate increased mortality over a 7.7-year follow-up in diabetics with CAD on combined treatment with metformin and glibenclamide.<sup>32</sup> This observation is in keeping with UKPDS reports demonstrating excess risk of all-cause mortality in the whole diabetic population receiving combined therapy, especially in patients in whom metformin was added at an early stage.<sup>9</sup>

### Clinical implications and future directions

Comprehensive risk reduction is mandatory for diabetic patients with CAD. General measures should comprise diet, physical activity, complete cessation of smoking, and weight and lipid profile management. However, fewer than 10% of patients achieve acceptable long-term glycemic values with nonpharmacological therapy only.<sup>33</sup> Special emphasis should be given to blood pressure control; we have recently reported the presence of widespread undiagnosed hypertension in this population,

which presented a 5-year mortality even higher than that in diabetics previously identified as hypertensives.<sup>34</sup> Moreover, the increased mortality associated with hypertension in mild diet-treated type 2 diabetes strongly supports the need for early onset of antihypertensive treatment in these patients.<sup>35</sup>

Evidence is available that long-term maintenance of normal or near-normal glucose levels using pharmacological means is protective in diabetics, improving microvascular disease (retinopathy, nephropathy, and neuropathy) and reducing both morbidity and mortality.<sup>36</sup> Taking into consideration that several degrees of undesirable cardiovascular effects have been reported for most antidiabetic drugs, is this also applicable to coronary diabetics? Current data indicate that the answer is yes, but alleviation of macrovascular complications remains dubious and the therapeutic criteria should not be automatically extrapolated to CAD patients, who need carefully customized treatment.

We believe that an oral antihyperglycemic agent, for example a sulfonylurea, or metformin in obese patients, should constitute first-line pharmacological therapy in type 2 diabetics with CAD; this is in keeping with recent recommendations of the American Heart Association.<sup>37</sup> As second-line therapy, ancillary medications such as  $\alpha$ -glucosidase inhibitors could be added if target glucose levels are not achieved, but glibenclamide and metformin should not be used together. Finally, there is no contraindication to add insulin at a later stage as third-line therapy, provided the risk of hyperinsulinemic hypoalbuminemia — especially when associated with low HDL cholesterol levels — is monitored.<sup>38</sup>

What should the policy be regarding the widely used sulfonylurea-metformin combined treatment? Following approval of a given therapy for a chronic condition, large prospective, randomized, placebo-controlled trials designed to check its long-term safety and effectiveness require many years to be completed, and sometimes such studies are not performed at all. This is the case with this combined treatment in CAD patients. The data available at present indicate increased mortality in patients receiving this ther-

apy,<sup>9,32,39</sup> suggesting that this combination should be used with caution in diabetics with proven CAD. The excessive mortality rate could reflect an additive expression of the adverse cardiovascular effects of each of these medications. However, we would like to stress that our own observations address specifically to the glibenclamide-metformin combined treatment,<sup>32</sup> and we have no information regarding combinations of metformin with other sulfonylureas, such as glimepiride or glizalide. Furthermore, glibenclamide-metformin therapy can be safely used in noncoronary diabetic patients.

Future directions of antidiabetic pharmacological control of coronary patients should focus on both problem-oriented epidemiological studies and molecular biology research. An important area of research would be to investigate more fully the structural and functional differences between pancreatic and cardiac isoforms of ATP-dependent potassium channels. This would allow development of specific insulinotropic compounds that interact exclusively with the pancreatic channel, leaving the cardiac channel unaffected. ■

## REFERENCES

- Wigard DL, Barrett-Connor E. Heart disease and diabetes. In: Harris MI, Cowie CC, Stern MP, Boyko EJ, Reiber GE, Bennett PH, eds. *Diabetes in America*. 2nd ed. Washington, DC: US Government Printing Office; 1995:429–448.
- Klimt CR, Knatterud GL, Meinert CL, Prout TE. The University Group Diabetes Program: a study of the effect of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. I. Design, methods and baseline characteristics. II. Mortality results. *Diabetes*. 1970;19(suppl 2):747–830.
- Smits P, Thien T. Cardiovascular effects of sulphonylurea derivatives. Implication for the treatment of NIDDM? *Diabetologia*. 1995;38:116–121.
- Brady PA, Terzic A. The sulfonylurea controversy: more questions from the heart. *J Am Coll Cardiol*. 1998;31:950–956.
- Innerfield RJ. Metformin-associated mortality in U.S. studies. *N Engl J Med*. 1996;334:1611–1613.
- Misbin RI, Green L, Stadel BV, Gueriguian JL, Gubbi A, Gleming GA. Lactic acidosis in patients with diabetes treated with metformin. *N Engl J Med*. 1998;338:265–266.
- Fisman EZ, Tenenbaum A, Benderly M, Goldbourt U, Behar S, Motro M. Antihyperglycemic treatment in diabetics with coronary disease: increased metformin-associated mortality over a 5-year follow-up. *Cardiology*. 1999;91:195–202.
- Consensus statement. The pharmacological treatment of hyperglycemia in NIDDM. *Diabetes Care*. 1996;19(suppl 1):S54–S61.
- Nathan DM. Some answers, more controversy, from UKPDS. *Lancet*. 1998;352:832–833.
- Fertig BJ, Simmons DA, Martin DB. Therapy for diabetes. In: Harris MI, Cowie CC, Stern MP, Boyko EJ, Reiber GE, Bennett PH, eds. *Diabetes in America*. 2nd ed. Washington, DC: US Government Printing Office; 1995:519–539.
- DeFronzo RA. Pharmacologic therapy for type 2 diabetes. *Ann Intern Med*. 1999;131:281–303.
- Taylor SI, Accili D, Imai Y. Perspectives in diabetes: insulin resistance or insulin deficiency: which is the primary cause of NIDDM? *Diabetes*. 1994;43:735–740.
- University Group Diabetes Program. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. VII. Evaluation of insulin therapy: final report. *Diabetes*. 1982;31(suppl 5):1–78.
- Adler AI, Neil HAW, Manley SE, Holman RR, Turner CT. Hyperglycemia and hyperinsulinemia at diagnosis of diabetes and their association with subsequent cardiovascular disease in the United Kingdom Prospective Diabetes Study (UKPDS 47). *Am Heart J*. 1999;138:S353–S359.
- Adams JF, Clark JS, Ireland JT, Kesson CM, Watson WS. Malabsorption of vitamin B12 and intrinsic factor secretion during biguanide therapy. *Diabetologia*. 1983;24:16–18.
- Mayer EL, Jacobsen DW, Robinson K. Homocysteine and coronary atherosclerosis. *J Am Coll Cardiol*. 1996;27:517–527.
- Goldner MG, Knatterud GL, Prout TE. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. III. Clinical implication of UGDP results. *JAMA*. 1971;218:1400–1410.
- Marchetti P, Navalesi R. Pharmacokinetic-pharmacodynamic relationships of oral hypoglycemic agents: an update. *Clin Pharmacokin*. 1989;16:100–128.
- Rosenstock J, Samols E, Muchmore DB, Schneider J. Glimepiride, a new once-daily sulfonylurea. A double-blind placebo-controlled study of NIDDM patients. Glimepiride Study Group. *Diabetes Care*. 1996;19:1194–1199.
- Duncker DJ, van Zon NS, Altman JD, Pavek DJ, Bache RJ. Role of K<sup>+</sup> ATP channels in coronary vasodilation during exercise. *Circulation*. 1993;88:1245–1253.
- Cole WC, McPherson CD, Sontag D. ATP-regulated K<sup>+</sup> channels protect the myocardium against ischemia/reperfusion damage. *Circ Res*. 1991;69:571–581.

22. Toombs CF, McGee DS, Johnston WE, Vinten-Johansen J. Myocardial protective effects of adenosine. Infarct size reduction with pretreatment and continued receptor stimulation during ischemia. *Circulation*. 1992;86:986–994.
23. Pogatsa G, Koltai ZM, Ballagi-Pordany G. Influence of hypoglycemic sulfonylurea compounds on the incidence of ventricular ectopic beats in non-insulin-dependent diabetic patients treated with digitalis. *Curr Ther Res*. 1993;53:329–339.
24. Grover GJ, Slep PG, Dzwonczwk S. Role of myocardial ATP-sensitive potassium channels in mediating preconditioning in the dog heart and their possible interactions with adenosine A1-receptors. *Circulation*. 1992;86:1310–1316.
25. Garratt KN, Brady PA, Hassinger NL, Grill DE, Terzic A, Holmes DR. Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. *J Am Coll Cardiol*. 1999;33:119–124.
26. Klepzig H, Kober G, Matter C, et al. Sulfonylureas and ischemic preconditioning. A double-blind, placebo-controlled evaluation of glimepiride and glibenclamide. *Eur Heart J*. 1999;20:439–446.
27. Rao SV, Bethel MA, Feinglos MN. Treatment of diabetes mellitus: implications of the use of oral agents. *Am Heart J*. 1999;138:S334–S337.
28. Saltiel AR, Olefsky JM. Thiazolidinediones in the treatment of insulin resistance and type II diabetes. *Diabetes*. 1996;45:1661–1669.
29. Fuhlendorff J, Rorsman P, Kofod H, Brand CL, Rolin B, MacKay P. Stimulation of insulin release by repaglinide and glibenclamide involves both common and distinct processes. *Diabetes*. 1998;47:345–351.
30. Fleming A. FDA approach to the regulation of drugs for diabetes. *Am Heart J*. 1999;138:S339–S345.
31. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin or insulin in patients with type 2 diabetes: progressive requirement for multiple therapies (UKPDS 49). UK Diabetes Prospective Study (UKPDS) Group. *JAMA*. 1999;281:2005–2012.
32. Fisman EZ, Tenenbaum A, Boyko V, et al. Oral antidiabetic treatment in patients with coronary disease: time-related increased mortality on combined glyburide/metformin therapy over a 7.7-year follow-up. *Clin Cardiol*. 2001;24:151–158.
33. Giugliano D. Does treatment of noninsulin-dependent diabetes mellitus reduce the risk of coronary heart disease? *Curr Opin Lipidol*. 1996;7:227–233.
34. Tenenbaum A, Fisman EZ, Boyko V, et al. Prevalence and prognostic significance of unrecognized systemic hypertension in patients with diabetes mellitus and healed myocardial infarction and/or stable angina pectoris. *Am J Cardiol*. 1999;84:294–298.
35. Tenenbaum A, Fisman EZ, Boyko V, et al. Hypertension in diet versus pharmacologically treated diabetics. Mortality over a 5-year follow-up. *Hypertension*. 1999;33:1002–1007.
36. American Association of Clinical Endocrinologists. Medical guidelines for the management of diabetes mellitus: the AACE system of intensive diabetes self-management — 1999 update. *Endocr Pract*. 2000;6:1–44.
37. Grundy SM, Benjamin IJ, Burke GL, et al. Diabetes and cardiovascular disease. A statement for health-care professionals from the American Heart Association. *Circulation*. 1999;100:1134–1146.
38. Saku K, Zhang B, Shirai K, Jimi S, Yoshinaga K, Arakawa K. Hyperinsulinemic hypoalbuminemia as a new indicator for coronary artery disease. *J Am Coll Cardiol*. 1999;31:1443–1451.
39. UK Diabetes Prospective Study (UKPDS) Group. Effect of intensive blood-glucose control on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;352:854–865.

# Imaging of cardiac autonomic function in diabetes mellitus: $^{123}\text{I}$ -metaiodobenzylguanidine with SPECT and $^{11}\text{C}$ -hydroxyephedrine with PET<sup>1</sup>

Michael R. Freeman, Anatoly Langer  
Division of Cardiology, Department of Medicine, St Michael's Hospital,  
University of Toronto, Canada

Correspondence: Dr Michael R. Freeman, St Michael's Hospital, 30 Bond Street, Suite 7-081 Queen, Toronto, Ontario M5B 1W8, Canada. Tel: +1 416 864 5895, fax: +1 416 864 5914, e-mail: freemanm@smh.toronto.on.ca

## Introduction

Patients with diabetes mellitus and autonomic dysfunction have a worse prognosis,<sup>1</sup> including an increase in sudden death,<sup>2,3</sup> than do diabetic patients without autonomic dysfunction. Autonomic neural function has generally been assessed indirectly by standardized bedside maneuvers.<sup>4</sup> However, several investigators using imaging techniques,<sup>5,6</sup> muscle biopsy,<sup>7</sup> or heart rate variability (HRV)<sup>8</sup> have suggested that these maneuvers are insensitive at detecting autonomic dysfunction. Myocardial imaging with  $^{123}\text{I}$ -labeled metaiodobenzylguanidine (MIBG), a norepinephrine analog that shares the same uptake mechanism into sympathetic nerve terminals,<sup>9,10</sup> is a direct, non-invasive, and quantitative assessment of cardiac sympathetic autonomic dysfunction. SPECT imaging is performed with concurrent evaluation of myocardial perfusion by  $^{201}\text{Tl}$  or  $^{99\text{m}}\text{Tc}$ -sestamibi. In addition, newer radiotracers such as  $^{11}\text{C}$ -hydroxyephedrine (HED) have become available to evaluate cardiac sympathetic function with PET. HED is stored in cardiac presynaptic sympathetic nerve terminals and accurately assesses sympathetic innervation.<sup>11</sup>

## Imaging methodology and normal distribution

### *Metaiodobenzylguanidine SPECT*

In the fasting state, patients are injected with 5–8 mCi  $^{123}\text{I}$ -MIBG intravenously for assessment of sympathetic denervation. Imaging is usually performed 5 h after injection. However, early imaging allows for the assessment of washout rates. Increased washout rates are an indication of sympathetic denervation. It is important to correct for perfusion abnormalities<sup>12</sup> with either thallium or sestamibi since initial uptake of MIBG is dependent upon blood flow. We and others<sup>12–14</sup> have previously reported and validated this methodology which corrects MIBG defects for assessment of perfusion by  $^{99\text{m}}\text{Tc}$ -sestamibi or  $^{201}\text{Tl}$  by means of dual tomographic imaging. Visual or quantitative assessment of the images for the presence, location, and severity of MIBG defects is performed to define the presence of abnormal sympathetic innervation. The ratio of lung, liver, or mediastinal uptake to myocardial uptake evaluates the presence or absence of diffuse abnormalities of sympathetic function.

MIBG uptake by SPECT imaging in normal man is not uniform in that there is lower uptake of MIBG at the apex than at the middle two-thirds of the left ventricle.<sup>12</sup> There is also lower uptake at the base and the inferior wall. It is therefore necessary to perform quantitative analysis of MIBG images in comparison with normal limits to evaluate the presence

<sup>1</sup> Supported in part by the Canadian Diabetes Association, Toronto, Canada.

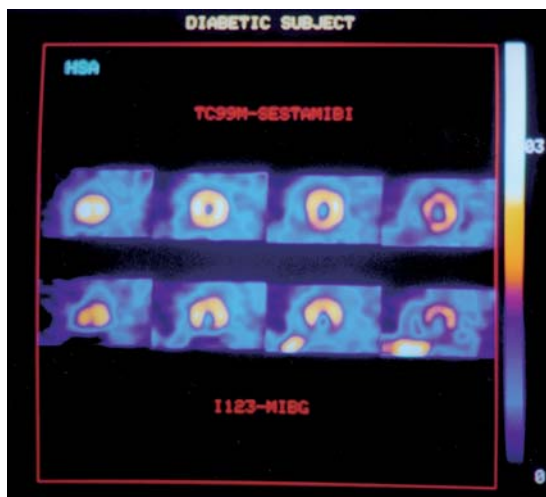


Figure 1A. Representative short axis slices (HSA) of <sup>99m</sup>Tc-sestamibi (normal perfusion) on the top and <sup>123</sup>I-MIBG on the bottom (larger inferior defect).

and extent of sympathetic dysfunction in diabetic subjects. An example of a normal subject and a diabetic patient is shown in Figure 1.

### Hydroxyephedrine PET

Intravenous infusion of 20 mCi <sup>11</sup>C-HED over 1 h is performed with dynamic PET acquisition. Myocardial perfusion is evaluated usually with <sup>13</sup>N-ammonia. Although the uptake of HED was less in the inferior wall (69 ± 7%) than in the lateral wall (82 ± 6%), this difference was not statistically significant, and thus the authors concluded that HED uptake is homogeneous.<sup>15</sup> PET imaging corrects for tissue attenuation and therefore is likely more accurate in evaluating the sympathetic distribution than MIBG SPECT imaging.

### Imaging in diabetes mellitus

MIBG uptake in diabetic patients is reduced at all levels of the left ventricle and in all vascular territories with the exception of the septum. The most prominent defects are seen in the inferior wall.<sup>12-14</sup> Diabetic patients have greater MIBG defects than do normal subjects (13 ± 15% vs. 2 ± 2%, *P* < 0.0001),<sup>12</sup> and have a lower MIBG heart/lung ratio (1.22 ± 0.18 vs. 1.56 ± 0.28, *P* = 0.05). In addition, dia-

betic patients with autonomic dysfunction, as defined by bedside hemodynamic maneuvers, have larger MIBG defects than do those with no autonomic dysfunction.<sup>12-14</sup> In addition to regional abnormalities of MIBG uptake in diabetic patients, there is evidence that this process is more generalized throughout the myocardium. The heart and mediastinal<sup>16</sup> or lung<sup>12</sup> ratios are significantly reduced in diabetic patients.

Most evaluations of MIBG have been performed in type 2 (noninsulin-dependent) diabetic patients but recent studies show that type 1 (insulin-dependent) diabetic patients, even early in their disease, have MIBG abnormalities. Turpeinen et al<sup>14</sup> suggested that type 1 diabetic patients have less severe sympathetic denervation than do type 2 patients. However, even in newly diagnosed insulin-dependent diabetics, inferior and apical MIBG abnormalities are common.<sup>17</sup>

Similarly, HED abnormalities are common in diabetic patients, with a frequency of 40% in diabetics with no clinical evidence of autonomic dysfunction. Almost all diabetic patients with clinical autonomic dysfunction have reduced HED retention and/or marked heterogeneity. The HED studies suggest proximal myocardial hyperinnervation accompanied by distal denervation.<sup>11,15</sup> Interestingly, these abnormalities of autonomic function are associated with altered myocardial blood flow and coronary flow reserve.<sup>15</sup>

### Prognostic value

The presence of MIBG abnormalities may predict a higher cardiac event rate in diabetic patients. Myocardial MIBG uptake is reduced in diabetic patients with stress-induced left ventricular dysfunction.<sup>18</sup> A linear correlation was found between left ventricular ejection fraction during handgrip and MIBG uptake. Thus, the greater the MIBG abnormality, the more depressed was the left ventricular function. Diabetic patients with hypertension have more profound MIBG abnormalities than do normotensive subjects, and the presence of extensive defects predicts higher mortality.<sup>19</sup> Therefore MIBG imaging abnormalities may

predict patients who are at high risk of left ventricular dysfunction, propensity for ventricular arrhythmia, and death.

The presence of concurrent hyperinnervation and denervation, as suggested by HED imaging,<sup>11</sup> is a plausible pathophysiologic link to the excess of sudden death that is evident in the diabetic population. This exaggerated sympathetic imbalance may put these patients at greater risk of ventricular arrhythmias and sudden death.

**Relationship with other indicators of autonomic function**

There is a striking difference in the extent of MIBG uptake abnormalities in diabetics with, compared with those without, autonomic dysfunction as defined by the five reproducible bedside hemodynamic maneuvers commonly performed to assess clinical autonomic function. Autonomic dysfunction is defined as an abnormal response to two of the five hemodynamic tests. After MIBG uptake was corrected for any perfusion abnormalities, patients with

Table 1. Lipoprotein particles in type 2 diabetes and their atherogenic potential.

	Autonomic dysfunction	
	No (n = 15)	Yes (n = 36)
Resting heart rate (bpm)	84 ± 9	85 ± 16
Low frequency	5.89 ± 0.79	5.13 ± 0.97 <sup>a</sup>
High frequency	4.31 ± 0.81	3.98 ± 1.08
Total power	10.2 ± 1.5	9.1 ± 2.0 <sup>b</sup>
Low frequency/high frequency	1.4 ± 0.2	1.3 ± 0.2
SDANN	121 ± 27	102 ± 34 <sup>c</sup>
SD	46 ± 11	37 ± 13 <sup>d</sup>
rMSSD	22 ± 6	22 ± 8
pNN50	4.0 ± 3.0	4.3 ± 4.0

<sup>a</sup>P = 0.0176, <sup>b</sup>P = 0.074, <sup>c</sup>P = 0.064, <sup>d</sup>P = 0.0427.  
 SDANN = the SD of 5-minute mean RR intervals  
 SD = the SD of mean HR



Figure 1B. The polar plots of <sup>99m</sup>Tc-sestamibi (left) and MIBG (right), shown with quantitative analysis below, demonstrating significantly reduced MIBG uptake in the inferior wall (uptake > 2 SD below normal) with normal perfusion.

autonomic dysfunction on quantitative analysis had larger MIBG defects than did those without autonomic dysfunction (17.2 ± 17.0% vs. 3.3 ± 5.2%, P = 0.0001).<sup>12,20</sup> In diabetic patients, MIBG abnormalities were also significantly more frequent than those detected by bedside hemodynamic maneuvers, suggesting superior sensitivity of the former.

The frequency and temporal domain measures of HRV are also commonly performed to evaluate cardiac autonomic function. We<sup>20</sup> and others<sup>21</sup> have shown a relationship between HRV and MIBG abnormalities in diabetic patients. Comparison of HRV measures in diabetic patients with and without abnormal bedside maneuvers is shown in Table 1. The 15 patients without autonomic dysfunction had a significantly smaller lower frequency component and standard deviation (SD) than the 36 patients with autonomic dysfunction. A correlation of MIBG defect size with HRV measurements is shown in Figure 2. A weak but significant inverse relationship was detected between the size of MIBG mismatch and the measure of sympathetic modulation of HRV expressed as the area under the curve of the low frequency band (r = -0.38, P = 0.006) (Figure 2A) and total power (r = -0.37, P = 0.007). Similarly there was a correlation with the area under the high frequency component (r = -0.33, P = 0.02) (Figure 2B).

All of the MIBG and HRV measures present-

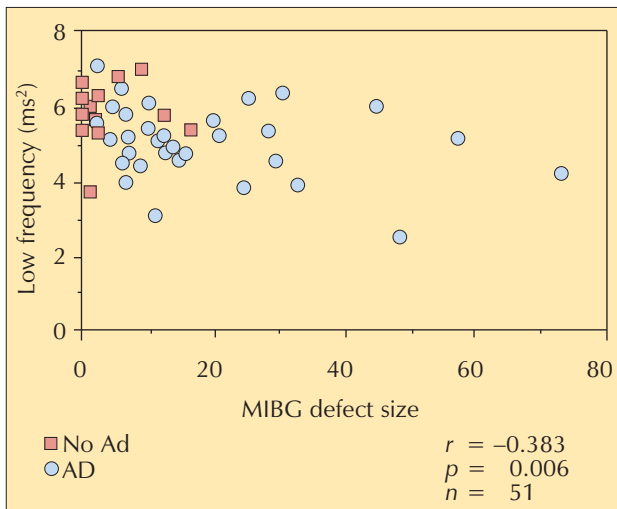


Figure 2A. Relationship between MIBG defect size and the high frequency component of HRV. AD, autonomic dysfunction.

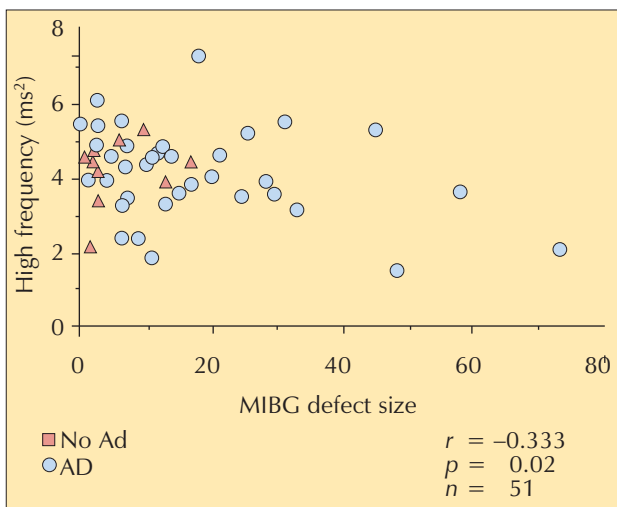


Figure 2B. Relationship between MIBG defect size and the low frequency component of HRV.

ed were assessed for their independent ability to identify autonomic dysfunction using multivariate logistic regression analysis with both forward and backward selection. The only significant variable was the quantitative assessment of MIBG mismatch ( $\chi^2 = 20.2$ ,  $P = 0.0005$ ). Myocardial MIBG uptake predicts autonomic function in patients with diabetes mellitus and is significantly related to indices reflecting sympathetic neural modulation of HRV.

### Therapeutic importance

Since autonomic dysfunction predicts higher mortality in diabetic patients, it is conceivable that improvement of autonomic function may also improve outcome. The impact of therapy on autonomic dysfunction is generally unknown and MIBG imaging may allow the sequential evaluation of autonomic function and thus predict those patients with an improved prognosis. Schnell et al<sup>22</sup> have shown that in long-term diabetic patients, MIBG abnormalities do not change in size or severity over a 3-year period. The same authors using HED have, however, shown that in early diabetes, cardiac autonomic function as assessed by MIBG may improve with aggressive metabolic control.<sup>23</sup> In a single case study treatment of diabetic neuropathy with epalrestat the washout rate and heart/mediastinal ratio of MIBG improved. In insulin-dependent diabetic patients near-normoglycemia prevented the progression of MIBG abnormalities over a 4-year period, whereas poor glycaemic control resulted in significant progression of MIBG abnormalities.<sup>24</sup>

### Conclusions

**SPECT and PET imaging using MIBG and HED are sensitive techniques for the evaluation of autonomic function in patients with diabetes mellitus. Abnormalities of regional uptake and retention are common and are directly related to other measures of autonomic dysfunction. These techniques have potential for assessment of therapeutic interventions in diabetic patients and for the evaluation of prognosis. Early detection of these abnormalities and the ability to evaluate their extent and severity should lead to a more focused therapeutic approach in the management of these patients. ■**

## REFERENCES

- Ewing DJ, Campbell JW, Clarke BF. Assessment of cardiovascular effects in diabetic autonomic neuropathy and prognostic implications. *Ann Intern Med.* 1980;92(part 2):308–311.
- Lloyd-Mostyn RH, Watkins PJ. Defective innervation of heart in diabetic autonomic neuropathy. *BMJ* 1975;3:15–17.
- Garcia-Banal L. Cardiorespiratory arrest in diabetic autonomic neuropathy. *Lancet.* 1978;1:935–936.
- Bennet T, Farquhar JK, Hosking DJ, Hampton JR. Assessment of methods for estimating nervous control of the heart in patients with diabetes mellitus. *Diabetes.* 1978;27:1167–1174.
- Mantysaari M, Kuikka J, Mustonen J, et al. Noninvasive detection of cardiac sympathetic nervous dysfunction in diabetic patients using [<sup>123</sup>I]metaiodobenzylguanidine. *Diabetes.* 1992;41:1069–1075.
- Crooner G, Waltz M, Fasching P, et al. Myocardial m-[<sup>123</sup>I]iodobenzylguanidine scintigraphy for the assessment of adrenergic cardiac innervation in patients with IDDM. Comparison with cardiovascular reflex tests and relationship to left ventricular function. *Diabetes.* 1995;44:543–549.
- Hoffman RP, Sinkey CA, Kienzle MG, Anderson EA. Muscle sympathetic nerve activity is reduced in IDDM before overt autonomic neuropathy. *Diabetes.* 1993;42:375–380.
- Bernardi L, Ricordi L, Lazzari P, et al. Impaired circadian modulation of sympathovagal activity in diabetes. A possible explanation for altered temporal onset of cardiovascular disease. *Circulation.* 1992;86:1443–1452.
- Wieland DM, Brown LE, Rogers L, et al. Myocardial imaging with a radioiodinated norepinephrine storage analog. *J Nucl Med.* 1981;22:22–31.
- Henderson EB, Kahn JK, Corbett JR, et al. Abnormal I<sup>123</sup> metaiodobenzylguanidine myocardial washout and distribution may reflect myocardial adrenergic derangement in patients with congestive cardiomyopathy. *Circulation.* 1988;78:1192–1199.
- Stevens MJ, Raffel DM, Allman KC, et al. Cardiac sympathetic dysinnervation in diabetes: implications for enhanced cardiovascular risk. *Circulation.* 1998;98:961–968.
- Langer A, Freeman MR, Josse RG, Armstrong PW. Metaiodobenzylguanidine imaging in diabetes mellitus. Assessment of cardiac sympathetic denervation and its relation to autonomic dysfunction and silent myocardial ischemia. *J Am Coll Cardiol.* 1995;25:610–618.
- Schnell O, Muhr D, Weiss M, Dresel S, Haslbeck M, Standl E. Reduced myocardial <sup>123</sup>I-metaiodobenzylguanidine uptake in newly diagnosed IDDM patients. *Diabetes.* 1996;45:801–805.
- Turpeinen AK, Vanninen E, Kuikka JT, Uusitupa MI. Demonstration of regional sympathetic denervation of the heart in diabetes. *Diabetes Care.* 1996;19:1083–1090.
- Stevens MJ, Dayanikli F, Raffel DM, et al. Scintigraphic assessment of regionalized defects in myocardial sympathetic innervation and blood flow regulation in diabetic patients with autonomic neuropathy. *J Am Coll Cardiol.* 1998;31:1575–1584.
- Kim SJ, Lee JD, Ryu YH, et al. Evaluation of cardiac sympathetic neuronal integrity in diabetic patients using iodine-123 metaiodobenzylguanidine. *Eur J Nucl Med.* 1996;23:401–406.
- Schnell O, Muhr D, Dresel S, Weiss M, Haslbeck M, Standl E. Partial restoration of scintigraphically assessed cardiac sympathetic denervation in newly diagnosed patients with insulin-dependent (type 1) diabetes mellitus at one-year follow-up. *Diabetic Med.* 1997;14:57–62.
- Scognamiglio R, Avogaro A, Casara D, et al. Myocardial dysfunction and adrenergic cardiac innervation in patients with insulin-dependent diabetes mellitus. *J Am Coll Cardiol.* 1998;31:404–412.
- Tamura K, Utsunomiya K, Nakatani Y, Saika Y, Onishi S, Iwasaka T. Use of iodine-123 metaiodobenzylguanidine scintigraphy to assess cardiac sympathetic denervation and the impact of hypertension in patients with non-insulin-dependent diabetes mellitus. *Eur J Nucl Med.* 1999;26:1310–1316.
- Freeman MR, Newman D, Dorian P, Barr A, Langer A. Relation of direct assessment of cardiac autonomic function with metaiodobenzylguanidine imaging to heart rate variability in diabetes mellitus. *Am J Cardiol.* 1997;80:247–250.
- Murata K, Sumida Y, Murashima S, et al. A novel method for the assessment of autonomic neuropathy in type 2 diabetic patients: a comparative evaluation of <sup>123</sup>I-MIBG myocardial scintigraphy and power spectral analysis of heart rate variability. *Diabetic Med.* 1996;13:266–272.
- Schnell O, Muhr D, Weiss M, et al. Three-year follow-up on scintigraphically assessed cardiac sympathetic denervation in patients with long-term insulin-dependent (type 1) diabetes mellitus. *J Diabetes Complications.* 1997;11:307–313.
- Stevens MJ, Raffel DM, Allman KC, Schwaiger M, Wieland DM. Regression and progression of cardiac sympathetic dysinnervation complicating diabetes: an assessment by C-11 hydroxyephedrine and positron emission tomography. *Metabolism.* 1999;48(1):92–101.
- Utsunomiya K, Narabayashi I, Nakatani Y, Tamura K, Onishi S. I-124 MIBG cardiac imaging in diabetic neuropathy before and after epalrestat therapy. *Clin Nucl Med.* 1999;24:418–420.

# Metabolic treatment of diabetic coronary patients

H. Szwed

Department of Ischemic Heart Disease, National Institute of Cardiology, Warsaw, Poland

Correspondence: Professor H. Szwed, Department of Ischemic Heart Disease, National Institute of Cardiology, Spartanska 1, 02637 Warsaw, Poland (biblnauk@ikard.waw.pl)

## Introduction

Diabetic patients suffer from a high incidence of morbidity and mortality from cardiovascular disorders. The incidence of mortality due to cardiac disease is twofold higher in diabetic men and fourfold higher in diabetic women than in their nondiabetic counterparts.<sup>1</sup> Diabetic patients have a two to three times higher risk of atherosclerosis compared with nondiabetic subjects.<sup>2</sup> Diabetes is an independent risk factor for coronary artery stenosis. Atherosclerosis of the epicardial arteries is more severe in diabetic patients than in the general population.<sup>3</sup> Moreover, in patients with diabetes, coronary artery disease leads to more severe left ventricular dysfunction.<sup>4</sup> In the heart of a diabetic patient several metabolic disturbances may be found. The transport of glucose is impaired<sup>5</sup> and the rate of glycolysis is significantly decreased,<sup>6</sup> resulting in a greater reliance on free fatty acids (FFA) as a source of ATP. The high plasma FFA level and increase of FFA oxidation result in metabolic disorders and impaired left ventricular function during and after ischemia in both the normal and the diabetic heart.<sup>7,8</sup> Consequently, there is a rationale for improving patients' clinical status and contractile function by suppressing FFA oxidation.

Trimetazidine is a metabolic agent with anti-ischemic properties that operates independently of any hemodynamic changes.<sup>9,10</sup> In a recent study it was demonstrated that the antianginal effects of trimetazidine may occur because of an inhibition of long-chain 3-ketoacyl CoA thiolase activity, resulting in inhibition of FFA oxidation and an increase in glucose oxidation, which protects the ischemic heart.<sup>11</sup>

## TRIMPOL-1

The efficacy of trimetazidine in diabetic patients was demonstrated in the TRIMPOL (Trimetazidine in Poland) studies.<sup>12</sup> The TRIMPOL-1 study was carried out at 100 centers in Poland between 1995 and 1997. It comprised an open multicenter trial divided into two phases: a 1-week observation period (visit  $W_{-1}$ – $W_0$ ) to confirm the stability of the patients' angina on existing antianginal monotherapy (with a long-acting nitrate,  $\beta$ -blocker, or calcium antagonist), followed by a 4-week treatment period ( $W_0$ – $W_4$ ), during which patients received trimetazidine 20 mg tid in addition to their existing antianginal therapy.

## Subjects

Subjects were age 18–70 years, with a history of stable, effort-induced angina for at least 3 months, and documented coronary artery disease (either 70% narrowing in at least one coronary artery on coronary angiography, or previous myocardial infarction). They had to have positive treadmill exercise tests during visits  $W_{-1}$  and  $W_0$  and the clinical stability of coronary artery disease confirmed by the difference in time duration (until the appearance of a positive result) of these tests <20%.

Treatment with concomitant antianginal medication (monotherapy with a nitrate,  $\beta$ -blocker, or calcium antagonist) was continued during both the observation and treatment phases of the study. Other therapies routinely used for coronary artery disease like antiplatelets (aspirin, ticlopidine etc), hypolipemic agents as well as therapies for concomitant diseases, were continued during the study. Short-acting nitrates were recommended to relieve anginal pain.

The study population comprised 700

patients. Among them were 50 diabetic patients who were also included in the sub-analysis. Six of these patients had insulin-dependent diabetes and 44 had noninsulin-dependent diabetes. Diabetic patients were treated with insulin ( $n = 6$ ), oral hypoglycemic agents ( $n = 28$ ), or diet ( $n = 16$ ). The patient characteristics at baseline are shown in *Table I*.

**Methods**

Clinical examinations and maximal treadmill exercise tests (Bruce protocol) were performed at the initial assessment ( $W_{-1}$ ), at study baseline ( $W_0$ ), and after a 4-week treatment with trimetazidine ( $W_4$ ). A positive exercise treadmill test was defined by either a horizontal or downward sloping depression in ST-segment

*Table I. Characteristics of diabetic patients (n = 50) with coronary heart disease: a TRIMPOL-1 substudy.*

Characteristic	Patients (n)
Average age (years)	58 ± 7
Weight (according to BMI)	
Normal	14
Overweight	28
Obese	8
Sex	
Male	40
Female	10
Previous MI	
One previous MI	39
Two previous MI	6
Three previous MI	1
Concomitant treatment for coronary artery disease	
Nitrates	25
β-Blockers	17
Calcium antagonists	8
Concomitant disease	
Hypertension	20
Dyslipidemia	11
Cerebrovascular disorder	1
Smoking status	
Never	15
Stopped	30
Current	5

BMI, body mass index; MI, myocardial infarction.

of 1 mm for >80 ms after J-point and anginal

pain, or 1.5 mm ST-segment depression without anginal pain. Laboratory safety assessments were made at  $W_0$  and  $W_4$ . All adverse events, evaluated by investigator questioning and patient information, were recorded. Patients completed a daily diary to report the occurrence of anginal pain and their consumption of interventional short-acting nitrates.

The primary efficacy criteria were: total exercise duration; total work (in MET); time to 1 mm ST-segment depression; and time to onset of anginal pain, evaluated at the exercise treadmill test performed after 4 weeks of therapy with trimetazidine ( $W_4$ ) vs. the study baseline ( $W_0$ ). Secondary assessment criteria were: mean weekly number of angina attacks; mean weekly nitrate consumption; mean Canadian Cardiovascular Society Classification (CCSC) score; and rate-pressure product (heart rate × systolic blood pressure) at peak exercise.

**Results**

After a 4-week treatment with trimetazidine 20 mg tid, coronary diabetic patients showed significant improvements in all exercise stress test parameters (*Table II*). Diabetic patients had an improvement in CCSC score compared with baseline.

Evaluation of the patients' daily diaries showed a significant decrease in the mean number of anginal attacks per week and in weekly nitrate consumption during treatment with trimetazidine. No significant changes in mean rate-pressure product at maximal exercise were noted (*Table II*).

Data were available on 49 patients for the tolerability and safety analysis. Trimetazidine therapy was well tolerated in the diabetic patients, with only 4 of 49 patients (8%) experiencing adverse events. However, no patients withdrew because of adverse events.

Trimetazidine did not produce any clinically significant changes in laboratory parameters, including glycemia. These results were confirmed by both the investigators' and the patients' global evaluation of efficacy (*Table III*).

Table II. Effects of trimetazidine on efficacy parameters in patients with stable angina and diabetes: a TRIMPOL-1 substudy.

Parameter	W <sub>0</sub>	W <sub>4</sub>	P-Value (W <sub>4</sub> vs. W <sub>0</sub> )
Total exercise time <sup>a</sup> (s)	383.2	440.2	<0.01
Total work <sup>a</sup> (MET)	8.67	9.39	<0.01
Time to onset of 1 mm ST-segment depression <sup>a</sup> (s)	301.6	358.3	<0.01
Time to onset of anginal pain <sup>a</sup> (s)	238.3	400.2	<0.01
Grade of anginal pain (CCSC)	1.78	1.39	<0.01
Mean no. of anginal attacks/week	4.79	3.06	<0.01
Mean weekly nitrate consumption (doses)	4.2	2.29	<0.01
Rate-pressure product at maximal exercise (heart rate ∞ systolic blood pressure)	20,827	20,876	ns

<sup>a</sup>Evaluated during an exercise treadmill test.  
ns, Not significant.

### Conclusion

The results of the TRIMPOL-1 study suggest that in diabetic patients with angina pectoris not controlled by conventional antianginal drugs, the addition of the metabolic agent trimetazidine significantly improves exercise stress test parameters and reduces the clinical symptoms of angina pectoris, with excellent tolerability.

Table III. Investigators' and patients' global evaluation of efficacy after 4 weeks of treatment with trimetazidine in diabetic patients with coronary heart disease: a TRIMPOL-1 substudy.

	Investigators	Patients
Excellent	3 (6.1%)	6 (12.2%)
Good	30 (61.2%)	31 (63.3%)
Moderate	12 (24.5%)	11 (22.5%)
Poor or worse	4 (8.2%)	1 (2.0%)

### TRIMPOL-2

The results of the efficacy and safety of trimetazidine in stable angina pectoris were confirmed in the TRIMPOL-2 study. This was a multicenter, double-blind, placebo-controlled study, completed in 1999. The final results of the study were presented at the XII Congress of the European Society of Cardiology in Amsterdam in 2000.<sup>13</sup>

### Methods

The study consisted of two phases: a 1-week open study to confirm the stability of disease on existing monotherapy with metoprolol 50 mg bid, followed by a 12-week, double-blind period during which patients randomly received either metoprolol 50 mg bid + trimetazidine 20 mg tid, or metoprolol 50 mg bid + placebo. The primary and secondary assessment criteria were the same as in the TRIMPOL-1 study (parameters were evaluated before and after 4 and 12 weeks of therapy).

## Patients and results

The data of 347 patients were available for analysis: 179 in the metoprolol-trimetazidine group and 168 in the metoprolol-placebo group.

After 12 weeks of therapy, trimetazidine produced a significant improvement of all exercise and clinical parameters in comparison with placebo.

Of 347 patients in the per protocol population, 25 were diabetic: 14 in the metoprolol-trimetazidine group and 11 in the metoprolol-placebo group. In a subgroup of diabetic patients, improvements in exercise test parameters were observed after 12 weeks of therapy with trimetazidine, but the differences in improvement were not significant in comparison with placebo because of the small sample size. As in the TRIMPOL-1 study, the tolerability of trimetazidine was excellent.

## Summary

**The results of the TRIMPOL studies suggest that trimetazidine is both effective and well tolerated in coronary diabetic patients when combined with conventional antianginal agents such as nitrates,  $\beta$ -blockers, or calcium channel blockers. The TRIMPOL-1 results are novel in that no previous study has investigated the efficacy of trimetazidine in treating angina in diabetic patients. However, these results must be confirmed by a larger, double-blind, randomized study.**

**Such a study is planned to be carried out in Poland, and will be known as the TRIM-DIAB study (the effects of trimetazidine 35 mg bid in combination with metoprolol 50 mg bid treatment in patients with stable effort angina and type 2 diabetes). It will be a 12-week, double blind, placebo-controlled, multicenter, randomized trial, comprising 400 patients. The design of the study and the evaluation criteria will be similar to those of TRIMPOL-2. ■**

## REFERENCES

1. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors and 12-year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care*. 1993;16:434–444.
2. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA*. 1979;241:2035–2038.
3. Henry P, Makowski S, Richard P, et al. Increased incidence of moderate stenosis among patients with diabetes. Substrate for myocardial infarction? *Am Heart J*. 1997;134:1037–1043.
4. Stone PH, Muller JE, Hartwell T, et al. The effect of diabetes mellitus on prognosis and serial left ventricular function after acute myocardial infarction: contribution of both coronary disease and diastolic left ventricular dysfunction to the adverse prognosis. *J Am Coll Cardiol*. 1989;14:49–57.
5. Barrett EJ, Schwartz RG, Francis CK, Zaret BL. Regulation by insulin of myocardial glucose and fatty acid metabolism in the conscious dog. *J Clin Invest*. 1984;74:1073–1079.
6. Gamble J, Lopaschuk GD. Glycolysis and glucose oxidation during reperfusion of ischemic hearts from diabetic rats. *Biochem Biophys Acta*. 1994;1225:191–199.
7. Lopaschuk GD. Abnormal mechanical function in diabetes: relationship to altered myocardial carbohydrate/lipid metabolism. *Coron Artery Dis*. 1996;7:116–123.
8. Oliver MF, Kurien VA, Greenwood TW. Relation between serum-free-fatty-acids and arrhythmias and death after acute myocardial infarction. *Lancet*. 1968;1:710–715.
9. Boddeke E, Hugtenburg J, Jap W, Heynis J, van Zwieten P. New anti-ischaemic drugs: cytoprotective action with no primary haemodynamic effects. *Trends Pharmacol Sci*. 1989;10:379–400.
10. Pornin M, Harpey C, Allal J, Sellier P, Ourbak P. Lack of effects of trimetazidine on systemic hemodynamics in patients with coronary artery disease: a placebo-controlled study. *Clin Trials Meta-Analys*. 1994;29:49–56.
11. Kantor PF, Lucien A, Kozak R, Lopaschuk GD. The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. *Circ Res*. 2000;17:580–588.
12. Szwed H, Sadowski Z, Pachocki R, et al. The anti-ischemic effects and tolerability of trimetazidine in coronary diabetic patients. A substudy from TRIMPOL 1. *Cardiovasc Drugs Ther*. 1999;13:217–222.
13. Szwed H, Sadowski Z, Elikowski W, et al. Efficacy and safety of trimetazidine in combination with metoprolol in patients with stable effort angina pectoris. TRIMPOL II — double-blind, randomised, placebo-controlled, multicentre trial. *Eur Heart J*. 2000;21(suppl 363):1921.

# Acute management of myocardial infarction in a diabetic patient

Ajay Jain, Jonathan Hill  
London Chest Hospital, and St Bartholomew's Hospital, London, UK

Correspondence: Dr Jonathan Hill, London Chest Hospital, London, UK.

A case is presented of a male patient with multiple risk factors for coronary artery disease, including type 2 diabetes. The acute management of myocardial infarction including thrombolysis and intervention is discussed with special reference to management in diabetes. Emphasis is placed on the requirements for precise glycaemic control and the additional metabolic risks of diabetes in acute coronary syndromes.

## Case report

A 58-year-old Asian man presented to our institution within 2 h of spontaneous onset of severe central chest pain. A history of CCS grade 2 angina for several months was described, in addition to type 2 diabetes mellitus, which had been diagnosed at the age of 50. Initial therapy had been with dietary restriction only; however, persistent hyperglycaemia had required the initiation of metformin tablets 6 months after the initial diagnosis. The patient was taking no other medication. Other than a neuropathic diabetic foot ulcer no other complications of diabetes were known to be present. He was also known to have hyperlipidemia, with plasma cholesterol 6.1 mmol/L, but no history of smoking, hypertension, or family history of coronary artery disease.

Initial examination was unrevealing. The ECG obtained in the emergency room revealed planar anterior ST-segment elevation, consistent with acute anterior myocardial infarction. Echocardiogram showed hypokinesia of the anterior wall of the left ventricle, with moderate left ventricular function. Laboratory data showed an elevated creatinine kinase and elevated cardiac troponin I. The blood glucose was 19 mmol/L.

Tissue plasminogen activator was given intravenously according to the standard regi-

men. Intravenous heparin was commenced, and in addition a glucose, insulin, and potassium (GIK) infusion was initiated. Partial resolution of acute ECG changes was seen with resolution of the chest pain. However, 2 h following completion of thrombolysis, severe pain returned, associated with further ST-segment elevation in the anterior chest leads.

Abciximab infusion was commenced and the patient was immediately transferred to the cardiac catheterization laboratory. Coronary angiography revealed a severe proximal stenosis in the left anterior descending coronary artery. Direct stenting was performed using a 3.5 x 18 mm slotted tube stent. TIMI 3 perfusion was restored with no residual stenosis in the LAD. Intravascular ultrasound revealed satisfactory stent deployment.

The patient made an uneventful recovery and was discharged on day 5 post-procedure, free of chest pain; a twice-daily regimen of subcutaneous insulin was commenced to improve his glycaemic control.

## Discussion

Despite the presence of type 2 diabetes and the increased risk of restenosis, acute intervention was the best option to preserve left ventricular function in this case. The use of adjunctive insulin (GIK) to improve outcome in the setting of acute coronary syndromes is well described. These studies have examined both diabetic and nondiabetic populations. However, the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI)<sup>1</sup> trial has investigated the role of GIK therapy in acute myocardial infarction. This trial looked solely at diabetic patients, and showed a significant reduction in mortality in those who were treated with glucose and insulin. A metaanalysis<sup>2</sup> of GIK trials in mainly nondiabetic patients suffering myocar-

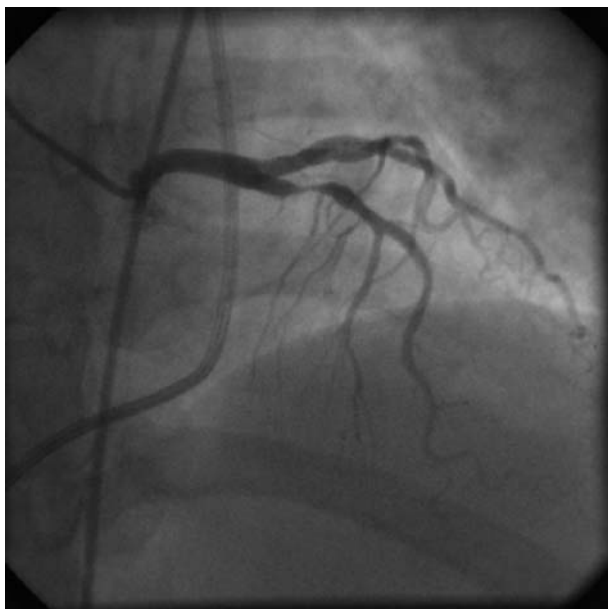


Figure 1. Severe proximal stenosis in left anterior descending artery.

dial infarction (which excluded the DIGAMI study) suggested a mortality reduction of 28% with the use of GIK treatment.

Several mechanisms for this beneficial effect have been offered. Myocardial ischemia has been shown to provoke increased levels of free fatty acids (FFA) via a mechanism mediated by increased sympathetic activity. These FFA lead to increased myocardial oxygen requirements and depression of myocardial contraction.<sup>3,4</sup> Delivery of exogenous glucose has been shown to provide a fuel that is more efficiently utilized than either FFA or glycogen, and is thus more likely to prevent ischemic myocardial injury.<sup>5</sup> Electrical instability and, consequently, ventricular arrhythmias may also be increased via the detrimental effect of FFA on calcium homeostasis and free radical production. Insulin lowers the plasma concentration of FFA by inhibiting lipolysis.

The possible effects of insulin upon coagulation may also play a role in the improved outcome in acute coronary syndromes.<sup>6</sup> Diabetes is associated with coagulation abnormalities including increased platelet activation and aggregation, increased fibrinogen concentration, and increased circulating von Willebrand

factor. Recent reports of the complementary role of GIK and reperfusion therapy are encouraging. Animal models suggest that GIK has the ability to protect ischemic myocardium for 10 h or longer.<sup>7</sup> This potentially may offer a longer period for optimal revascularization. GIK may reduce reperfusion injury after successful revascularization, again via suppression of FFA and limitation of the extent of ischemic myocardial injury. Reperfusion in turn may increase the effectiveness of GIK therapy, since GIK alone can only delay the onset of myocardial necrosis, and restoration of blood flow is required to prevent lactic acidosis and hydrogen ion accumulation.

The BARI (Bypass Angioplasty Revascularization Investigation) and EAST (Emory Angioplasty versus Surgery Trial) trials<sup>8,9</sup> compared multivessel PTCA with multivessel CABG in a mixed population of diabetic and nondiabetic patients. However, subgroup analysis in both studies tended towards a worse long-term outcome for the diabetic compared with the nondiabetic patient. With improvements in stent technology and deployment,<sup>10,11</sup> and the advent of IIb/IIIa platelet inhibitors such as abciximab, the immediate and long-term outcomes for diabetics continue to improve.<sup>12</sup>

## Conclusions

This case illustrates that in addition to conventional revascularization methods, close attention should also be paid to the metabolic consequences of myocardial infarction, especially in patients with diabetes. An understanding of glucose and FFA metabolism, and their interaction with the coagulation cascade, will enhance reperfusion therapy in this high-risk group of patients. ■

## REFERENCES

1. Malmberg K, Ryden L, Efendic S, et al, on behalf of the DIGAMI Study Group. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI): effect on mortality at one year. *J Am Coll Cardiol*. 1995;26:57–65.
2. Fath-Ordoubadi F, Beatt K. Glucose-insulin-potassium therapy for treatment of acute myocardial infarction. *Circulation*. 1997;96:1152–1156.
3. Opie L, Lamp S. Glycolysis preferentially inhibits ATP-sensitive K<sup>+</sup> channels in isolated guinea pig cardiac myocytes. *Science*. 1987;238:67–69.
4. Oliver M, Opie L. Effects of glucose and fatty acids on myocardial ischaemia and arrhythmias. *Lancet*. 1994;343:155–158.
5. Runnman E, Weiss J. Exogenous glucose utilization is superior to glycogenolysis at preserving cardiac function during hypoxia [abstract]. *Circulation*. 1988;78(suppl II):261.
6. Davi G, Catalan I, Aversa M, et al. Thromboxane biosynthesis and platelet function in type 2 diabetes mellitus. *N Engl J Med*. 1990;322:1769–1774.
7. Eberli F, Weinberg E, Grice W, Horowitz G, Apstein C. Protective effect of increased glycolytic substrate against systolic and diastolic dysfunction and increased coronary resistance from prolonged global underperfusion and reperfusion in isolated rabbit hearts perfused with erythrocyte suspensions. *Circ Res*. 1991;68:466–481.
8. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass graft surgery with angioplasty in patients with multivessel disease. *N Engl J Med*. 1996;335:217–225.
9. Weintraub WS, Stein B, Kosinski A, et al. Outcome of coronary bypass surgery versus coronary angioplasty in diabetic patients with multivessel coronary artery disease. *J Am Coll Cardiol*. 1998;31:10–19.
10. Savage M, Fischman D, Slatá P, et al. Coronary intervention in the diabetic patient: improved outcome following stent implantation versus balloon angioplasty. *J Am Coll Cardiol*. 1997;29(suppl A):188A.
11. Thierry J, Fajadet J, Jordan C, et al. Coronary stenting in diabetics: immediate and mid-term clinical outcome. *Catheter Cardiovasc Intervent*. 1999;47:279–284.
12. Lincoff A, Tchong J, Cabot C, et al. Marked benefit in diabetic patients treated with stent and abciximab combination: 6 month outcome of the EPISTENT trial. *J Am Coll Cardiol*. 1999;33(suppl A):82–84.