Contents

Editorial

Metabolic syndrome and its management

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

Correspondence: Gary D. Lopaschuk, 423 Heritage Medical Research Centre, University of Alberta, Edmonton, Canada, T6G 2S2.
Tel: +1 780 492 2170; fax: +1 780 492 9753; e-mail: gary.lopaschuk@ualberta.ca

In broad terms, 'metabolic syndrome' refers to a cluster of atherogenic risk factors that increase the risk of cardiovascular disease. This cluster of factors includes obesity, hypertension, hypertriglyceridemia, low high-density lipoprotein cholesterol concentrations, and hyperglycemia. Despite agreement on the broad definition of metabolic syndrome, the clinical criteria that specifically define the syndrome differ between organizations. These different criteria for definition are discussed in this issue of *Heart and Metabolism*, in articles by Boehm and Scheikofer and by van Zwieten and Visser. Because of the major impact of metabolic syndrome on the risk of developing heart disease and stroke, considerable interest has focused on its treatment. For the most part, recommendations for treatment have focused on modifying the individual components of the syndrome. Specifically, this involves the treatment of hyperglycemia, obesity, hypertension, and dyslipidemia. The article by van Zwieten and Visser provides a concise overview of the drug therapies currently available to treat this syndrome. These pharmacotherapies should be used in conjunction with therapeutic lifestyle modification and preventative measures, to lessen the impact of metabolic syndrome on cardiovascular disease.

Given the major impact that metabolic syndrome has on the risk of cardiovascular disease, a significant research effort is focusing on the effects of the syndrome on organ physiology, and on a better understanding of how patients with the syndrome might be effectively treated clinically. One particularly important area that has received recent research attention has focused on the alterations in fatty acid metabolism that occur in metabolic syndrome. The accumulation of fatty acids within non adipose tissue, such as muscle, can have a number of deleterious consequences on the function of the tissue concerned. Excessive supply of fatty acids to heart and skeletal muscle can lead to the accumulation of fatty acids within these muscles – a condition termed 'lipotoxicity'. The basic science paper by Peura and Schaffer describes how these lipotoxic changes can have an impact on muscle function, including the development of insulin resistance and the development of skeletal and cardiac muscle myopathies. Because abnormalities in lipid metabolism can have a significant impact on heart function, a better understanding of cardiac energy metabolism in metabolic syndrome is desirable. In this issue of *Heart and Metabolism*, the use of positron emission tomography to characterize myocardial metabolism in diabetes, hypertension, and hyperlipidemia is described. This noninvasive approach to imaging cardiac metabolism should not only provide a better understanding of the metabolic changes that occur in the metabolic syndrome, but also be a useful tool to help define novel therapeutic approaches to treatment of the syndrome. One such therapeutic approach may involve the use of trimetazidine, an inhibitor of fatty acid oxidation. A paper in this issue by Fragasso and colleagues provides intriguing evidence, not only that trimetazidine may improve glucose metabolism in diabetic patients, but also that it may improve endothelial cell function. These combined actions suggest a possible use of trimetazidine in the treatment of the hyperglycemic and hypertensive components of metabolic syndrome, although further studies are needed to confirm this.

Metabolic syndrome is a major risk factor for the development of cardiovascular disease. Optimal treatment of the syndrome is therefore essential. Emerging evidence has identified abnormalities in fatty acid metabolism as important contributors to abnormalities of cardiac and skeletal muscle function in metabolic syndrome. Therapeutic management of these abnormalities in fatty acid meta-bolism may present clinicians with one further weapon with which to fight the problem of metabolic syndrome.

Lipotoxicity in cardiac and skeletal muscle

Jennifer L. Peura and Jean E. Schaffer
Center for Cardiovascular Research, Division of Cardiology, Department of Internal Medicine, Washington University School of Medicine, St Louis, Missouri, USA

Correspondence: Jean Schaffer, Box 8086, Washington University School of Medicine, 660 South Euclid Avenue, St Louis, Missouri, 63110, USA.
E-mail: jschaff@wustl.edu

Abstract

Lipotoxicity is defined as the untoward consequences of the accumulation of excess lipid in non-adipose tissue. Fatty acids are an important substrate for myocyte metabolism, yet mismatch of cellular uptake and utilization results in lipid accumulation that is clearly detrimental. Within the myocyte, lipotoxicity can lead to cellular dysfunction, resulting in defective contraction or relaxation or both, alterations in key signaling pathways, and apoptotic cell death. In this review we discuss the significance of myocyte lipotoxicity in human disease and present insights into the pathophysiology gained from transgenic animal models of toxic lipid overload in skeletal and cardiac muscle.
Heart Metab. 2006;30:4–6.

Keywords: Lipotoxicity, cardiomyopathy, myopathy, fatty acids, triglycerides

Skeletal and cardiac muscle have limited capacity for de novo fatty acid synthesis and thus rely on uptake of fatty acids from the circulation, given their high metabolic utilization of this substrate. Free fatty acids (FFAs) can be released from adipose stores and are transported to the heart through the circulation, bound to albumin. Fatty acids are also supplied to the heart and skeletal muscle as chylomicron and very-low-density lipoprotein particles. Local hydrolysis of triglyceride from these particles by lipoprotein lipase* tethered to the endothelium provides FFAs in close proximity to the target tissues that use this metabolic substrate. The findings of recent studies suggest that the latter mechanism accounts for the majority of fatty acids transported to the heart for metabolism [1]. Several proteins have been shown to facilitate the subsequent import of FFA substrates across the plasma membrane of myocytes, and these proteins may serve as molecular targets for regulation of the use of substrate in response to hormonal and metabolic cues [2].

Lipotoxicity in the myocyte occurs in the setting of increased substrate availability or decreased substrate utilization, or both. In humans, disease states associated with pathologic concentrations of serum lipids provide increased substrate to muscle tissues. Increased fasting and postprandial concentrations of FFAs and triglyceride are observed in obesity and metabolic syndrome – highly prevalent disorders characterized by excess adiposity. Dyslipidemia is also a central feature of lipodystrophies in which affected individuals have congenital absence or acquired loss of adipose tissue. High serum concentrations of FFA and triglyceride result from dysregulated adipose tissue function in the case of obesity and the metabolic syndrome, and from lack of appropriate storage depot for these lipids in the case of lipodystrophies. In these disorders, excess FFA is taken up into non-adipose tissues such as the heart and skeletal muscle, resulting in the accumulation of triglyceride. In contrast, congenital defects in fatty acid oxidation are characterized by the inability of target tissues to utilize FFAs. This sets the stage for massive accumulation of unmetabolized substrate in the heart and skeletal muscle – tissues that normally take up this substrate for the generation of ATP.

The accumulation of lipid in skeletal and cardiac muscle may lead to clinical manifestations of muscle dysfunction. First, epidemiological studies have shown that the incidence of heart failure is increased

in obese individuals and in patients with diabetes mellitus [3]. Impaired diastolic function and structural abnormalities are early evidence for cardiomyopathy that can be detected noninvasively in obese and diabetic individuals, using transthoracic echocardiography [4,5]. These may progress over time to result in both diastolic and systolic dysfunction [6]. There have been no systematic studies to examine the contributions of specific metabolic abnormalities in cardiac dysfunction in these disorders, but observations of cardiac accumulation of triglyceride [7] and cardiomyocyte apoptosis in pathological specimens [8] suggest a causal link. Secondly, individuals with inborn errors in fatty acid oxidation have intracellular accumulation of lipids in cardiac and skeletal muscle, and are known to develop skeletal myopathy, heart failure, and arrhythmic sudden cardiac death [9,10]. Thirdly, obese diabetic and prediabetic individuals, in addition to those with lipodystrophy, have intramyocellular triglyceride accumulation that is associated with insulin resistance [11].

Animal models of obesity and diabetes provide insights into mechanisms of the toxic consequences of lipid overload. Perhaps the best characterized with respect to lipotoxicity in muscle, are Zucker Diabetic Fatty rats, which have genetic unresponsiveness to leptin*, leading to increased serum lipid concentrations, morbid obesity, and diabetes [12]. On a standard diet, these rodents have increased cardiac uptake and esterification of FFA, decreased fatty acid oxidation, and evidence of cardiomyocyte apoptosis and fibrosis [13]. These biochemical and histological changes are associated with impaired contractility and relaxation, consistent with endstage cardiomyopathy. Another leptin-resistant model that has been extensively characterized is the obese diabetic db/db mouse*, in which an early phase of increased fatty acid oxidation precedes the development of contractile dysfunction [14,15]. In a third leptin-unresponsive model, the ob/ob mouse*, the accumulation of lipid is accompanied by diastolic dysfunction [16]. Together, these models provide experimental systems in which a number of groups have effectively examined changes in cardiac metabolism, structure, and function that accompany extreme obesity, insulin resistance and diabetes.

Transgenic models with tissue-restricted increases in lipid uptake, in the absence of systemic metabolic disturbances, have provided independent evidence for a central role of altered lipid homeostasis in the genesis of myopathy. In mice with skeletal muscle overexpression of lipoprotein lipase, increased tissue uptake of FFAs leads to myofibrillar degeneration, mitochondrial and peroxisome proliferation, and insulin resistance [17,18]. The findings of a number of animal studies suggest that accumulation of fatty acid metabolites (eg, triglycerides, diacylglycerols, acyl coenzyme As [CoA]) activates a serine/threonine kinase* cascade that phosphorylates insulin receptor substrates in such a way that they fail to activate glucose transport in response to insulin [19]. Mice with cardiac overexpression of long-chain acyl CoA synthetase (MHC-ACS)*, peroxisome proliferator activated receptor alpha (MHC-PPARα)* or a glycophosphatidylinositol-linked lipoprotein lipase* (hLpL^{GPI}) also demonstrate increased cardiac uptake of FFA substrates. Each of these models develops dilated cardiomyopathy characterized by systolic dysfunction with accompanying diastolic dysfunction [20–22]. Different lipid species accumulate in the different models (triglyceride in the cases of MHC-ACS and MHC-PPARα, compared with cholesterol in hLpL^{GPI}), but several show evidence of oxidative stress [23,26], suggesting a common lipid stress response pathway. Apoptosis is observed in MHC-ACS and hLpL^{GPI} hearts, consistent with the inexorable progression of heart failure in these models. A fourth transgenic model with cardiac restricted overexpression of the fatty acid transport protein 1 (MHC-FATP1) demonstrates a contrasting phenotype. In this model, increased uptake and metabolism of FFAs lead to diastolic dysfunction and electrophysiological disturbances [24]. These models represent the spectrum of cardiac dysfunction in obesity and diabetes, and they serve as powerful tools with which to study the lipotoxic events that contribute to early (primarily diastolic) and late (both diastolic and systolic) lipotoxic cardiomyopathy.

These transgenic models have also been used to evaluate novel therapeutic approaches to cardiac lipotoxicity. Treatment of the obese Zucker Diabetic Fatty rats with troglitazone was found to reduce cardiac triglyceride, and to prevent apoptosis and loss of function [12]. In the MHC-PPARα model, myocyte lipotoxicity was observed when mice were fed a normal diet, was exacerbated by a diet enriched in long-chain triglycerides, and was improved by a diet enriched in medium-chain triglycerides. Reversibility of the phenotype in these mice is consistent with the lack of evidence for cardiomyocyte cell death [23]. Treatment of MHC-ACS mice with an adenovirus encoding the hormone leptin effected a marked improvement in cardiac triglyceride accumulation and function [25]. These three examples suggest that measures which divert lipid to adipose stores, decrease overall serum lipid concentrations, or increase myocyte β-oxidation will be beneficial in lipotoxic myopathies in humans.

Summary

Human patients with disease states associated with pathologic concentrations of serum lipids suffer from

myocyte dysfunction, cardiomyopathy, and early cardiovascular death. The findings from studies in transgenic and genetic animal models suggest that changes in cardiac lipid metabolism underlie the changes in heart structure and function that accompany extreme obesity, insulin resistance, and diabetes. Evidence of oxidative stress and apoptotic cell death suggests a common metabolic stress pathway. Continued investigation may lead to novel therapeutic targets that could significantly reduce the morbidity and mortality associated with obesity and diabetes.

Acknowledgment

This work was supported by a grant from the NIH (DK064989 to J.E.S.). ■

* See glossary for definition of these terms.

REFERENCES

1. Augustus AS, Kako Y, Yagyu H, Goldberg IJ. Routes of FA delivery to cardiac muscle: modulation of lipoprotein lipolysis alters uptake of TG-derived FA. *Am J Physiol Endocrinol Metab*. 2003;284:E331–E339.
2. Schaffer JE. Fatty acid transport: the roads taken. *Am J Physiol Endocrinol Metab*. 2002;282:E239–E246.
3. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. *N Engl J Med*. 2002;347:305–313.
4. Perez JE, McGill JB, Santiago JV, et al. Abnormal myocardial acoustic properties in diabetic patients and their correlation with the severity of disease. *J Am Coll Cardiol*. 1992;19:1154–1162.
5. Boyer JK, Thanigaraj S, Schechtman KB, Perez JE. Prevalence of ventricular diastolic dysfunction in asymptomatic, normotensive patients with diabetes mellitus. *Am J Cardiol*. 2004;93:870–875.
6. Zarich SW, Nesto RW. Diabetic cardiomyopathy. *Am Heart J*. 1989;118:1000–1012.
7. Alavaikko M, Elfving R, Hirvonen J, Jarvi J. Triglycerides, cholesterol, and phospholipids in normal heart papillary muscle and in patients suffering from diabetes, cholelithiasis, hypertension, and coronary atheroma. *J Clin Pathol*. 1973;26:285–293.
8. Frustaci A, Kajstura J, Chimenti C, et al. Myocardial cell death in human diabetes. *Circ Res*. 2000;87:1123–1132.
9. Galloway JH, Cartwright IJ, Bennett MJ. Abnormal myocardial lipid composition in an infant with type II glutaric aciduria. *J Lipid Res*. 1987;28:279–284.
10. Kelly DP, Strauss AW. Inherited cardiomyopathies. *N Engl J Med*. 1994;330:913–919.
11. Shulman GI. Unraveling the cellular mechanism of insulin resistance in humans: new insights from magnetic resonance spectroscopy. *Physiology (Bethesda)*. 2004;19:183–190.
12. Zhou YT, Grayburn P, Karim A, et al. Lipotoxic heart disease in obese rats: implications for human obesity. *Proc Natl Acad Sci U S A*. 2000;97:1784–1789.
13. Young ME, Guthrie PH, Razeghi P, et al. Impaired long-chain fatty acid oxidation and contractile dysfunction in the obese Zucker rat heart. *Diabetes*. 2002;51:2587–2595.
14. Aasum E, Belke DD, Severson DL, et al. Cardiac function and metabolism in Type 2 diabetic mice after treatment with BM 17.0744, a novel PPAR-alpha activator. *Am J Physiol Heart Circ Physiol*. 2002;283:H949–H957.
15. Belke DD, Larsen TS, Gibbs EM, Severson DL. Altered metabolism causes cardiac dysfunction in perfused hearts from diabetic (db/db) mice. *Am J Physiol Endocrinol Metab*. 2000;279:E1104–E1113.
16. Christoffersen C, Bollano E, Lindegaard ML, et al. Cardiac lipid accumulation associated with diastolic dysfunction in obese mice. *Endocrinology*. 2003;144:3483–3490.
17. Levak-Frank S, Radner H, Walsh A, et al. Muscle-specific overexpression of lipoprotein lipase causes a severe myopathy characterized by proliferation of mitochondria and peroxisomes in transgenic mice. *J Clin Invest*. 1995;96:976–986.
18. Kim JK, Fillmore JJ, Chen Y, et al. Tissue-specific overexpression of lipoprotein lipase causes tissue-specific insulin resistance. *Proc Natl Acad Sci U S A*. 2001;98:7522–7527.
19. Shulman GI. Cellular mechanisms of insulin resistance. *J Clin Invest*. 2000;106:171–176.
20. Chiu HC, Kovacs A, Ford DA, et al. A novel mouse model of lipotoxic cardiomyopathy. *J Clin Invest*. 2001;107:813–822.
21. Finck BN, Lehman JJ, Leone TC, et al. The cardiac phenotype induced by PPARalpha overexpression mimics that caused by diabetes mellitus. *J Clin Invest*. 2002;109:121–130.
22. Yagyu H, Chen G, Yokoyama M, et al. Lipoprotein lipase (LpL) on the surface of cardiomyocytes increases lipid uptake and produces a cardiomyopathy. *J Clin Invest*. 2003;111:419–426.
23. Finck BN, Han X, Courtois M, et al. A critical role for PPARalpha-mediated lipotoxicity in the pathogenesis of diabetic cardiomyopathy: modulation by dietary fat content. *Proc Natl Acad Sci U S A*. 2003;100:1226–1231.
24. Chiu HC, Kovacs A, Blanton RM, et al. Transgenic expression of fatty acid transport protein 1 in the heart causes lipotoxic cardiomyopathy. *Circ Res*. 2005;96:225–233.
25. Lee Y, Naseem RH, Duplomb L, et al. Hyperleptinemia prevents lipotoxic cardiomyopathy in acyl CoA synthase transgenic mice. *Proc Natl Acad Sci U S A*. 2004;101:13624–13629.
26. Borradaile NM, Buhman KK, Listenberger LL, et al. A critical role for eukaryotic elongation factor 1 A-1 in lipotoxic cell death. Mol Biol Cell 2006. In press.

The metabolic syndrome

Bernhard O. Boehm and Stephan Schiekofer
Division of Endocrinology and Diabetes, Ulm University, Ulm, Germany

Correspondence: Professor Bernhard O. Boehm, Division of Endocrinology and Diabetes, Ulm University, Robert-Koch-Str 8, 89070 Ulm/Donau, Germany.
Tel: +49-731-500-24304; fax: +49-731-500-23938; e-mail: bernhard.boehm@medizin.uni-ulm.de

Abstract

The metabolic syndrome is characterized by the cooccurrence of central obesity, dyslipidemia, altered glucose concentrations, and hypertension. Very recently, the International Diabetes Federation has published a consensus worldwide definition of the metabolic syndrome. However, as yet, no consensus exists for specific thresholds for establishing the diagnosis. The individual traits of the syndrome cluster together to a notably greater degree than expected by chance alone – a fact that lends substantial support to the idea of a common set of mechanisms with pleiotropic effects leading to the metabolic syndrome. Lifestyle modification is currently the preferred universal treatment option of the metabolic syndrome. In addition, treatment of modifiable risk factors of the syndrome should be addressed specifically.
■ *Heart Metab.* 2006;30:7–10.

Keywords: Diabetes, hyperglycemia, dyslipidemia, pleiotropic effects, lifestyle modification, metabolic syndrome

Introduction

The metabolic syndrome is characterized by the co-occurrence of central obesity, dyslipidemia (which is typically defined by high concentrations of triglycerides and low concentrations of high-density lipoprotein cholesterol, dysglycemia or hyperglycemia or both according to standard diabetes criteria), and hypertension [1–4].

The syndrome is a highly prevalent multifaceted clinical entity. Various prospective epidemiological studies across several populations have shown that the metabolic syndrome is a dynamic phenotype featuring a continuum of metabolic derangements. As yet, no consensus exists for specific thresholds for establishing the diagnosis of each of these traits as components of the syndrome.

The individual traits of the metabolic syndrome cluster together to a notably greater degree than expected by chance alone – a fact that also lends substantial support to the existence of a discrete disorder [5–9].

Current definition of the metabolic syndrome

Current definitions of the metabolic syndrome take into account two major outcomes, cardiovascular disease and type 2 diabetes, thereby perceiving the metabolic syndrome as 'prediabetes'. *Tables I–III* summarize the current definitions, including a very recent consensus statement provided by the International Diabetes Federation (IDF) [1–4].

Prevalence of the metabolic syndrome

Because of the lack of standardized criteria for recognizing the metabolic syndrome, a comparison of published prevalences for different populations is rather difficult. Nevertheless, despite differences in the criteria used, certain inferences can be made: prevalence of the metabolic syndrome is highly age-dependent (USA National Health and Nutrition Examination Survey [NHANES III]) [10]. The Framingham Offspring Study also revealed that the metabolic risk factors worsen continuously across the spectrum

Table I. National Cholesterol Education Program–Third Adult Treatment Panel III 2001 definition of the metabolic syndrome. (Adapted from [1]).

3 or more of the following 5 risk factors:		
Central obesity		Waist circumference:
	Men	> 102 cm (> 40 inches)
	Women	> 88 cm (> 35 inches)
Hypertriglyceridemia		Triglycerides: ≥ 1.7 mmol/L (≥ 150 mg/dL)
Low HDL cholesterol concentration	Men	< 1.0 mmol/L (< 40 mg/dL)
	Women	< 1.3 mmol/L (< 50 mg/dL)
Hypertension		Blood pressure: ≥ 130/85 mm Hg, *or* medication, *or* both
Fasting plasma glucose		≥ 6.1 mmol/L (> 110 mg/dL)

LDL, low-density lipoprotein.

of nondiabetic glucose tolerance, suggesting a continuous risk [11,12]. Using the Adult Treatment Panel III criteria, prevalence of the metabolic syndrome in Germany was also found to be age-dependent, and dependent on social status [13].

Treatment

Once a diagnosis of the metabolic syndrome is made, the management of the condition should be 'aggressive' in its aim to reduce the risk of both cardiovascular disease (CVD) and type 2 diabetes. Patients should undergo a full cardiovascular risk assessment that includes smoking status [3–5]. Lifestyle intervention includes a healthy diet – which means eating plenty of fruit and vegetables, lean cuts of white meat or fish rather than red meat, and avoidance of processed or deep-fried dinners. Items rich in dietary fiber, such as whole grains, beans, fruit and vegetables, which can decrease (pro)insulin concentrations, should also be used. Physical activity should be implemented with at least 30 min of moderately strenuous activity most days of the week. This intervention should be accompanied by regular checks of modifiable risks such as blood pressure, cholesterol and blood sugar concentrations. For primary intervention, the IDF recommends promotion of a healthy lifestyle, including moderate calorie restriction (to achieve a 5–10% loss of body weight in the first year), an increase in physical activity (5 × 30 min of moderate activity per week), and a change in dietary composition. Both a Finnish and an American (Diabetes Prevention Program) diabetes prevention study revealed that lifestyle modification will at least prevent the conversion to type 2 diabetes among high-risk individuals with glucose intolerance who were, generally, obese [14–16]. In addition, in people for whom lifestyle change is not enough and who are considered to be at high risk for CVD, secondary intervention with drug therapy may be suggested. However, pharmacotherapy that can modulate the underlying mechanisms of the metabolic syndrome as a whole and thereby reduce the impact of all the risk factors and the long-term metabolic and cardiovascular consequences is currently not available. Therefore, it is necessary to treat the individual components of the metabolic syndrome, in order that a reduction in the individual risk associated with each one will reduce the overall impact on CVD and diabetes risk [4].

Current controversies

The existing guidelines from the World Health Organization (WHO) and National Cholesterol Education

Table II. World Health Organization clinical criteria for the metabolic syndrome, 1999. (Adapted from [3]).

In order to make a diagnosis of the metabolic syndrome, a patient must present with glucose intolerance, impaired glucose tolerance or diabetes, or insulin resistance, or both, together with two or more of the following components:		
Obesity		BMI: > 30 kg/m^2 *or* Waist to hip ratio:
	Men	> 0.9
	Women	> 0.85
Dyslipidemia		Triglycerides: ≥ 1.7 mmol/L (≥ 150 mg/dL) *or* HDL cholesterol:
	Men	< 1.0 mmol/L(< 40 mg/dL)
	Women	< 1.3 mmol/L (< 50 mg/dL)
Hypertension		Blood pressure: > 140/90 mm Hg, *or* medication, *or* both
Microalbuminuria		Albumin excretion: ≥ 20 μg/min, *or* Albumin : creatinine ratio: ≥ 30 mg/g

BMI, body mass index; HDL, high-density lipoprotein.

Table III. The new International Diabetes Federation (IDF) definition, 2005. (Adapted from [4]).

According to the new IDF definition, for a person to be defined as having the metabolic syndrome they must have:		
Central obesity (defined as waist circumference ≥ 94 cm for Europid men and ≥ 80 cm for Europid women, with ethnicity-specific values* for other groups)		
Plus any two of the following four factors:		
Increased triglyceride concentration		≥ 150 mg/dL (1.7 mmol/L), *or* Specific treatment for this lipid abnormality
Reduced HDL cholesterol	Men	< 40 mg/dL (1.03 mmol/L†)
	Women	< 50 mg/dL (1.29 mmol/L†), *or* Specific treatment for this lipid abnormality
Increased blood pressure		SBP ≥ 130 mm Hg or DBP ≥ 85 mm Hg, *or* Treatment of previously diagnosed hypertension
Increased FPG		≥ 100 mg/dL (5.6 mmol/L), *or* Previously diagnosed type 2 diabetes. If FPG is > 5.6 mmol/L or > 100 mg/dL, an OGTT is strongly recommended, but is not necessary to define presence of the syndrome

*Central obesity is most easily measured by waist circumference; values that are specific for sex and ethnic group (not country of residence) should be used. The IDF consensus group acknowledged that the following are pragmatic cutoff points taken from various different data sources and that better data will be needed to link them to risk:
Europids: ≥ 94 cm (men); ≥ 80 cm (women).
USA: The Adult Treatment Panel (ATP) III values are likely to continue to be used for clinical purposes: 102 cm (men); 88 cm (women).
South Asians, based on a Chinese, Malay and Asian-Indian population: ≥ 90 cm (men); ≥ 80 cm (women).
Chinese: ≥ 90 cm (men), ≥ 80 cm (women).
Japanese: ≥ 85 cm (men), ≥ 90 cm (women).
Ethnic South and Central Americans: Use South Asian recommendations until more specific data are available.
Sub-Saharan Africans: Use European data until more specific data are available.
Eastern Mediterranean and Middle East (Arab) populations: Use European data until more specific data are available.

†These values have been updated from those originally presented, to ensure consistency with ATP III cutoff points.
DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; OGTT, oral glucose tolerance test; SBP, systolic blood pressure.

Program–Third Adult Treatment Panel (NCEP–ATP III) did not provide exact diagnostic criteria for identifying individuals with metabolic syndrome [1–3]. However, there is a strong need for a single, universally accepted diagnostic tool that may allow direct comparisons of the prevalences of the metabolic syndrome and may also make it possible to monitor the efficacy of any therapeutic intervention [4]. An additional difficulty is that no consensus exists for specific thresholds for establishing the diagnosis of each of these traits as components of the syndrome.

A unifying pathophysiological concept of the syndrome is also lacking. It has long been believed that insulin resistance may provide the unifying hypothesis, but current evidence has been questioned in a joint statement by the American Diabetes Association and the European Diabetes Association [17,18]. Even though most people who have the metabolic syndrome are insulin resistant, this is most probably attributable to the fact that almost all people with an increased blood glucose value are insulin resistant. Conversely, many studies have shown that only a minority of nondiabetic individuals with insulin resistance will suffer from the metabolic syndrome.

The value of including diabetes in the definition of the metabolic syndrome has been questioned in view of the lack of a clear rationale for including/excluding various CVD risk factors. Most importantly, the overall CVD risk value is variable and dependent on the specific individual risk factors present.

The syndrome is managed by treating each of its components. Provided that classical risk profiling has been performed, the medical value of diagnosing the syndrome is unclear.

Further points have been raised. (i) It remains unclear how the syndrome is best defined. (ii) Are all risk factors equally important, if combinations of risk factors portend greater CVD risk than others? (iii) A definition of the metabolic syndrome in which variables have defined lower and upper cutoff points or that uses continuous variables in a multivariate score system (eg, Framingham/UK Prospective Diabetes Study risk engine) requires more detailed study [17,19–21].

Perspective – the search for a unifying concept

The idea that a common set of factors with several diverse effects might influence obesity, type 2 diabetes, and related traits such as sensitivity to the effects of insulin, is not novel [5,7]. New data may provide further evidence of a common molecular link between insulin resistance, obesity, and type 2 diabetes. Very recently, the gene *ENPP1* (which encodes ectonucleotide pyrophosphatase/phosphodiesterase 1*, also known as plasma cell membrane glycoprotein PC-1) was shown to mediate some of the effects of the hormone insulin on glucose metabolism while simultaneously being associated with obesity and type 2

diabetes. This observation supports the idea that a common molecular mechanism underlies features of the body's response to the effects of the hormone insulin, in addition to the predisposition to develop obesity and type 2 diabetes [22]. These findings also suggest that several variants of *ENPP1* may have a primary role in mediating insulin resistance and in the development of both obesity and type 2 diabetes, implying that an underlying molecular mechanism is common to both conditions.

The AMP-activated protein kinase (AMPK) pathway* is an evolutionarily conserved sensor of cellular energy status that plays a critical role in systemic energy balance. Complex signaling networks suggested that AMPK may prevent insulin resistance, in part by inhibiting pathways that antagonize insulin signaling. Through signaling, metabolic, and gene expression effects, AMPK enhances insulin sensitivity and fosters a metabolic milieu that may reduce the risk for obesity and type 2 diabetes [23]. It was recently shown that metformin, one of the drugs most widely prescribed for type 2 diabetes therapy, requires leukotriene B_1* and subsequent AMPK activation in the liver in order to decrease blood glucose concentrations [24].

Conclusion

The metabolic syndrome is a multifaceted clinical entity resulting from the interaction of genetic, hormonal, and lifestyle factors. Over the past two decades, the number of people diagnosed with the syndrome has steadily increased. A better understanding of the underlying molecular pathophysiology should lead to novel preventive strategies. A research agenda to identify the underlying cause(s) is recommended [4,13,19,25].

Universally speaking, the metabolic syndrome is a huge clinical problem and is one that is growing at an alarming rate. The new IDF criteria provide a robust framework for making the diagnosis of the syndrome and for implementing lifestyle changes, at least, in the individuals diagnosed. The opportunity should not be missed, in view of this worldwide epidemic. ■

* See glossary for definition of these terms.

REFERENCES

1. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
2. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus: provisional report of a WHO consultation. *Diabet Med*. 1998;15:539–553.
3. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO Consultation. Part 1: Diagnosis and classification of diabetes mellitus. Geneva, Switzerland: World Health Organization, 1999. Available from: http://whqlibdoc.who.int/hq/1999/WHO_NCD_NCS_99.2.pdf. [Accessed 2003 Dec 12]
4. Alberti K, Zimmet P, Shaw J, for the IDF Epidemiology Task Force Consensus. The metabolic syndrome – a new worldwide definition. *Lancet*. 2005;366:1059–1062.
5. Haller H, Leonhardt W, Moser W, Hanefeld M. Relation of blood pressure to the body weight index and to metabolic parameters. *Z Gesamte Inn Med*. 1973;28S:211–213.
6. Meigs JB, D'Agostino RB Sr, Wilson PW, Cupples LA, Nathan DM, Singer DE. Risk variable clustering in the insulin resistance syndrome: the Framingham Offspring Study. *Diabetes*. 1997;46:1594–1600.
7. Reaven GM. Syndrome X. *Blood Press*. 1992;4S:13–16.
8. Ferrannini E, Haffner SM, Mitchell BD, Stern MP. Hyperinsulinaemia: the key feature of a cardiovascular and metabolic syndrome. *Diabetologia*. 1991;34:416–422.
9. Reaven GM. Role of insulin resistance in human disease. *Diabetes*. 1988;37:1595–1607.
10. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA*. 2002;287:356–359.
11. Meigs JB, Nathan DM, Wilson PW, Cupples LA, Singer DE. Metabolic risk factors worsen continuously across the spectrum of nondiabetic glucose tolerance: the Framingham Offspring Study. *Ann Intern Med*. 1998;128:524–533.
12. Gerstein HC. Is glucose a continuous risk factor for cardiovascular mortality? *Diabetes Care*. 1999;22:659–660.
13. Boehm BO, Claudi-Boehm S, Yildirim S, et al. Prevalence of the Metabolic Syndrome in Southwest Germany. *Scand J Clin Lab Invest*. 2005;240:122–128.
14. Lindström J, Louheranta A, Mannelin M. The Finnish Diabetes Prevention Study (DPS): lifestyle intervention and 3-year results on diet and physical activity. *Diabetes Care*. 2003;26:3230–3236.
15. Tuomilehto J, Lindström J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *New Engl J Med*. 2001;344:1343–1350.
16. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New Engl J Med*. 2002;346:393–403.
17. Kahn R, Ferranini E, Buse J, et al. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2005;28:2289–2304.
18. Reaven GM. The metabolic syndrome: requiescat in pace. *Clin Chem*. 2005;51:931–938.
19. Golden SH, Folsom AR, Coresh J, Sharrett AR, Szklo M, Brancati F. Risk factor groupings related to insulin resistance and their synergistic effects on subclinical atherosclerosis: the atherosclerosis risk in communities study. *Diabetes*. 2002;51:3069–3076.
20. Wilson PWF. Estimating cardiovascular disease risk and the metabolic syndrome: a Framingham view. *Endocrinol Metab Clin N Am*. 2004;33:467–481.
21. Wilson PWF, Kannel WB, Silbershatz H, D'Agostino RB. Clustering of metabolic factors and coronary heart disease. *Arch Intern Med*. 1999;159:1104–1109.
22. Meyre D, Bouatia-Naji N, Tounian A, et al. Variants of ENPP1 are associated with childhood and adult obesity and increase the risk of glucose intolerance and type 2 diabetes. *Nat Genet*. 2005;37:863–867.
23. Kahn B, Alquier T, Carling D, Hardie D. AMP-activated protein kinase: ancient energy gauge provides clues to modern understanding of metabolism. *Cell Metab*. 2005;1:15–25.
24. Shaw RJ, Lamina KA, Vasquez D, et al. The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. *Science*. 2005;310:1642–1646.
25. Pouliot MC, Després JP, Lemieux S, et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *Am J Cardiol*. 1994;73:460–468.

Metabolic imaging in the metabolic syndrome

L. Peterson
Cardiovascular Division, Washington University School of Medicine

Correspondence: Washington University School of Medicine, Cardiovascular Division, Campus Box 8086, 660 S. Euclid Avenue, St. Louis, MO 63110, USA.
Tel: +1(314) 362 4577; fax: +1(314) 362 9982; e-mail: lpeterso@im.wustl.edu

Abstract

The metabolic syndrome is associated with a well known increased risk of coronary disease, but the syndrome or its components are also associated with adverse cardiac remodeling and decreased function [1,2]. Changes in myocardial substrate preference, efficiency, and energetics probably contribute to cardiac remodeling and dysfunction [3–5]. The focus of this review is on noninvasive imaging techniques and the insights they have provided on myocardial metabolism and the pathogenesis of noncoronary heart disease associated with the metabolic syndrome.
■ *Heart Metab.* 2006;30:11–14.

Keywords: Metabolic syndrome, metabolism, positron emission tomography, heart, magnetic resonance spectroscopy

Introduction

The healthy myocardium is an omnivore, able to use several different substrates for the production of ATP. Animal studies of obesity and insulin resistance, hallmarks of the metabolic syndrome, suggest that excessive myocardial fatty acid metabolism, whether oxidation, storage, or both, is directly detrimental to cardiac function [1,2]. There is little information evaluating the effect of the metabolic syndrome as a whole on human myocardial metabolism, but insights may come from evaluating how the different components of the metabolic syndrome affect myocardial metabolism.

The components of the metabolic syndrome are: abdominal obesity, triglyceride concentrations $\geq$ 150 mg/dL, high-density lipoprotein (HDL) concentration $<$ 40 mg/dL (men) or $<$ 50 mg/dL (women), blood pressure $\geq$ 130/85 mm Hg, or a fasting glucose concentration $\geq$ 110 mg/dL [3]. If a patient has any three of these, they have the metabolic syndrome, according to Adult Treatment Panel III guidelines. The metabolic syndrome is also associated with insulin resistance.

Imaging techniques for quantification of myocardial metabolism

Positron emission tomography

Positron emission tomography (PET) imaging in humans enables quantification of rates of myocardial substrate uptake and metabolism using radiolabeled tracers. Myocardial oxygen consumption (MVO_2) is quantified using carbon-11-labeled acetate; glucose uptake and utilization are quantified using fluorine-18-labeled fluorodeoxyglucose (FDG) or ^{11}C-glucose; fatty acid uptake, utilization, and oxidation are quantified either using compounds labeled with [^{11}F]-6-thia-heptadecanoic acid or using [^{11}C]palmitate; and lactate is quantified using [^{11}C]lactate. A PET scanner collects the gamma rays released after the collision of a positron (from a radiopharmaceutical) with an electron in tissue. *Figure 1* shows sample images from two [^{11}C]palmitate PET studies and the time–activity curves that are used in conjunction with compartmental modeling to quantify the myocardial uptake and utilization of fatty acid.

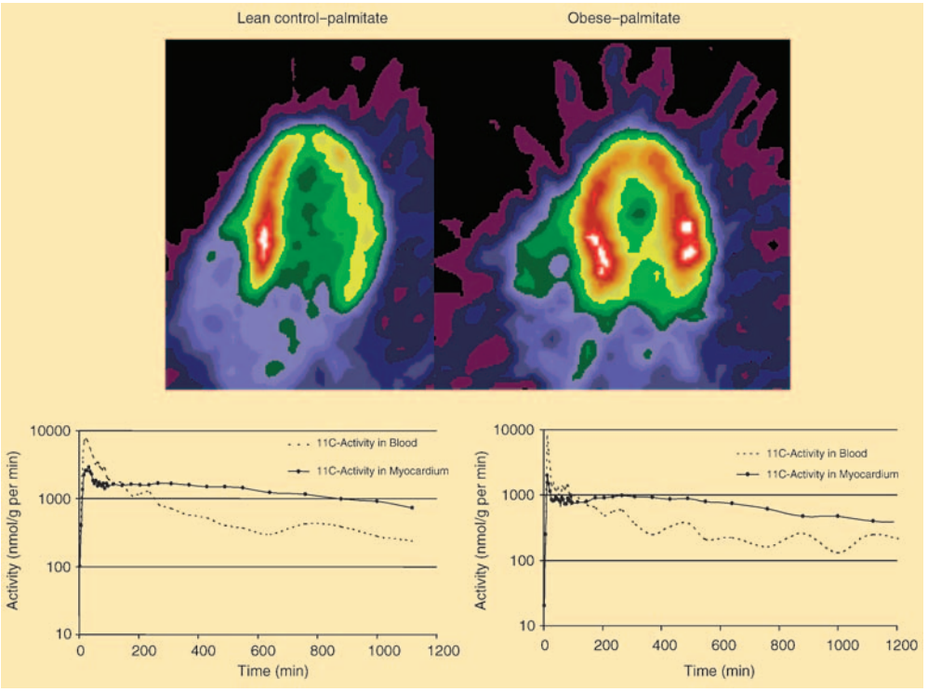

Figure 1. Top: Composite positron emission tomography (PET) myocardial images obtained from a young lean male (left) and a young obese female (right), 3–30 min after injection of [^{11}C]1-palmitate tracer. Images are displayed on the horizontal long axis with the base of the heart on top, septal wall on the left and lateral wall on the right. Compared with the lean control, the obese heart shows greater accumulation of tracer, indicative of greater uptake of free fatty acid (FFA). Bottom: Blood (···) and myocardial (–•–) time–activity curves obtained from the corresponding dynamic PET images of the same individual were used in conjunction with kinetic modeling to measure FFA uptake and oxidation (both in nmol/g per min). The obese individual had greater myocardial uptake, utilization, and oxidation of FFA than the lean control (eg, myocardial fatty acid utilization = 433 nmol/g per min compared with 87.6 nmol/g per min).

Limitations of PET include its high cost, and the need for a cyclotron to manufacture certain tracers. (Myocardial scintigraphy, another nuclear cardiology technique, is able to evaluate myocardial metabolism in a semiquantitative manner.)

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) is similar to magnetic resonance imaging, in that both use the same type of scanner equipped with a large magnet to generate images. However, in addition to measuring the total signal emitted by the nuclei within the body and displaying an image, MRS allows for different chemicals or metabolites within a given volume of tissue to be tracked and displayed on a spectrum. For example, phosphorus-31 MRS is used to determine the relative amount of high-energy phosphates, eg, phosphocreatine (PCr) and adenosine triphosphate (ATP), within the heart. A low PCr : ATP ratio is generally believed to be deleterious, and is a predictor of cardiovascular mortality in patients with dilated cardiomyopathy [4]. Measurement of absolute concentrations of human cardiac high-energy phosphate is possible using 3-dimensionally resolved spectra [5].

Hydrogen-1 MRS may be used to quantify triglycerides deposited within the myocardium [6]. MRS-quantified triglyceride content correlates well with histochemical triglyceride quantification. Challenges in applying this approach to study of the metabolism of the human heart include accounting for the motion of the myocardium and contamination of the myocardial spectrum by pericardial fat. Because of the latter, the volume of interest is often placed in the interventricular septum.

Applying these imaging approaches to the metabolic syndrome

Myocardial metabolism in abdominal obesity and insulin resistance

In a study of young women, PET imaging demonstrated that body mass index (BMI) was linearly and positively correlated with MVO_2 and with the myocardial uptake, utilization, and oxidation of fatty acid [7]. Insulin resistance was even more closely related to fatty acid uptake and metabolism than was BMI [7]. Increased BMI also predicted decreased cardiac

efficiency [7]. Glucose utilization was not different between obese and nonobese individuals, although it was low in all (fasting) individuals. These data are consistent with studies in animal models of insulin resistance, which have demonstrated that increased myocardial fatty acid uptake and metabolism precede and contribute to decreased cardiac function [1,2,8]. The failure of other studies to demonstrate differences in myocardial fatty acid uptake and oxidation between those who were glucose intolerant and normal controls may relate to differences in tracers, numbers of individuals studied, sex, age, or baseline endogenous myocardial fat stores [9,10].

Accumulation of excess lipid in the myocardium may also be detrimental to the heart in obese individuals, via a process known as 'lipotoxicity' [1]. Supporting this, an [^{1}H]-MRS study showed that increased BMI was related to increased accumulation of triglyceride in human myocardium, and that this was related to impaired cardiac contractility [6,7].

Myocardial metabolism in diabetes mellitus

Fasting hyperglycemia, a component of the metabolic syndrome, is common to both type 1 and 2 diabetes mellitus. In a recent study, PET was used to demonstrate that individuals with type 1 diabetes mellitus had greater plasma free fatty acid concentrations, MVO_2, myocardial fatty acid utilization and oxidation, and lower glucose utilization, compared with nondiabetic controls [11]. A hyperinsulinemic/euglycemic clamp may increase glucose utilization in diabetic patients such that it is not different from controls [12,13]. This increased reliance on fatty acid metabolism at the expense of glucose metabolism by the myocardium is concordant with findings from animal studies and results in a loss of metabolic flexibility [14].

In type 2 diabetes mellitus, the data are more mixed. Some PET studies have demonstrated decreased myocardial glucose uptake, but others did not [15–17]. Nevertheless, rosiglitazone, an antidiabetic drug, has been shown to improve myocardial glucose uptake in patients with type 2 diabetes, with or without coronary artery disease [18,19].

A myocardial [^{31}P]-MRS study of patients with type 2 diabetes mellitus, however, clearly demonstrated that myocardial energy metabolism is abnormal, as diabetic patients (without overt cardiac disease) had impaired myocardial energy metabolism, manifested by a lower PCr : ATP ratio compared with controls. Moreover, myocardial PCr : ATP ratios correlated negatively with fasting plasma free fatty acid concentrations, suggesting a pathophysiologic link between excessive fatty acid availability to the heart and impaired energy metabolism [20].

Myocardial substrate metabolism in hypertension

In contrast to obesity and diabetes mellitus, humans with hypertension-induced cardiac hypertrophy have decreased myocardial uptake, utilization, and oxidation of fatty acid compared with controls, as demonstrated by PET [21]. This is similar to observations in animal models [22]. Whether there is an increase in myocardial glucose utilization in humans with hypertension is not known.

Myocardial substrate metabolism in hyperlipidemia

Animal models and coronary arterial–venous balance studies in humans have shown that triglycerides are a fuel for the myocardium and that, if their delivery to the heart is increased, so is their myocardial metabolism [23]. There is little information evaluating this in humans by means of noninvasive imaging, however, and there are no studies on the effect of low concentrations of HDL cholesterol on myocardial metabolism. The net effect of the metabolic syndrome on myocardial metabolism in persons with insulin resistance, hypertension, and other components is probably determined by the degree and interaction of all components.

Conclusion

Many components of the metabolic syndrome are associated with abnormalities in myocardial energy metabolism that may contribute to decreased cardiac function. Noninvasive imaging modalities are being used to quantify myocardial substrate preferences, and the oxidation, storage and energetics of the substrates that are particular to the metabolic syndrome. The sum of the data from human studies of the effects of most of the components of the metabolic syndrome (except hypertension) suggest that there is an overdependence on and an increase in myocardial uptake, metabolism, and storage of fatty acid. Further development and application of cardiac metabolic imaging techniques to the metabolic syndrome will help to define novel therapeutic targets and assess their efficacy. ■

REFERENCES

1. Unger RH. Lipotoxic diseases. *Annu Rev Med*. 2002;53:319–336.
2. Aasum E, Hafstad AD, Severson DL, Larsen TS. Age-dependent changes in metabolism, contractile function, and ischemic sensitivity in hearts from db/db mice. *Diabetes*. 2003;52:434–441.

3. Grundy SM, Brewer HB, Cleeman JI, et al. Definition of Metabolic Syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition. *Circulation*. 2004;109: 433–483.
4. Neubauer S, Horn M, Cramer M, et al. Myocardial phosphocreatine-to-ATP ratio is a predictor of mortality in patients with dilated cardiomyopathy. *Circulation*. 1997;96:2190–2196.
5. Bottomley PA, Atalar E, Weiss RG. Human cardiac high-energy phosphate metabolite concentrations by 1D-resolved NMR spectroscopy. *Magn Reson Med*. 1996;35:664–670.
6. Szczepaniak LS, Dobbins RL, Metzger GJ, et al. Myocardial triglycerides and systolic function in humans: in vivo evaluation by localized proton spectroscopy and cardiac imaging. *Magn Reson Med*. 2003;49:417–423.
7. Peterson LR, Herrero P, Schechtman KB, et al. Effect of obesity and insulin resistance on myocardial substrate metabolism and efficiency in young women. *Circulation*. 2004;109:2191–2196.
8. Zhou YT, Grayburn P, Karim A, et al. Lipotoxic heart disease in obese rats: implications for human obesity. *Proc Natl Acad Sci U S A*. 2000;97:1784–1789.
9. Turpeinen AK, Takala TO, Nuutila P, et al. Impaired free fatty acid uptake in skeletal muscle but not in myocardium in patients with impaired glucose tolerance: studies with PET and 14(R,S)-[18F]fluoro-6-thia-heptadecanoic acid. *Diabetes*. 1999;48:1245–1250.
10. Knuuti J, Takala TO, Nagren K, et al. Myocardial fatty acid oxidation in patients with impaired glucose tolerance. *Diabetologia*. 2001;44:184–187.
11. Herrero P, Peterson L, McGill J, et al. Increased myocardial fatty acid metabolism in patients with type 1 diabetes mellitus. *J Am Coll Cardiol*. In press.
12. vom Dahl J, Herman WH, Hicks RJ, et al. Myocardial glucose uptake in patients with insulin-dependent diabetes mellitus assessed quantitatively by dynamic positron emission tomography. *Circulation*. 1993;88:395–404.
13. Nuutila P, Knuuti J, Ruotsalainen U, et al. Insulin resistance is localized to skeletal but not heart muscle in type 1 diabetes. *Am J Physiol*. 1993;264:E756–E762.
14. Randle PJ, Newsholme EA, Garland PB. Regulation of glucose uptake by muscle. 8. Effects of fatty acids, ketone bodies and pyruvate, and of alloxan-diabetes and starvation, on the uptake and metabolic fate of glucose in rat heart and diaphragm muscles. *Biochem J*. 1964;93:652–665.
15. Jagasia D, Whiting JM, Concato J, Pfau S, McNulty PH. Effect of non-insulin-dependent diabetes mellitus on myocardial insulin responsiveness in patients with ischemic heart disease. *Circulation*. 2001;103:1734–1739.
16. Iozzo P, Chareonthaitawee P, Dutka D, Betteridge DJ, Ferrannini E, Camici PG. Independent association of type 2 diabetes and coronary artery disease with myocardial insulin resistance. *Diabetes*. 2002;51:3020–3024.
17. Utriainen T, Takala T, Luotolahti M, et al. Insulin resistance characterizes glucose uptake in skeletal muscle but not in the heart in NIDDM. *Diabetologia*. 1998;41:555–559.
18. Lautamaki R, Airaksinen KE, Seppanen M, et al. Rosiglitazone improves myocardial glucose uptake in patients with type 2 diabetes and coronary artery disease: a 16-week randomized, double-blind, placebo-controlled study. *Diabetes*. 2005;54: 2787–2794.
19. Hallsten K, Virtanen KA, Lonnqvist F, et al. Rosiglitazone but not metformin enhances insulin- and exercise-stimulated skeletal muscle glucose uptake in patients with newly diagnosed type 2 diabetes. *Diabetes*. 2002;51:3479–3485.
20. Scheuermann-Freestone M, Madsen PL, Manners D, et al. Abnormal cardiac and skeletal muscle energy metabolism in patients with type 2 diabetes. *Circulation*. 2003;107: 3040–3046.
21. de las Fuentes L, Herrero P, Peterson LR, Kelly DP, Gropler RJ, Davila-Roman VG. Myocardial fatty acid metabolism: independent predictor of left ventricular mass in hypertensive heart disease. *Hypertension*. 2003;41:83–87.
22. Young ME, Laws FA, Goodwin GW, Taegtmeyer H. Reactivation of peroxisome proliferator-activated receptor alpha is associated with contractile dysfunction in hypertrophied rat heart. *J Biol Chem*. 2001;276:44390–44395.
23. Carlson LA, Kaijser L, Rossner S, Wahlqvist ML. Myocardial metabolism of exogenous plasma triglycerides in resting man. Studies during alimentary lipaemia and intravenous infusion of a fat emulsion. *Acta Med Scand*. 1973;193:233–245.

Metabolic syndrome: pharmacological treatment

P.A. van Zwieten[1,2] and F.C. Visser[2]
[1]Departments of Pharmacotherapy, Cardiology and Cardiothoracic Surgery, Academic Medical Centre, Amsterdam, The Netherlands, and [2]Department of Cardiology, Free University Medical Centre, Amsterdam, The Netherlands

Correspondence: Prof.Dr P.A. van Zwieten, Departments of Pharmacotherapy, Cardiology and Cardiothoracic Surgery, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.
Tel: +31 20 566 49 76; fax: +31 20 696 8704

Abstract

Patients with the metabolic syndrome have a clustering of the following risk factors: detrimental changes in glucose tolerance and insulin resistance, abdominal (visceral) obesity, atherogenic dyslipidemia, hypertension. In addition to appropriate changes in lifestyle, the majority of patients with the syndrome will require pharmacological treatment, usually for the remainder of their lives. We present here an exhaustive and critical review of the drug treatment of the risk factors associated with the metabolic syndrome. Emphasis will be upon antihypertensive treatment and on the influence of various drugs on insulin resistance, an important background to the metabolic syndrome.
■ *Heart Metab.* 2006;30:15–20.

Keywords: Metabolic syndrome, insulin resistance, antihypertensive drugs, diabetes mellitus (type 2), obesity, hyperlipidemia

Introduction

The most relevant components of the metabolic syndrome [1,2] can be listed as follows:

- unfavorable changes in glucose tolerance (↓) and insulin resistance (↑);
- abdominal (visceral) obesity;
- atherogenic dyslipidemia;
- hypertension.

Taking into account the complex character of the metabolic syndrome, it is not surprising that its definition and nomenclature have been subject to considerable and even polemic discussions and debate. Secondary to the initial term 'syndrome X', other names for metabolic syndrome have been proposed, such as 'insulin resistance syndrome', 'Reaven's syndrome' and 'metabolic cardiovascular syndrome' [3].

Both the National Cholesterol Education Programme (NCEP) and the World Health Organization (WHO) have established definitions of the metabolic syndrome that are fairly similar. Both definitions comprise markers for abdominal obesity, glucose and lipid metabolism, and blood pressure. The WHO definition contains, in addition, criteria for urinary albumin excretion as a marker for renal damage, and in more general terms as a sensitive predictor for cardiovascular disease in an early stage [4].

The pathophysiological backgrounds of metabolic syndrome, a very heterogenous syndrome, are complex. Two major issues are discussed as possible common backgrounds of the metabolic syndrome: (a) insulin resistance/glucose intolerance (see *Figure 1*) and (b) hyperactivity of the sympathetic nervous system. Both phenomena and their relationship with the metabolic syndrome have been discussed exhaustively in recent reviews [5,6].

Metabolic syndrome is associated with important cardio/cerebrovascular and metabolic risks. Prevention and treatment are therefore of great importance. Preventive measures involving lifestyle are mandatory. In addition, patients with the metabolic syndrome will

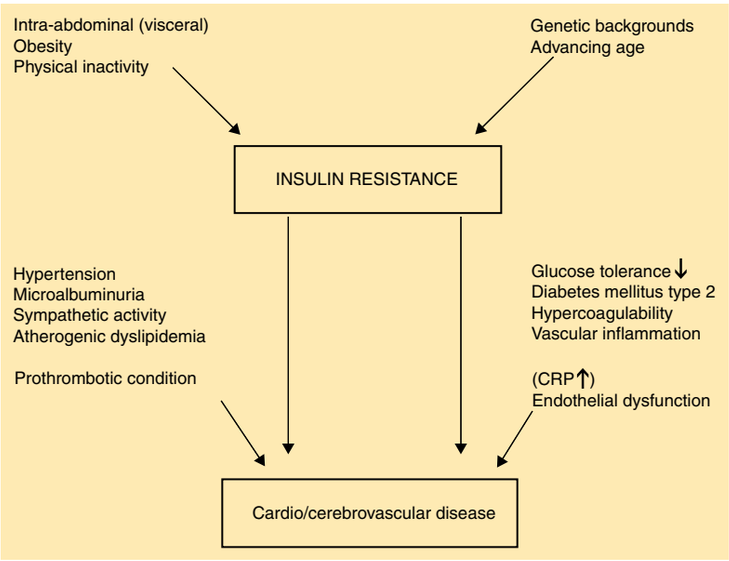

Figure 1. Pathological processes that have roles in the metabolic syndrome and can hence lead to cardio/cerebrovascular diseases. Insulin resistance appears to be of pivotal importance as a background to several pathological mechanisms.

require pharmacological treatment, usually for the remainder of their lives.

Taking into account the heterogenous character of the metabolic syndrome and its various components, the pharmacological interventions are bound to be complex. Consequently, the evaluation of pharmacological interventions will require appropriately designed, rather complicated clinical trials.

The present survey will deal with the various aspects of pharmacological treatment of the metabolic syndrome, including some newer therapeutic approaches.

Prevention and general aspects of intervention

It goes without saying that prevention is a crucial approach for reducing the various risks brought about by the metabolic syndrome. The preventive approach holds for virtually all important components of metabolic syndrome, such as glucose intolerance/insulin resistance, diabetes mellitus type 2, obesity, hyperlipidemia, and hypertension. Generally speaking, the recommended changes in lifestyle run parallel to reduction of risk for these pathophysiological processes. Accordingly, the following recommendations for intervention should be taken into account as preventive measures [7]:

- Obesity, glucose intolerance, insulin resistance, diabetes mellitus type 2: correction of overweight by adequate changes in diet (Mediterranean diet, less saturated fat, fewer calories, reduction of alcohol consumption), and by more and regular physical activity.
- Hyperlipidemia: as discussed above for obesity etc.
- Hypertension: as discussed above for obesity etc.; in addition, moderation of salt (Na^+) and alcohol consumption.

From a more general perspective, all patients are urgently advised to stop smoking. On the basis of the concept that the metabolic syndrome is associated with sympathetic hyperactivity, preventive measures aiming at reducing this hyperactivity could be considered. Correction of overweight and enhanced physical activity may be expected to reduce sympathetic hyperactivity somewhat. Prevention of the prothrombotic condition can be achieved only by drug treatment.

Drug therapy and the metabolic syndrome

General aspects

Although the preventive measures described above should always be the primary approach to intervention in patients with the metabolic syndrome, this approach is not always successful, in particular in the long term. Accordingly, the vast majority of patients with the metabolic syndrome require pharmacological treatment, in spite of all the good intentions with respect to prevention and lifestyle improvements. Once established, drug treatment has to be followed daily, and usually for the remainder

of the patient's life. Guidelines on prevention of cardiovascular disease do not usually make extensive reference to the metabolic syndrome [8]. When they do, they usually advise that this condition is predominantly approached by improvements in lifestyle. It is likely that this conservative approach will change in the future towards a more interventional one, with a more important role of pharmacological treatment [8].

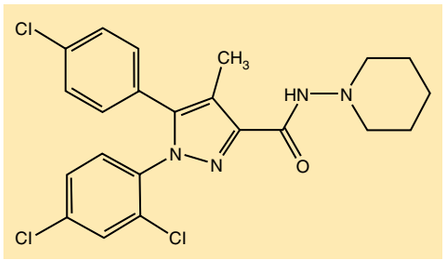

Figure 2. Chemical structure of rimonabant, an inhibitor of the cannabinoid (CB_1) receptor in the endocannabinoid system.

Obesity

Pharmacological treatment of obesity had been attempted for several decades, but so far this approach has been disappointing. In most European countries, two drugs are registered for the treatment of obesity: sibutramine and orlistat.

Sibutramine, an anorexant chemically derived from amphetamine, inhibits the reuptake of both norepinephrine and serotonin by their respective nerve endings, in both the periphery and the central nervous system. Consequently, appetite is reduced and energy expenditure is increased. Adverse responses to sibutramine can be problematic as a result of activation of the sympathetic nervous system. Long-term beneficial effects of the drug are the subject of debate.

Orlistat reduces the intestinal absorption of nutritional fat by inhibition of the enzyme lipase in the pancreas and the stomach. Orlistat, indeed, appears to be able to reduce body weight in the long term, but its adverse reactions (mainly gastrointestinal) are most unpleasant, leading to poor patient compliance.

Metformin, a biguanide-type antidiabetic agent, is not classified as an anti-obesity drug, but in diabetic patients treated with this agent, body weight is usually decreased [9].

Rimonabant, an antagonist of cannabinoid (CB_1-type) receptors in the endocannabinoid system of the brain, offers a new approach in the management of obesity. Stimulation of CB_1 receptors is involved in an increase in appetite, increased accumulation of fat in adipocytes, and increased motivation to smoke. Conversely, blockade of the CB_1 receptor by an antagonist will counteract both hyperphagia/obesity and the increased motivation to smoke. Rimonabant (*Figure 2*), the first clinically applicable CB_1 receptor antagonist, exhibits these beneficial effects, to date in studies lasting 1 year [10]. Further and large-scale studies will be required to establish the position of rimonabant, which appears to offer a new approach in the management of obesity, including in patients with the metabolic syndrome.

Overall, the pharmacological treatment of obesity has to date been largely disappointing. Appropriate improvements are highly desirable. In this respect, the endocannabinoid system and its receptors can be thought of as an interesting target for new drugs.

In recent years, several hormones involved in the regulation of appetite and saturation have been discovered, such as leptin*, ghrelin, resistin and peptide PYY. It is conceivable that derivatives, analogs, agonists, or antagonists of these hormones may provide the basis for the development of new drugs that can be used to counteract obesity.

Glucose intolerance, insulin resistance, and type 2 diabetes mellitus

In addition to the classical oral antidiabetic drugs (tolbutamide and related sulfonylurea derivatives, glinides, and acarbose), the biguanide, *metformin*, has experienced a renaissance of interest since it was discovered that it exhibits insulin-sensitizing activity. For this and other reasons, metformin is considered the oral antidiabetic drug of choice in patients with metabolic syndrome [9].

Glitazones, such as pioglitazone and rosiglitazone, are the newer type of insulin sensitizer. They reduce insulin resistance via the activation of the peroxisome-proliferator-activated receptor subtype γ (PPAR-γ). On theoretical grounds, they would be beneficial oral antidiabetic agents in patients with metabolic syndrome. Their position will be established by means of current clinical trials [11].

Insulin resistance

As insulin resistance is now widely recognized as an important background to the various components of the metabolic syndrome, it appears useful to review the differential influences of the various cardiovascular and antidiabetic drugs used in the management of the metabolic syndrome [12]. As summarized in *Table I*, insulin resistance can be modulated in a differential manner by various types of drugs. In particular, various types of antihypertensive agent display a clearly differential activity. As will be discussed in the next paragraph, this issue is of vital importance, in particular with respect to the long-term

Table I. Overview of the effects of cardiovascular and antidiabetic drugs that influence insulin resistance.

Drug	Effects on insulin resistance (IR)	Details
Thiazolidinediones (glitazones)	IR ↓ (favorable)	PPAR-γ receptor agonism
Metformin	IR ↓ (favorable)	Hepatic glucose production ↓
α_1-Adrenoreceptor antagonists (eg, doxazosin)	IR ↓ (favorable) Weak effect	
Calcium antagonists	No direct effect (neutral)	
ACE inhibitors	IR ↓ (favorable)	Possibly via angiotensin II/endothelium
Angiotensin II receptor antagonists (AT_1-blockers; ARBs; sartans) Exception: telmisartan	No effect IR ↓ (favorable)	PPAR-γ receptor agonism
Thiazide diuretics	IR ↑ (unfavorable)	Pancreatic insulin release ↓
β-Blockers	IR ↑ (unfavorable)	
Centrally acting antihypertensives (clonidine; α-methyl-DOPA; moxonidine; rilmenidine)	IR ↓ (probably) Weak effects	Via depression of sympathetic nervous system activity

ACE, angiotensin-converting enzyme; ARB, angiotensin II type 1 receptor blocking agent; AT_1, angiotensin II type 1; DOPA, dihydroxyphenylalanine; PPAR, peroxisome proliferator activated receptor.

treatment of essential hypertension, which is usually continued for several decades.

Hypertension

Taking into account that patients with the metabolic syndrome are clearly at increased cardio/cerebrovascular risk, strict control of blood pressure is mandatory, aiming at values of 130/85 mm Hg or even less. Although it has not been studied in a specific trial, it seems very likely that patients with the metabolic syndrome including hypertension would also benefit from decreasing their blood pressure by pharmacological treatment, probably almost irrespective of the type of drug used. However, in this connection it should be borne in mind that the development of diabetes and other metabolic problems are associated with the long-term use of certain antihypertensive agents.

The European Society of Hypertension/European Society of Cardiology 2003 guidelines proposed five groups of antihypertensive drugs as first-line treatment of hypertension: thiazide diuretics, β-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor antagonists (angiotensin II type 1 [AT_1] blockers; angiotensin II type 1 receptor blocking agents; sartans).

Other drugs that can be considered are the α-blockers and the older centrally acting antihypertensives such as clonidine and α-methyl-dihydroxyphenylalanine. If used correctly, these various agents have largely comparable blood pressure decreasing activities. However, recent investigations indicate that the metabolic changes associated with the various categories of antihypertensive agent are differential, and therefore highly relevant within the framework of the metabolic syndrome.

A recent review paper by Opie and Schall [13] dealt in detail with the metabolic, and in particular the diabetogenic, actions of various groups of antihypertensive agents. In this connection, 'older' and 'modern' antihypertensive drugs were distinguished. Thiazide diuretics and β-blockers were classified as the 'older' antihypertensive agents, whereas calcium antagonists, ACE inhibitors and AT_1 receptor blockers were considered to be the 'modern' antihypertensive drugs. These two categories of drug were compared by means of a meta-analysis, including seven large-scale intervention trials, involving 58 010 patients. In a follow-up period of 4 years, particular attention was paid to newly developed diabetes. ACE inhibitors and AT_1 blockers reduced the number of new cases of diabetes by 20%, whereas for the calcium antagonists this reduction amounted to 16%. In contrast, the 'older' antihypertensives significantly increased the incidence of new cases of diabetes, probably by a factor of 4.

Furthermore the Antihypertensive Treatment and Lipid Profile in the North of Sweden Efficacy Evaluation (ALPINE) trial [14], performed in patients with hypertensive metabolic syndrome, has demonstrated important metabolic differences between two different treatment regimens: hydrochlorothiazide + atenolol, and candesartan + felodipine. Both treatment schedules caused a satisfactory and similar control of blood pressure. Interestingly, treatment with the diuretic + β-blocker combination appeared to be associated with a significantly larger number of new cases of diabetes mellitus type 2, and was accompanied by higher plasma triglyceride concentrations. In contrast, treatment with combination candesartan + felodipine, leading to the same degree of decrease in blood pressure, was not accompanied by any significant metabolic/endocrine changes. The former treatment also enhanced the occurrence of new cases of the

metabolic syndrome, whereas the latter treatment did not [14].

Taking together the findings of Opie and Schall and ALPINE, the potential diabetogenic action of thiazide diuretics and β-blockers would speak against their use in patients with the metabolic syndrome, for whom the more modern antihypertensive agents (ACE inhibitors, AT_1 receptor blockers, calcium antagonists) appear to be preferable [15].

Irrespective of the occurrence of the metabolic syndrome, it should be assumed that young hypertensive patients will be treated for several decades. Accordingly, these modern antihypertensive agents appear to be preferable over the metabolically unfavorable thiazide diuretics or β-blockers.

Finally, it may be of interest to note the dual activity of the AT_1 blocker, *telmisartan*, which is also an insulin sensitizer, thanks to its PPAR-γ-stimulating activity [16]. The clinical relevance of these dual activities remains to be established.

Atherogenic dyslipidemia

Improvement in the diet, already mentioned with respect to prevention and general measures, remains the cornerstone of the treatment of atherogenic dyslipidemia; this is true also for patients with the metabolic syndrome. A significant percentage of the latter patients additionally require treatment with lipid-decreasing drugs (antilipemics, hypolipemics). In this context, antilipemic drug treatment will be mandatory more and more often in patients with hypertension or type 2 diabetes mellitus, or both.

The management of hyperlipidemia in patients with the metabolic syndrome is performed according to the same principles as in patients without this syndrome, and is based upon aberrations in the plasma lipids. The hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins) have acquired and maintained a very important position. In most countries, several statins are registered. To date, it is not possible to express a preference for one particular preparation to be used in patients with the metabolic syndrome. The widest experience in various categories of patients has been acquired with simvastatin, now available as a generic preparation.

The importance of the high triglyceride concentrations in patients with the metabolic syndrome may require the additional use of fibrates, nicotinic acid or its derivatives, or both. (For reviews of lipid decreasing treatment, see references [17] and [18].)

Enhanced coagulability (prothrombotic state)

If necessary, enhanced coagulability can be corrected by means of an antithrombotic drug; in practice, acetylsalicylic acid (ASA, aspirin), a classic antiplatelet drug, has always been used. According to the general advice of the American Heart Association, aspirin prophylaxis should be applied in patients with a $\geq$ 10% risk of developing a coronary event within a period of 10 years, based upon the criteria of the Framingham risk schedule [19]. Some, but not all, patients with the metabolic syndrome will meet these criteria.

Conclusions and perspectives

The awareness of the metabolic syndrome as a well-defined and relevant pathological entity has stimulated interest in pharmacological intervention. The heterogenous backgrounds of the syndrome mean that clinical trials concerning drug treatment of the syndrome are bound to be complex and difficult to design. Furthermore, drug treatment targeting the various components of the metabolic syndrome has been demonstrated to be largely differential for the categories of the drugs required for this purpose.

The recognition that insulin resistance is an important background to the metabolic syndrome has led to a new classification of *antihypertensive drugs*, to be differentiated into 'old' and 'new' categories. Newer drugs, such as ACE inhibitors, AT_1 blockers (ARBs), and probably also the calcium antagonists, appear to offer a better metabolic profile than the older thiazide diuretics and β-blockers, in particular for the long-term treatment of young patients who have hypertension and the metabolic syndrome. The same holds for the treatment of *type 2 diabetes mellitus*, for which the newer insulin sensitizers, the thiazolidinediones (glitazones), offer a potentially more favorable metabolic profile than the classical oral antidiabetic agents.

The pharmacological treatment of atherogenic dyslipidemia has made substantial progress, in particular owing to the development of the statins. Although little studied in specific trials targeting the metabolic syndrome, the use of statins in patients with the metabolic syndrome who have hyperlipidemia appears to be mandatory, although to date none of the statins can be put forward as preferable over the others. Furthermore, the relevance of decreasing increased triglyceride concentrations and increasing high-density lipoprotein concentrations by means of fibrates or derivatives of nicotinic acid is now accepted widely, including in patients with the metabolic syndrome.

Finally, the pharmacological treatment of *obesity* remains a difficult and disappointing issue. The two drugs registered for this purpose (sibutramine and orlistat) are far from optimal and are difficult to use in the long term. New approaches based on modulating

the endocannabinoid system by means of the CB_1 receptor antagonist, rimonabant, do at least offer a potentially new route of intervention. In addition, improved knowledge of the several hormones involved in the control of body weight regulation (such as ghrelin, leptin, PYY) may offer new approaches to the pharmacological treatment of obesity.

Generally speaking, it can be concluded that the drug treatment of hypertension and atherogenic dyslipidemia, including that in patients with metabolic syndrome, can be considered to be satisfactory. The management of type 2 diabetes remains a more difficult and less successful issue, although the introduction of the newer insulin sensitizers may offer better perspectives. The drug treatment of obesity, a very major component in the metabolic syndrome, also continues to be disappointing. A few newer perspectives for this purpose are emerging, and improvements in this field are highly desirable. ■

* See glossary for definition of these terms.

REFERENCES

1. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. 2005;365:1415–1428.
2. Grenrodic SM, Brewer HB, Cleeman JI, et al. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation*. 2004;109: 433–438.
3. Dandona P, Aljada A, Chaudhuri A, Mohanty P, Garg R. Metabolic syndrome. *Circulation*. 2005;11:1448–1454.
4. Pedrinelli R, Dell'Omo G, Penno G, et al. Microalbuminuria, a parameter independent of metabolic influences in hypertensive men. *J Hypertens*. 2003;21:1163–1169.
5. Malik S, Wong ND, Franklin SS, et al. Impact of the metabolic syndrome on mortality from coronary heart disease, and all causes in United States adults. *Circulation*. 2004;110:1245–1250.
6. Isomaa B. A major health hazard: the metabolic syndrome. *Life Sci*. 2003;73:2395–2411.
7. Grundy SM, Hansen B, Smith SC Jr et al. Clinical management of metabolic syndrome: report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association conference on scientific issues related to management. *Circulation*. 2004;109:551–556.
8. De Backer G, Ambrosioni E, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and other Societies on Cardiovascular Disease in Clinical Practice. *Eur J Cardiovasc Prev Rehabil*. 2003;10:S1–S78.
9. Hundal RS, Inzucchi SE. Metformine. *Drugs*. 2003;63:1879–1894.
10. Van Gaal LF, Rissanen AM, Scheen AJ, et al., for the RIO-Europe Study Group. Effects of the cannabinoid-1-receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet*. 2005;365:1389–1397.
11. Yki-Järvinen H. Thiazolidinediones. *N Engl J Med*. 2004;351: 1106–1118.
12. Kendale DM, Sobel BE, Coulston AM, et al., for the Partners Against Insulin Resistance Advisory Panel. The insulin resistance syndrome and coronary artery disease. *Coron Artery Dis*. 2003;14:335–348.
13. Opie LH, Schall R. Old antihypertensives and new diabetes. *J Hypertens*. 2004;22:1453–1458.
14. Lindholm LH, Persson M, Alanpovic P, Carlberg B, Svensson A, Samuelsson O. Metabolic outcome during 1 year in newly detected hypertensives: results of the Antihypertensive Treatment and Lipid Profile in the North of Sweden Efficacy Evaluation (ALPINE-study). *J Hypertens*. 2003;21:1563–1574.
15. Ruilope LM, Segure J, Schiffrin E. ACE-inhibition of angiotensin receptor blockade: which should we use in diabetic patients? *J Renin Angiotensin Aldosterone Syst*. 2003;4:74–79.
16. Schupp M, Janke J, Clasen R, Unger T, Kintscher U. Angiotensin type I receptor blockers induce peroxisome proliferator-activated receptor activity. *Circulation*. 2004;109: 2054–2057.
17. Low MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ*. 2003;326:1423–1427.
18. Vrecer M, Turk S, Drinovec J, Mrhar A. Use of statins in primary and secondary prevention of coronary heart disease and ischemic stroke. Meta-analysis of randomized trials. *Int J Clin Pharmacol Ther*. 2003;41:567–577.
19. Peasson TA, Blair SM, Daniels SR, et al., for the American Heart Association Science Advisory and Coordinating Committee. AHA guidelines for primary prevention of cardiovascular disease and stroke: 2002 update. Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. *Circulation*. 2002;106:388–391.

Effect of selective 3-ketoacyl coenzyme A thiolase inhibition on glucose metabolism in cardiac patients

Gabriele Fragasso, Altin Palloshi and Amarild Cuko
Heart Failure Clinic, Istituto Scientifico/Universita' San Raffaele, Milan, Italy

Correspondence: Gabriele Fragasso, Heart Failure Clinic, Istituto Scientifico/ Universita' San Raffaele, Via Olgettina 60, 20132 Milan, Italy.
Tel: +39-02-26437395; fax: +39-02-26437395; e-mail: gabriele.fragasso@hsr.it

Abstract

It has recently been shown that trimetazidine, a 3-ketoacyl coenzyme A thiolase inhibitor, improves overall glucose metabolism in diabetic patients with left ventricular dysfunction. Forearm glucose and lipid metabolism and forearm release of endothelial vasodilator and vasoconstrictor factors during prolonged partial inhibition of fatty acid oxidation by trimetazidine have recently been evaluated in patients with postischemic left ventricular dysfunction. Trimetazidine significantly improved both insulin-induced forearm oxidation of glucose and release of cyclic guanosine monophosphate, whereas forearm release of endothelin-1 was decreased. Although these findings need further confirmation, the combined beneficial effects of trimetazidine on left ventricular function and glucose metabolism make the use of this drug particularly attractive, especially in those cardiac patients in whom abnormalities of both myocardial and glucose metabolism coexist.
■ *Heart Metab.* 2006;30:21–24.

Keywords: Trimetazidine, diabetes, glucose metabolism, left ventricular function, endothelial function, 3-ketoacyl coenzyme A thiolase inhibition

Introduction

Regulation of glucose metabolism is an important target in the control of cardiovascular risk factors. Abnormalities of glucose homeostasis range from frank diabetes to a state of insulin resistance, a definition used to indicate a need to increase insulin concentrations in order to maintain normal glycemic conditions. Recent studies have identified a direct relationship between endothelial dysfunction and insulin resistance [1]. Endothelin-1 (ET-1)* concentrations have been shown to correlate significantly with fasting insulin concentrations, systolic and diastolic blood pressure, visceral obesity, and triglyceride concentrations, confirming a close relationship between insulin resistance and endothelial function [2]. When present, insulin resistance has been found to be operative in both cardiac and skeletal muscles [3]. Different degrees of endothelial dysfunction associated with a state of insulin resistance have been reported in most cardiovascular diseases, such as hypertension [4], coronary artery disease [5,6], microvascular angina [7], and heart failure [8]. In contrast, insulin resistance is a pathological condition that is rarely diagnosed as a distinct entity. In a recent study, our group showed that more than 50% of patients submitted to coronary stenting for ischemic heart disease and with normal baseline blood glucose concentrations exhibit abnormal hyperglycemia after an oral glucose tolerance test [9]. This abnormality is associated with a higher probability of restenosis [9]. Our results are supported by previous studies showing

that individuals with impaired glucose tolerance not only run the risk of developing overt diabetes and its associated microvascular complications, but also have an increased risk of cardiovascular morbidity and mortality compared with healthy glucose-tolerant patients [10]. Therefore, early detection of impaired glucose tolerance would permit initiation of secondary preventive treatment measures in such patients.

Uptake of glucose in heart and arm skeletal muscle is inversely related to serum free fatty acid (FFA) concentrations [11], and increased FFA flux from adipose tissue to non adipose tissue amplifies metabolic derangements that are characteristic of the insulin resistance syndrome [12]. In addition, new findings suggest that increased FFA concentrations not only impair glucose uptake in heart and skeletal muscle, but also cause alterations in the metabolism of vascular endothelium, leading to premature cardiovascular disease [13].

Effects of selective 3-ketoacyl coenzyme A thiolase inhibition on glucose metabolism

Decreasing increased plasma triglyceride and FFA concentrations could be the first therapeutic option for decreasing the reliance of the heart on fatty acids and overcoming the fatty acid inhibition of myocardial glucose utilization. Indeed β-blockers, by reducing peripheral lipolysis, should reduce FFA availability. Interestingly enough, a recent study has shown that one of the main effects of the β-blocker, carvedilol, is the reduction of FFA utilization in favor of greater utilization of glucose in patients with stable New York Heart Association functional class III heart failure [14]. This change in myocardial energetics could provide a potential mechanism for the decreased myocardial oxygen consumption and improved energy efficiency that is seen with β-adrenoreceptor blockade in the treatment of heart failure.

Another approach is to induce muscles directly to reduce FFA utilization in favor of glucose oxidation. In this context, the use of a partial fatty acid inhibitor could have a very specific role. Trimetazidine [1-(2,3,4 trimethoxybenzyl-piperazine dihydrochloride)] has been reported to exert several beneficial effects in cardiac patients, without affecting myocardial oxygen consumption and blood supply [15]. This agent has been shown to preserve intracellular concentrations of phophocreatine and ATP [16] and to reverse the harmful effects of increased triglyceride concentrations, normalizing the impaired myocardial recovery from low-flow ischemia by decreasing myocardial oxidation of lipid and release of citrate [17]. These effects could be a consequence of the main mechanism of action of trimetazidine – ie, inhibition of oxidative phosphorylation by shifting energy production from FFA to glucose oxidation [3]. This beneficial metabolic adaptation is predominantly caused by a selective block of long-chain 3-ketoacyl coenzyme A thiolase activity, the final enzyme involved in β-oxidation [18]. Partial inhibition of fatty acid oxidation may therefore explain the beneficial effects of trimetazidine in cardiac patients.

Therapeutic approach to abnormal glucose metabolism in cardiac patients

As previously outlined, most cardiac diseases are associated with combined insulin resistance and endothelial dysfunction. In these contexts, improving the cardiac metabolic milieu by partially inhibiting FFA utilization could be particularly effective. In patients with ischemic left ventricular dysfunction, trimetazidine has been shown to exert significant beneficial effects [19,20]. These beneficial effects of the molecule have been incidentally observed to be mainly operative in patients who, in addition to ischemic cardiomyopathy, also have diabetes [21,22] (*Figures 1–3*). After trimetazidine, there was a clear trend towards a decrease in blood glucose, although the difference compared with placebo was not statistically significant. Conversely, both glycosylated hemoglobin and endothelin were significantly reduced after treatment with trimetazidine. Together, these data indicate a significant trimetazidine-induced improvement in glucose metabolism in cardiac patients.The mechanism of action is related to the property of trimetazidine to facilitate myocardial utilization of glucose instead of FFAs which, in the context of malfunctioning myocardial cells, appear to be deleterious. Interestingly, compounds such as dichloroacetate, which stimulate pyruvate dehydrogenase activity, thereby facilitating glucose oxidation

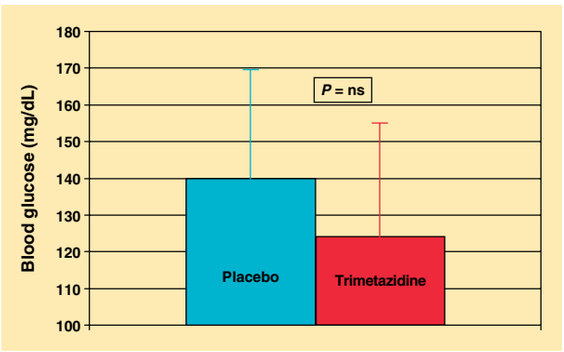

Figure 1. Long-term effects of trimetazidine and placebo on (mean ± SD) blood glucose concentrations in diabetic patients with postischemic cardiomyopathy. (From Fragasso et al [21], with permission.)

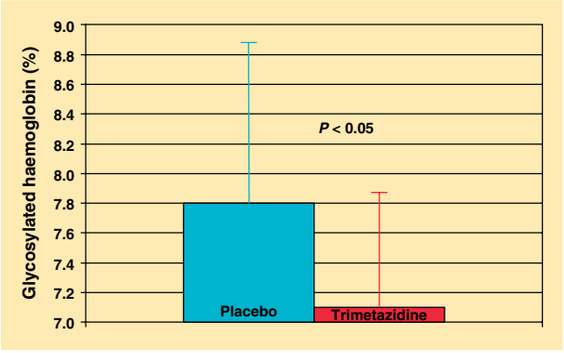

Figure 2. Long-term effects of trimetazidine and placebo on (mean ± SD) glycosylated hemoglobin concentrations in diabetic patients with postischemic cardiomyopathy. (From Fragasso et al [21], with permission.)

and inhibiting FFA oxidation, have also been shown to improve left ventricular function in patients with heart failure [23].

Bearing in mind the concept that trimetazidine should, therefore, be able to promote the utilization of glucose and nonfatty substrates by the mitochondria, attention has been focused on this specific issue.

Effects of trimetazidine on endothelial function

It has recently been observed that trimetazidine was able to reduce the release of endothelin in cardiac patients (*Figure 3*) [21,24]. Growth factors, vasoactive substances, and mechanical stress are involved in the increase in ET-1 concentrations in patients with heart failure. Despite the known adaptive aspect of supporting contractility of the failing heart, persistent increases in cardiac expression of ET-1 in the failing heart have a pathophysiological maladaptive aspect and are associated with the severity of myocardial dysfunction [25].

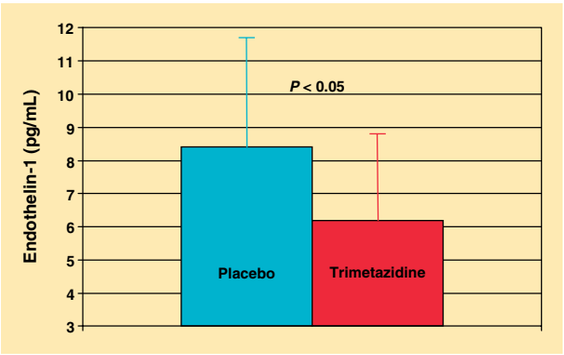

Figure 3. Long-term effects of trimetazidine and placebo on (mean ± SD) endothelin-1 concentrations in diabetic patients with postischemic cardiomyopathy. (From Fragasso et al [21], with permission.)

Trimetazidine-induced reduction in intracellular acidosis in ischemic myocardium [26] could influence, not only myocardial, but also endothelial, membranes. By decreasing endothelial damage, trimetazidine could inhibit ET-1 release – which, in turn, will ultimately decrease myocardial damage. A second hypothesis is that, simply by decreasing the effects of chronic myocardial ischemia, trimetazidine could inhibit the release of ET-1. The observed decrease in ET-1 release that is associated with trimetazidine may therefore be linked to the trimetazidine-induced reduction in myocardial ischemia. Finally, keeping in mind the close relationship between endothelium and insulin sensitivity, the observed effects of trimetazidine on endothelial function could also explain the beneficial action of trimetazidine on glucose metabolism.

Effects of trimetazidine on glucose metabolism

It has recently been shown that, apart from improving left ventricular function in cardiac patients, trimetazidine also improved overall glucose metabolism in the same patients (*Figure 1*), indicating an attractive ancillary pharmacological property of this class of drug [21]. The known insulin-resistant state in most cardiac patients is certainly aggravated in those patients with overt diabetes. This is particularly relevant in patients with both diabetes and left ventricular dysfunction. In this context, the availability of glucose and the ability of cardiomyocytes and skeletal muscle to metabolize glucose are grossly reduced. Indeed, as a major factor in the development and progression of heart failure is an already reduced availability of ATP, alterations in glucose metabolism could further impair the efficiency of cardiomyocytes in producing energy. By inhibiting fatty acid oxidation, trimetazidine stimulates total glucose utilization, including both glycolysis and glucose oxidation. The effects of trimetazidine on glucose metabolism could therefore be dependent on improved cardiac efficiency, and on improved peripheral extraction and utilization of glucose. Finally, in view of the known relationship between ET-1 concentration and abnormalities of glucose metabolism [1], the observed beneficial effects of trimetazidine on glucose metabolism could also be partly ascribed to the positive effect of the drug on the reduction in ET-1 concentrations.

Animal studies have also suggested that trimetazidine improves blood glucose utilization in rats with fasting hyperglycemia [27]. In this respect, we have recently evaluated both forearm metabolism of glucose and lipid and forearm release of endothelial vasodilator and vasoconstrictor factors during prolonged

inhibition of β-oxidation by trimetazidine in patients with postischemic left ventricular dysfunction. Trimetazidine increased both insulin-induced forearm glucose oxidation and release of cyclic guanosine monophosphate, whereas forearm release of ET-1 was decreased [28]. Although these findings need further confirmation, the effects of trimetazidine at the skeletal muscle level add a new therapeutic window in the treatment of patients with ischemic heart disease and type 2 diabetes.

Conclusions

Most cardiac diseases are associated with abnormalities of glucose homeostasis, which undoubtedly contribute to the progression of the primary disease. If not adequately treated, in most cardiac patients glucose metabolism abnormalities will contribute heavily to the occurrence of complications, among which severe left ventricular dysfunction is at present one of the most frequent and insidious. In addition to meticulous metabolic control of frank diabetes, special attention should be also paid to insulin resistance, a condition that is generally underdiagnosed as a distinct clinical entity. The combined beneficial effects of trimetazidine on left ventricular function and glucose metabolism make the use of this drug particularly attractive, especially in those cardiac patients in whom myocardial and glucose metabolism abnormalities coexist. ■

* See glossary for definition of these terms.

REFERENCES

1. Piatti PM, Monti LD, Galli L, et al. Relationship between endothelin-1 concentrations and the metabolic alterations typical of the insulin resistance syndrome. *Metabolism*. 2000;49:748–752.
2. Piatti PM, Monti LD, Zavaroni I, et al. Alterations in nitric oxide/cyclic-GMP pathway in nondiabetic siblings of patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2000;85:2416–2420.
3. Stanley WC, Lopaschuk GD, Hall JL, McCormack JG. Regulation of myocardial carbohydrate metabolism under normal and ischemic conditions: potential for pharmacological interventions. *Cardiovasc Res*. 1997;33:243–257.
4. Natali A, Taddei S, Quiñones Galvan A, et al. Insulin sensitivity, vascular reactivity, and clamp-induced vasodilatation in essential hypertension. *Circulation*. 1997;96:725–726.
5. Despres JP, Lamarche B, Mauriege P, et al. Hyperinsulinemia as an independent risk factor for ischemic heart disease. *N Engl J Med*. 1996;334:952–957.
6. Yoshimura T, Hisatomi A, Kajihara S, et al. The relationship between insulin resistance and polymorphisms of the endothelial nitric oxide synthase gene in patients with coronary artery disease. *J Atheroscler Thromb*. 2003;10:43–47.
7. Piatti PM, Fragasso G, Monti LD, et al. Endothelial and metabolic characteristics of patients with angina and angiographically normal coronary arteries. *J Am Coll Cardiol*. 1999;34:1452–1460.
8. Paolisso G, De Riu S, Marrazzo G, Verza M, Varricchio M, D'Onofrio F. Insulin resistance and hyperinsulinemia in patients with chronic heart failure. *Metabolism*. 1991;40:972–977.
9. Piatti P, Di Mario C, Monti LD, et al. Association of insulin resistance, hyperleptinemia, and impaired nitric oxide release with in-stent restenosis in patients undergoing coronary stenting. *Circulation*. 2003;108:2074–2081.
10. The Decode Study Group. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet*. 1999; 354:617–621.
11. Nuutila P, Knuuti MJ, Raitakari M, et al. Effect of antilipolysis on heart and skeletal muscle glucose uptake in overnight fasted humans. *Am J Physiol Endocrinol Metab*. 1994; 267:E941–E946.
12. Lewis GF, Carpentier A, Adeli K, Giacca A. Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. *Endocr Rev*. 2002;23:201–229.
13. Steinberg HO, Baron AD. Vascular function, insulin resistance and fatty acids. *Diabetologia*. 2002;45:623–634.
14. Wallhaus TR, Taylor M, DeGrado TR, Russell DC. Myocardial free fatty acid and glucose use after carvedilol treatment in patients with congestive heart failure. *Circulation*. 2001; 103:2441–2446.
15. Chierchia S, Fragasso G. Metabolic management of ischaemic heart disease. *Eur Heart J*. 1993;14 (suppl G):2–5.
16. Fragasso G, De Cobelli F, Perseghin G, et al. Improved myocardial high-energy phosphate metabolism induced by partial fatty acid inhibition in patients with heart failure. *J Am Coll Cardiol*. 2004;43:190A.
17. Monti LD, Allibardi S, Piatti PM, et al. Triglycerides impair postischemic recovery in isolated hearts: roles of endothelin-1 and trimetazidine. *Am J Physiol Heart Circ Physiol*. 2001; 281:H1122–H1130.
18. 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;86:580–588.
19. Brottier L, Barat JL, Combe C, Boussens B, Bonnet J, Bricaud H. Therapeutic value of a cardioprotective agent in patients with severe ischemic cardiomyopathy. *Eur Heart J*. 1990;11:207–212.
20. Lu C, Dabrowski P, Fragasso G, Chierchia SL. Effects of trimetazidine on ischemic left ventricular dysfunction in patients with coronary artery disease. *Am J Cardiol*. 1998; 82:898–901.
21. Fragasso G, Piatti PM, Monti L, et al. Short and long term beneficial effects of partial free fatty acid inhibition in diabetic patients with ischemic dilated cardiomyopathy. *Am Heart J*. 2003;146:E1–E8.
22. Rosano GMC, Vitale C, Sposato B, Mercuro G, Fini M. Trimetazidine improves left ventricular function in diabetic patients with coronary artery disease: a double-blind placebo-controlled study. *Cardiovasc Diabetol*. 2003;2:16/1–16/9.
23. Bersin RM, Wolfe C, Kwasman M, et al. Improved hemodynamic function and mechanical efficiency in congestive heart failure with sodium dichloroacetate. *J Am Coll Cardiol*. 1994;23:1617–1624.
24. Fragasso G, Piatti P, Monti L, et al. Acute effects of heparin administration on the ischemic threshold of patients with coronary artery disease: evaluation of the protective role of the metabolic modulator trimetazidine. *J Am Coll Cardiol*. 2002;39:413–419.
25. Yamauchi-Kohno R, Miyauchi T, Oshino T, et al. Role of endothelin in deterioration of heart failure due to cardiomyopathy in hamsters: increase in endothelin production in the heart and beneficial effect of endothelin A antagonist on survival and cardiac function. *Circulation*. 1999;99:2171–2176.
26. Maridonneau-Parini I, Harpey C. Effects of trimetazidine on membrane damage induced by oxygen free radicals in human red cells. *Br J Clin Pharmacol*. 1985;20:148–151.
27. Cano C, Bermúdez VJ, Medina MT, et al. Trimetazidine diminishes fasting glucose in rats with fasting hyperglycemia: a preliminary study. *Am J Ther*. 2003;10:444–446.
28. Monti LD, Setola E, Fragasso G, et al. Metabolic and endothelial effects of trimetazidine on forearm muscle in patients with type 2 diabetes and ischemic cardiomyopathy. *Am J Physiol Endocrinol Metab*. 2006;290:E54–E59.

Hypercalcemia and the cardiovascular system

V.J. Karthikeyan, J.M. Khan and G.Y.H. Lip
University Department of Medicine, City Hospital, Birmingham, UK

Correspondence: Professor G. Y. H. Lip, University Department of Medicine, City Hospital, Birmingham, UK. Tel: +44 121 507 5080; e-mail: g.y.h.lip@bham.ac.uk

Abstract

Hypercalcemia, acute and chronic, irrespective of the cause, is known to have effects on the heart and the vascular system that are potentially life-threatening. Some of these effects include accelerated atherosclerosis, uncontrolled hypertension, structural effects, and progressive cardiac dysfunction. This case report demonstrates the effects of hyperparathyroidism-induced hypercalcemia on the cardiovascular system and clinical management in a patient with hypertension that was difficult to control.

Heart Metab. 2006;30:25–29.

Keywords: Hypercalcemia, hyperparathyroidism, hypertension, heart failure, complete heart block, renal failure

Case report

A 45-year-old woman was referred to the hypertension clinic by her general practitioner, for assessment of a persistently increased blood pressure (> 160/110 mm Hg) over a 2-month period. On routine blood tests, she was noted to have an increased calcium concentration (corrected calcium 3.52 mmol/L), and was then admitted to hospital for further evaluation and treatment. Further blood tests revealed increased parathyroid hormone concentrations (266 pg/ml). Her alkaline phosphatase and vitamin D concentrations were normal. She was previously fit and well, with no significant past medical history, and was commenced on atenolol 50 mg a few days before her admission to hospital for control of her high blood pressure. Further questioning revealed that she had been feeling tired and low in the recent past. The patient had never smoked, and consumed alcohol only occasionally. Her father and brother were known to have high blood pressure.

On assessment, her pulse was 60 beats/min and her blood pressure was 145/85 mm Hg. There were no cardiac murmurs, and her lung fields were clear. The initial management was aimed at achieving normocalcemia and the patient was treated with intravenous fluids and pamidronate. Further investigations were carried out, and a parathyroid iodine/methoxyl isobutyl isonitrile (I/MIBI) scan (*Figure 1*) revealed a parathyroid adenoma at the lower pole of the right thyroid gland. Her calcium concentrations were monitored throughout her treatment. Echocardiography revealed normal left ventricular function, with no left ventricular hypertrophy. The heart valves were normal, with no significant aortic valve or left ventricular outflow tract gradient. Blood pressure was monitored during her hospital stay and found to have decreased with treatment of her hypercalcemia (*Table I, Figure 2*).

The patient was subsequently referred to the surgeons and underwent a partial parathyroidectomy and resection of the adenoma. Her serum calcium concentration decreased during the postoperative period (2.69 mmol/L) and her blood pressure decreased to 110/60 mm Hg.

Four months later, the patient was reviewed in the hypertension clinic and found to be well and asymptomatic, with a blood pressure of 125/71 mm Hg, although her calcium concentrations (2.85 mmol/L) were increased again.

The calcium concentrations gradually increased over the next few months (*Table I, Figure 3*), with a

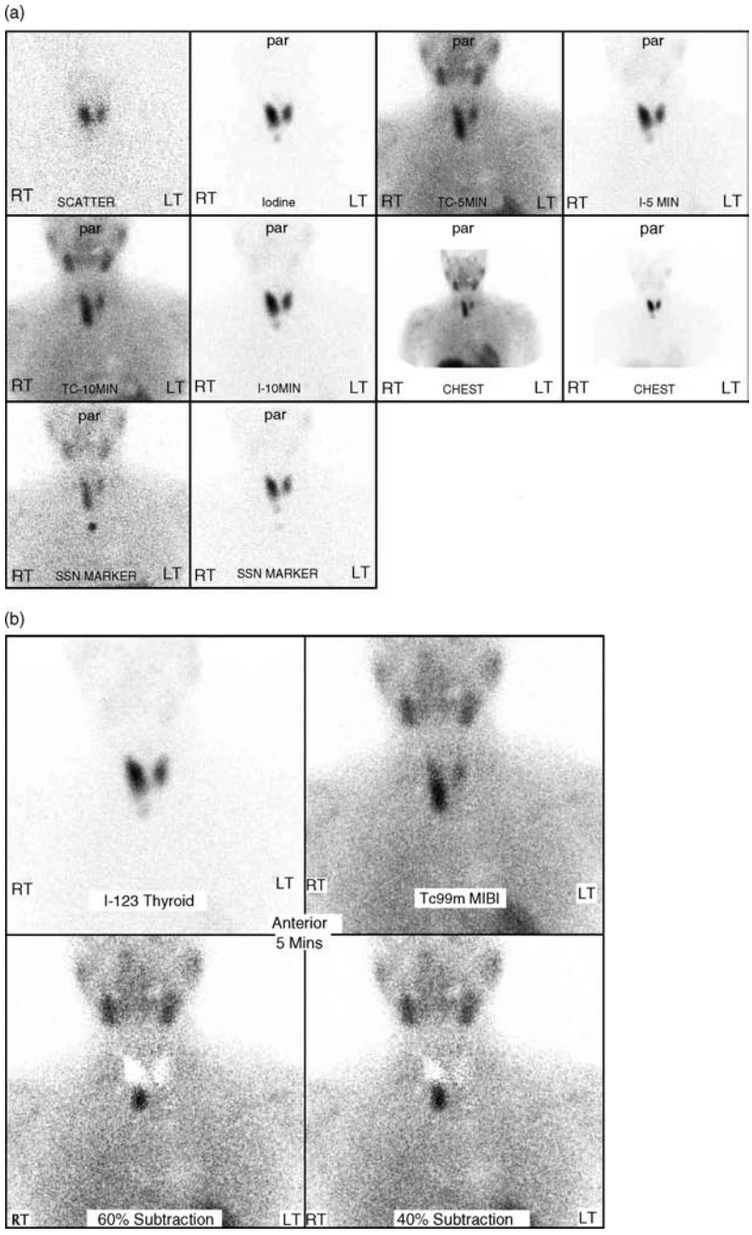

Figure 1. Parathyroid I/MIBI Scans at initial workup.

Table I. The patient's serum calcium and parathyroid hormone concentrations and blood pressure profile, from October 2004 to August 2005.

	Month and year								
	Oct 04	Oct 04	Nov 04	Dec 04	Feb 05	Mar 05	Apr 05	Jun 05	Aug 05
Serum calcium[a] (mmol/l)	3.52	2.69	2.81	3.25	3.02	2.92	2.84	3.03	2.85
Serum PTH (pg/ml)	266			126	156	124	117	116	76
Blood pressure (mm Hg)	147/87	110/70	110/66	153/92				142/95	125/71

[a]Corrected value. PTH, parathyroid hormone.

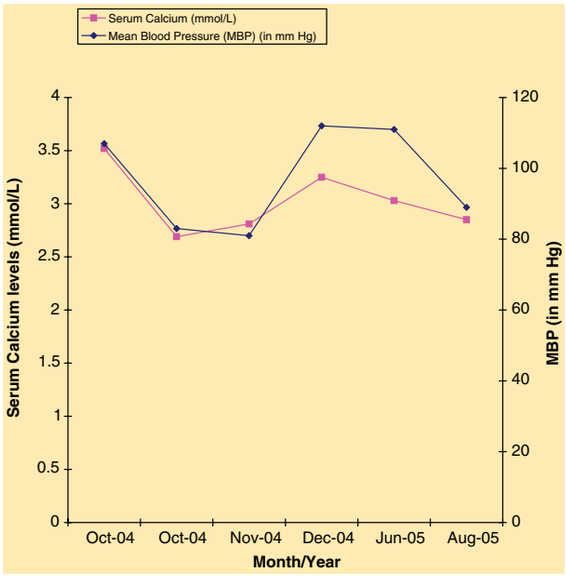

Figure 2. Serum Calcium vs Mean Blood Pressure.

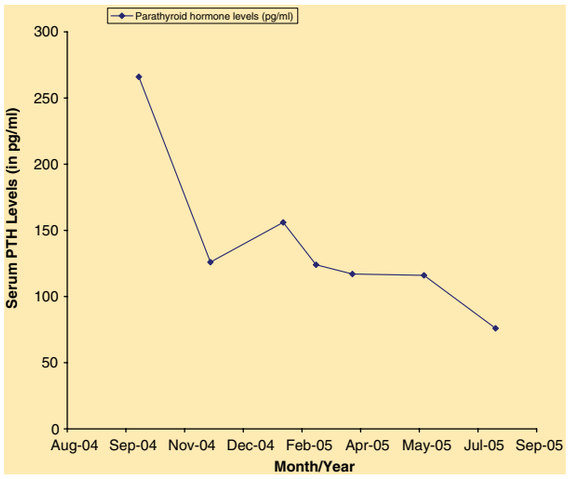

Figure 4. Trend in Serum Parathyroid hormone levels(PTH) (in pg/ml).

corresponding increase in parathyroid hormone concentrations (*Table I*, *Figure 4*). The patient also developed symptoms of polyuria and polydipsia. Repeat imaging of the neck was performed. A sonography of the neck (*Figure 5*) showed a single benign nodule in the lower pole of right lobe of the thyroid gland. However, an MRI scan (*Figure 6*) revealed a 10 × 10-mm focal area of high signal, seen in the inferior aspect of the right thyroid lobe, and a subsequent parathyroid I/MIBI scan (*Figure 7*) confirmed increased uptake in the inferior aspect of the right lobe of the thyroid, suggesting a recurrence of the adenoma. Her blood pressure increased to 142/95 mm Hg. She currently awaits a parathyroidectomy.

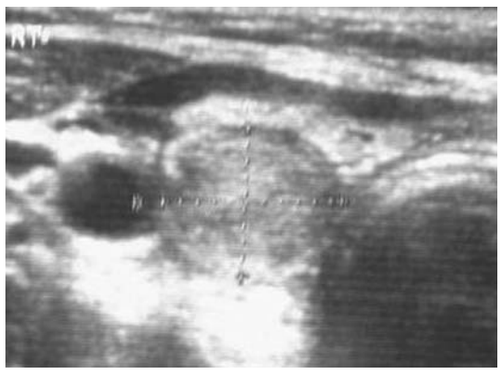

Figure 5. Sonography of the neck. Parathyroid Adenoma.

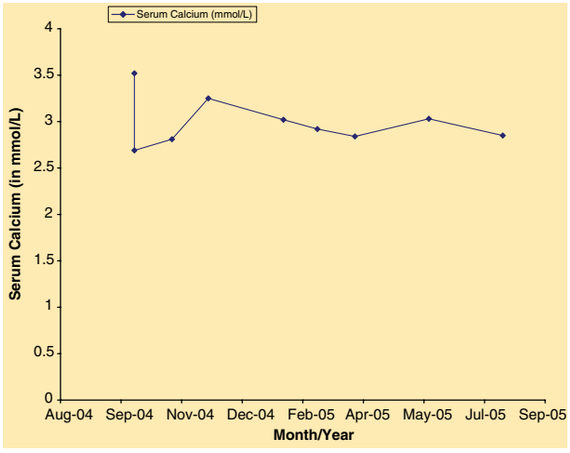

Figure 3. Trend in Serum Calcium levels (in mmol/L).

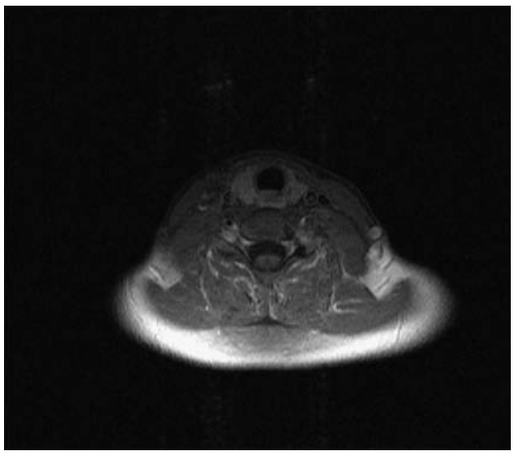

Figure 6. MRI Scan Neck.

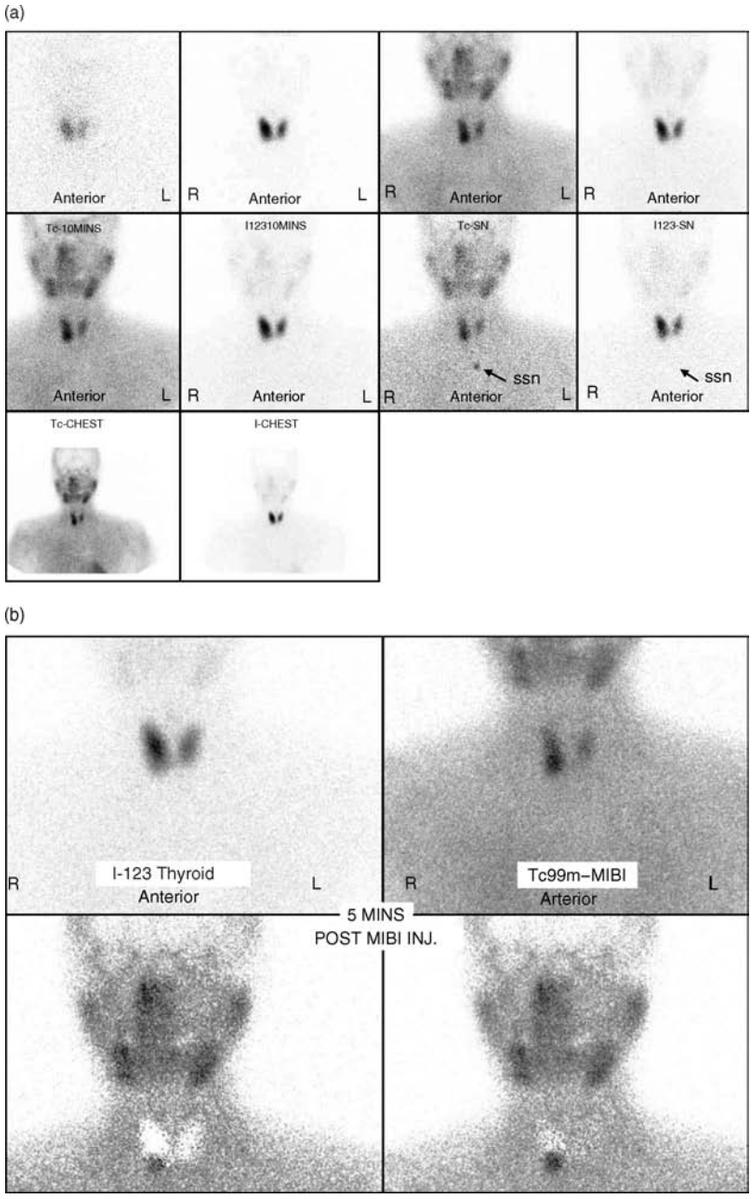

Figure 7. Repeat parathyroid I/MIBI Scan a few months later.

Discussion

Hyperparathyroidism is characterized by hypercalcemia resulting from excessive release of parathyroid hormone (PTH), most cases being discovered accidentally when hypercalcemia is noted during a routine serum chemistry profile. In most patients, symptoms are mild at the time of presentation and resolve with surgical correction of the disorder. In 85% of affected persons, primary hyperparathyroidism (PHPT) results from an adenoma in a single parathyroid gland. Hypertrophy of all parathyroid glands causes hyperparathyroidism in 15% of patients. Parathyroid malignancies account for a small number of cases of hyperparathyroidism. The parathyroid glands regulate calcium and phosphorus concentrations by releasing variable amounts of parathyroid hormone, which increases serum calcium concentrations while decreasing serum phosphorus. Under usual conditions, the rate of secretion of parathyroid hormone is inversely proportional to the serum calcium concentration.

Hyperparathyroidism, particularly PHPT, with changes in the serum calcium and PTH, is known to affect cardiovascular function. The cardiovascular effects of hypercalcemia include hypertension, left ventricular hypertrophy, arrhythmias, vascular calcification, and a shortened QT interval on the

electrocardiogram. Once a symptomatic disorder characterized by significant hypercalcemia, PHPT today is most commonly seen in asymptomatic individuals with serum calcium concentrations that are within 1 mg/dL of the upper limits of normal, with a consequent change in the cardiovascular manifestations [1]. It is hypothesized that calcium is related to the development of hypertension by its effect on smooth muscle vasoconstriction.

Of note, both acute and chronic hypercalcemia can cause hypertension. Acute hypercalcemic hypertension is postulated to be related to the effects of calcium on the vascular smooth muscle cells, with increased calcium ion influx through calcium channels and a direct effect on vascular smooth muscle cells and increased vascular resistance. In addition, increased catecholamines have been demonstrated in hypercalcemia-induced hypertension. Indeed, the release of catecholamine is dependent upon calcium ion activity, with calcium ions facilitating the release of epinephrine from the adrenal medulla and norepinephrine from sympathetic nerve ending. Catecholamines, via binding with α_2-adrenergic receptors, could induce vasoconstriction [2]. However, Maheswaran and Beevers [3] did not find a significant correlation between calcium concentrations and preoperative blood pressure in 115 patients with PHPT who subsequently underwent parathyroidectomy.

Increased PTH, with its direct positive chronotropic and mediated inotropic effects on the heart, has been associated with the development of left ventricular hypertrophy [1]. Although there have been suggestions of a role of increased PTH concentrations in the pathogenesis of hypertension, infusion of synthetic PTH has been reported to cause a decrease in the blood pressure [4].

Patients with PHPT were considered to be at high risk of death from cardiovascular disease [5–8]. A Swedish study that followed patients with hyperparathyroidism for more than 10 years showed that mortality from cardiovascular disease was greater in the study individuals with hyperparathyroidism than in the control population. Patients with hyperparathyroidism are also more likely than control individuals to have hypertension and congestive heart failure, and are more likely to exhibit changes on the electrocardiogram [9]. Hypertrophic cardiomyopathy and a decrease in function of the muscles of ventilation may account for some of this effect [10].

Summary

Hypercalcemia and PHPT are associated with the development of hypertension that may be difficult to control, with resulting end-organ effects such as left ventricular hypertrophy, heart failure, and renal damage. The evaluation and work-up of patients with hypertension that is uncontrolled or difficult to control should include a check of the patient's serum calcium concentrations to rule out hypercalcemia and PHPT, as treatment of the high serum calcium concentrations may improve blood pressure control and prevent end-organ damage. ■

REFERENCES

1. Silverberg SJ. Cardiovascular disease in primary hyperparathyroidism. *J Clin Endocrinol Metab*. 2000;85:3513–3514.
2. Eiam-Ong S, Eiam-Ong S, Punsin P, Sitprija V, Chaiyabutr N. Acute hypercalcemia-induced hypertension: the roles of calcium channel and alpha-1 adrenergic receptor. *J Med Assoc Thai*. 2004;87:410–418.
3. Maheswaran R, Beevers DG. Clinical correlates in parathyroid hypertension. *J Hypertens Suppl*. 1989;7:S190–S191.
4. Pang PKT, Yang MCM, Tenner TE, Chang JK, Shimizu M. Hypotensive action of synthetic fragments of parathyroid hormone. *J Pharmacol Exp Ther*. 1981;26:567–571.
5. Palmer M, Adami HO, Bergstrom R, Akerstrom G. Mortality after surgery for primary hyperparathyroidism: a follow-up of 441 patients operated on from 1956 to 1979. *Surgery*. 1987;102:1–7.
6. Hedback G, Tisell LE, Bengtsson BA, Hedman I, Oden A. Premature death in patients operated on for primary hyperparathyroidism. *World J Surg*. 1990;14:829–835.
7. Ljunghall S, Jakobsson S, Joborn C, Palmer M, Rastad J, Akerstrom G. Longitudinal studies of mild primary hyperparathyroidism. *J Bone Miner Res*. 1991;6:S11–S16.
8. Hedback G, Oden A. Increased risk of death from primary hyperparathyroidism – an update. *Eur J Clin Invest*. 1998;28:271–276.
9. Lind L, Ljunghall S. Pre-operative evaluation of risk factors for complications in patients with primary hyperparathyroidism. *Eur J Clin Invest*. 1995;25:955–958.
10. Clark O. *Current surgical diagnosis and treatment (CD-ROM)*. 10th edn. Stanford, Conn.: Appleton & Lange;1994.

What is insulin resistance?

Gurushankar Govindarajan, Harvinder Gill, Michael Rovetto and James R. Sowers
University of Missouri School of Medicine, Departments of Internal Medicine and Medical Pharmocology and Physiology, and Harry S. Truman VA Medical Center, Columbia, MO, USA

Correspondence: James Sowers, Department of Internal Medicine, Division of Nephrology, MA410, DC043.00, One Hospital Dr., Columbia, MO 65212, USA.
E-mail: sowersj@health.missouri.edu

Abstract

Reduced insulin responses and subsequent compensatory elevated plasma insulin concentrations result in abnormal function in all body tissues and present clinically as serious cardiovascular, renal, and diabetic related diseases. Insulin resistance most frequently results from changes in post-insulin receptor signalling pathways although insulin receptor changes may occur, (eg, production of receptor antibodies). Insulin resistance is genetically linked but obesity and lack of exercise are causes. Insulin resistance precedes type 2 diabetes and is strongly associated with hypertension, the cardiometabolic syndrome and polycystic ovary disease. There are a number of markers of insulin resistance and its treatment includes lifestyle changes and drug therapy for components of the syndrome.
■ *Heart Metab.* 2006;30:30–34.

Keywords: Hypertension, polycystic ovary disease, cardiometabolic syndrome, diabetes mellitus, cardiovascular disease, renal disease

Definition of insulin resistance

Insulin resistance is a state in which there are impaired biological and physiological responses to insulin in tissue. In its early stages, there is a compensatory increase in insulin concentrations. Although hyperinsulinemia may compensate for resistance to some biological actions of insulin, it may result in overexpression of actions in tissues that retain normal or minimally impaired sensitivity to insulin. This metabolic dysfunction leads to a cluster of abnormalities with serious clinical consequences – most importantly, cardiovascular disease (CVD), chronic kidney disease and type 2 diabetes.

Mechanism of insulin resistance

Insulin resistance can be caused by prereceptor, receptor, or postreceptor abnormalities [1]. Prereceptor causes include the presence of anti-insulin antibody and abnormal insulin (mutation). The receptor causes for insulin resistance include decreased number of receptors, structural modification of the insulin receptor, and the presence of insulin receptor-blocking antibody. Both prereceptor and receptor causes of insulin resistance occur infrequently; the most usual cause is postreceptor in nature and involves the postreceptor signaling pathway.

Insulin has many physiological effects, which can be divided into acute and chronic: the acute effects include those that regulate intermediary metabolism, and chronic effects include the growth and proliferative effects of insulin. These two different actions are possible because of activation of two different cascades of actions by insulin. One pathway transmits the insulin signal through insulin receptor substrate (IRS) proteins and phosphatidyl inositol 3-kinases (PI3-K) to a series of intracellular proteins (*Figure 1*). Activation of this pathway is crucial for transducing the actions of insulin/insulin like growth factor-1 (IGF-1) in cardiovascular tissue, in addition to conventional insulin-sensitive tissues [1]. PI3-K mediates the increases in nitric oxide, Na^+ pump, K^+ channel, and calcium (Ca^{2+}) myofilament sensitivity by increasing the trafficking and translocation of nitric oxide synthase and cation pump units, in addition to glucose transporters. The second pathway involves activation of the mitogen-activation protein kinase (MAPK) pathway*, which increases growth and mitogenic processes

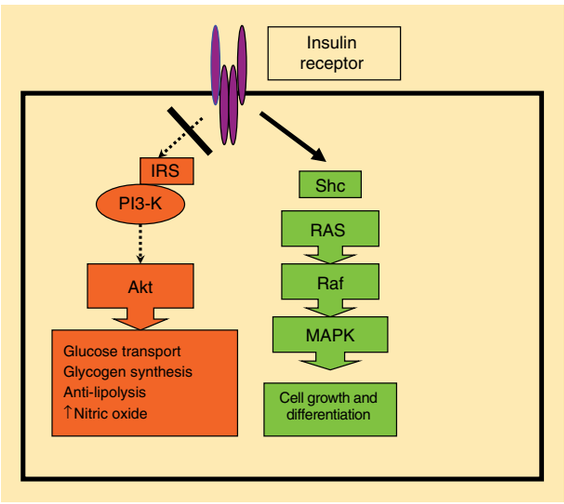

Figure 1. Insulin mediates its intracellular action through two different pathways. One, the phosphatidyl inositol 3-kinase/insulin receptor substrate (PI3-K/IRS) pathway through protein kinase B (Akt), regulates intermediary metabolism involved with glucose transport. The other pathway, through the adaptor protein (Shc), the guanine nucteotide binding protein (RAS) and serine-threonine kinase (Raf), and the mitogen-activated protein kinase (MAPK) cascade, regulates the growth and mitogenic pathway. In clinical insulin resistance, the resistance occurs in the PI3-K/IRS pathway.

[2,3]. In the vast majority of patients, the insulin resistance observed clinically is one that involves glucose metabolism through the PI3-K pathway (*Figure 2*). For this reason, the term 'insulin resistance', as used in clinical and experimental settings, is a state in which there is impaired glucose metabolism. Therefore, resistance to the actions of insulin and IGF-1 in these tissues occurs whenever there is reduced activation of PI3-K. In biological and physiological terms, however, it could apply to impaired response of the tissue to either of the two pathways.

Etiology of insulin resistance

Insulin resistance is postulated to have a genetic etiology, as it is observed to run in families. Other notable causes for insulin resistance include obesity and lack of exercise. Indeed, weight loss and exercise tend to reduce insulin resistance. Other causes of insulin resistance are listed in *Table I*.

Table I. Major causes of insulin resistance.

- Genetic abnormalities.
- Obesity and inactivity (leptins, cytokines, and excess free fatty acids may be involved).
- Counter-regulatory hormones.
- Immune-mediated (anti-insulin antibodies, anti-insulin receptor antibodies).
- Medications.
- Fetal malnutrition.
- Miscellaneous clinical conditions (eg, stress, chronic infections, pregnancy, starvation, cirrhosis, ketoacidosis, and uremia).

Table II. Prevalence of insulin resistance (IR) in certain clinical states. (From the Bruneck Study [5], with permission.)

Clinical state	Prevalance of IR (%)
Type 2 diabetes mellitus	84
Impaired glucose tolerance	66
Hypercholesterolemia	54
Low HDL and high triglyceridemia	85
Hypertension	58

HDL, high-density lipoprotein.

Prevalence of insulin resistance

The prevalence of insulin resistance in the general population varies with the criteria used for its definition. In certain studies it has been estimated that insulin resistance is prevalent in 30% of the adult population [4]. The prevalence of the condition is even greater in metabolic disease such as diabetes and the cardiometabolic syndrome [5]. *Table II*. lists the prevalence of insulin resistance in various disease entities. The increased prevalence of insulin resistance and the consequent cardiometabolic syndrome is being increasingly recognized in the USA, as obesity is becoming a major epidemic [6].

Insulin resistance and type 2 diabetes mellitus

Insulin resistance predates the onset of clinical type 2 diabetes mellitus by years. Most people have β-cell function that is adequate to fulfill normal tissue insulin requirements; the majority of these people also have considerable reserve, and could increase their insulin secretion considerably if necessary. However, a significant segment of the population exists that has limited reserve function. In this population, insulin resistance increases the insulin requirement of the tissue beyond the secretory capacity of the β cells. The recent surge in the incidence of diabetes mellitus worldwide can be attributed to an increased prevalence of insulin resistance in the general population as a result of the epidemic of obesity.

Insulin resistance and hypertension

It is estimated that about 25–47% of individuals with hypertension have insulin resistance [7]. Similarly, there is considerable evidence for an increased prevalence of hypertension in disease processes associated

Table III. Mechanisms of insulin resistance in hypertension.

Decreased nonoxidative glucose metabolism by skeletal muscle.
Post-insulin receptor defects:
- Decreased signaling through the PI3-K–Akt pathway.
- Decreased mobilization of GLUT-4 to the plasma membrane.
- Decreased insulin-mediated glucose transport.
- Decreased glycogen synthase activity.

Increased reactive oxygen species.
Altered skeletal muscle fiber type:
- Increased adipose tissue.
- Decreased insulin-sensitive slow twitch skeletal muscle fibers.

Decreased skeletal muscle blood flow with reduced delivery of insulin and glucose:
- Reduced generation of nitric oxide.
- Vascular rarefaction.

Vascular hypertrophy.
Increased vasoconstriction.

Akt, protein kinase B; GLUT-4, glucose transporter-4; PI3-K, phosphatidyl inositol 3-kinase. (from Reference [10], with permission).

with insulin resistance, such as type 2 diabetes mellitus [8]. Several mechanisms have been postulated for the high prevalence of insulin resistance in patients with essential hypertension (*Table III*) [9,10]. Some of the mechanisms suggested to underlie the coexistence of insulin resistance and hypertension include [11–17]:

- upregulation of the renin–angiotensin–aldosterone system;
- activation of the sympathetic nervous system;
- increased renal tubular sodium retention;
- increased intracellular calcium concentration;
- vascular smooth muscle cell proliferation and atherosclerosis;
- impaired nitric oxide metabolism in skeletal muscle.

Therapies targeted at insulin resistance, such as aerobic exercise or thiazolidinedione drugs, also result in a decrease in blood pressure [18,19].

Insulin resistance and the cardiometabolic syndrome

Metabolic dysfunction associated with insulin resistance leads to a cluster of abnormalities with serious clinical consequences – most importantly, CVD, type 2 diabetes mellitus, or both. This cluster of CVD and diabetic risk factors (which include central obesity, hypertension, dyslipidemia, microalbuminuria, and hypercoagulability) is known as the cardiometabolic syndrome. It was identified in 1988 by Reaven, who named the cluster 'syndrome X' [20]. Since Reaven, it has been given many other names; the more popular ones that are still applied to it include: the insulin resistance syndrome, the deadly quartet, obesity dyslipidemic syndrome, and the metabolic syndrome. This collection of risk factors increases the risk of CVD endpoints, such as stroke, congestive heart failure, chronic kidney disease, and overall mortality [6,10,21–23] (*Table IV*). The presence of even one or two of the risk factors multiplies the risk for both CHD and CVD [24]. The World Health Organization (*Table V*) [25] and the National Cholesterol Education Program (*Table VI*) [26] have produced diagnostic criteria for the identification of this syndrome among the general population (*Figure 2*).

Polycystic ovarian disease

Polycystic ovary syndrome (PCOS) is an exceptionally common disorder of premenopausal women, characterized by hyperandrogenism and chronic anovulation. The condition affects about 5–10% of women in the reproductive age group. Insulin resistance has proved to be a key factor in the pathogenesis of PCOS. The treatment of PCOS has, so far, been focused on treatment of the clinical signs and symptoms. Oral contraceptives have been the standard treatment. There is now a greater focus on the management of the metabolic consequences of PCOS, primarily through lifestyle intervention to achieve weight loss and increase physical activity. Insulin-sensitizing drugs such as metformin and thiazolidinediones have proved to be effective in the management of the

Table IV. The manifestations of metabolic syndrome that are associated with increased risk of cardiovascular disease.

- Impaired glucose tolerance
- Visceral obesity
- Microalbuminuria
- Chronic kidney disease
- Dyslipidemia
- Increased PAI/PA ratio
- Increased serum fibrinogen concentration
- Increased serum C-reactive proteins
- Increased uric acid concentration
- Increased production of interleukin-6
- Increased blood viscosity
- Increased systolic and pulse pressures
- Left ventricular hypertrophy
- Premature atherosclerosis
- Enhanced tissue RAAS
- Salt sensitivity
- Endothelial dysfunction

PAI/PA, plasminogen activator inhibitor/plasminogen activator; RAAS, renin–angiotensin–aldosterone system.

Table V. World Health Organization (WHO) clinical criteria for metabolic syndrome. (Data from Alberti et al. [26].)

Insulin resistance, identified by 1 of the following:
- Type 2 diabetes
- Impaired fasting glucose
- Impaired glucose tolerance or...
- For those with normal fasting glucose concentrations (< 110 mg/dL), glucose uptake below the lowest quartile for the background population under investigation under hyperinsulinemic, euglycemic conditions.

Plus any 2 of the following:
- Antihypertensive medication or high blood pressure (≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic) or both
- Plasma triglycerides ≥ 150 mg/dL (≥ 1.7 mmol/L)
- Low HDL cholesterol: < 35 mg/dL (< 0.9 mmol/L) in men < 39 mg/dL (< 1.0 mmol/L) in women
- BMI > 30 kg/m^2 or waist : hip ratio > 0.9 in men, > 0.85 in women or both
- Urinary albumin excretion rate ≥ 20 μg/min or albumin : creatinine ratio ≥ 30 mg/g

BMI, body mass index; HDL, high-density lipoprotein. Similar to National Cholesterol Education Program–Adult Treatment Panel (ATP) III, the WHO consultation group also recognized cardiovascular disease as the primary outcome of this syndrome. However, demonstration of insulin resistance was required for diagnosis, which differs from the recent ATP III guidelines. In addition to insulin resistance, the presence of two other risk factors are sufficient for the diagnosis of cardiometabolic syndrome.

metabolic disturbances, anovulation, and hirsutism, and are now widely accepted therapies.

Laboratory studies to identify insulin resistance

The gold standard for the assessment of insulin resistance is the euglycemic hyperinsulinemic clamp test

Table VI. National Cholesterol Education Program–Adult Treatment Panel III clinical identification of the metabolic syndrome. (Adapted from McFarlane et al. [6], with permission.)

Risk factor	Cutoff value
Abdominal obesity, given as waist circumference	
Men	≥ 102 cm (≥ 40 inches)
Women	≥ 88 cm (≥ 35 inches)
Triglycerides	≥ 150 mg/dL
High-density lipoprotein	
Men	< 40 mg/dL
Women	< 50 mg/dL
Blood pressure	≥ 130/85 mm Hg
Fasting glucose	≥ 110 mg/dL

These risk factors include a combination of categorical and borderline risk factors that can be readily measured in clinical practice. When three of the five listed characteristics are present, a diagnosis of metabolic syndrome can be made.

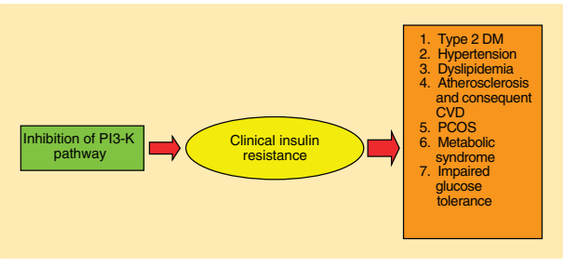

Figure 2. Clinical disease resulting from insulin resistance. Insulin resistance seen clinically is the result of impaired glucose metabolism arising out of inhibition of the phosphatidyl inositol 3-kinase/insulin receptor substrate (PI3-K/IRS) pathway. The consequences of insulin resistance depend partly on the background genetic makeup of the individual. CVD, cardiovascular disease; DM, diabetes mellitus; PCOS, polycystic ovary syndrome.

[27]. This technique involves the continuous intravenous administration of insulin and glucose over 3 hours, and the calculation of insulin sensitivity (the inverse of insulin resistance) by measuring the amount of glucose required to maintain normal glucose concentrations (euglycemia). However, the technique is impractical for routine clinical use, and therefore a number of surrogate indexes for insulin sensitivity or insulin resistance have been developed. The simplest and most commonly used marker in clinical practice is the homeostasis assessment (HOMA) model, which requires measurement only of the fasting plasma insulin and plasma glucose [28]. Using a patient's fasting blood values, the HOMA index for insulin resistance (HOMA-IR) can be calculated (*Table VII*):

$$\text{HOMA-IR} = (\text{fasting plasma insulin}\,(\mu\text{U/ml}) \times \text{fasting plasma glucose}\,(\text{mmol/L})/22.5$$

Similar to the HOMA index, there are other surrogate markers for insulin resistance such as log(HOMA) and the quantitative insulin-sensitivity check index (QUICKI). Chen et al [29] showed that log(HOMA) and QUICKI have an excellent linear correlation with the euglycemic hyperinsulinemic clamp test and are superior to many other surrogate indexes currently used.

Table VII. HOMA index for insulin resistance (HOMA-IR).

Group	Mean HOMA-IR
Normal individuals	2.1–2.7
Individuals with impaired glucose tolerance	4.3–5.2
Individuals with type 2 diabetes	8.3–9.5

Treatment of insulin resistance

Therapeutic lifestyle changes and drug treatment for individual components of insulin resistance are the current norm of clinical practice. Lifestyle changes – including a healthy diet and regular exercise – contribute to weight loss, improved blood glucose control, and reduced hypertension and other cardiovascular risk factors, and can even prevent the development of type 2 diabetes mellitus in persons with insulin resistance. When the therapeutic lifestyle changes are not sufficient, pharmacotherapy with an insulin sensitizer should be added. The thiazolidinediones are the only drugs approved specifically for the treatment of insulin resistance. Thiazolidinediones are novel drugs that specifically target insulin resistance. They are agonists for the nuclear transcription factor, peroxisome proliferator-activated receptor-γ, and reduce insulin resistance and increase the uptake of glucose into peripheral tissues, which results in decreased insulin concentrations; they are also involved in lipid metabolism.

Conclusion

In summary, the development of insulin resistance can have a profound impact upon a number of disease states and has led to the widespread prevalence of the cardiometabolic syndrome. As researchers are becoming able to identify the mechanism of insulin resistance, health care professionals will be able to counsel and treat their patients in a more effective manner. This will be of the utmost importance in the years to come, as the epidemic of diabetes continues to grow and afflict people all around the world. ■

* See glossary for definition of these terms.

REFERENCES

1. Hunter SJ, Garvey WT. Insulin action and insulin resistance: diseases involving defects in insulin receptors, signal transduction, and the glucose transport effector system. *Am J Med*. 1998;105:331–345.
2. Sasaoka T, Ishiki M, Sawa T, et al. Comparison of the insulin and insulin-like growth factor 1 mitogenic intracellular signaling pathways. *Endocrinology*. 1996;137:4427–4434.
3. Sasaoka T, Rose DW, Jhun BH, Saltiel AR, Draznin B, Olefsky JM. Evidence for a functional role of Shc proteins in mitogenic signaling induced by insulin, insulin-like growth factor-1, and epidermal growth factor. *J Biol Chem*. 1994;269:13689–13694.
4. Haffner SM, Mykkanen L, Festa A, Burke JP, Stern MP. Insulin-resistant prediabetic subjects have more atherogenic risk factors than insulin-sensitive prediabetic subjects: implications for preventing coronary heart disease during the prediabetic state. *Circulation*. 2000;101:975–980.
5. Bonora E, Kiechl S, Willeit J, et al. Prevalence of insulin resistance in metabolic disorders: the Bruneck Study. *Diabetes*. 1998;47:1643–1649.
6. McFarlane SI, Banerji M, Sowers JR. Insulin resistance and cardiovascular disease. *J Clin Endocrinol Metab*. 2001;86:713–718.
7. Lind L, Berne C, Lithell H. Prevalence of insulin resistance in essential hypertension. *J Hypertens*. 1995;13:1457–1462.
8. National High Blood Pressure Education Program Working Group report on hypertension in diabetes. *Hypertension*. 1994; 23:145–158.
9. Sloniger JA, Saengsirisuwan V, Diehl CJ, et al. Defective insulin signaling in skeletal muscle of the hypertensive TG(mREN2)27 rat. *Am J Physiol Endocrinol Metab*. 2005; 288:E1074–E1081.
10. Sowers JR. Insulin resistance and hypertension. *Am J Physiol Heart Circ Physiol*. 2004;286:H1597–H1602.
11. Modan M, Halkin H. Hyperinsulinemia or increased sympathetic drive as links for obesity and hypertension. *Diabetes Care*. 1991;14:470–487.
12. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care*. 1991;14:173–194.
13. DeFronzo RA. The effect of insulin on renal sodium metabolism. A review with clinical implications. *Diabetologia*. 1981;21:165–171.
14. Anderson EA, Hoffman RP, Balon TW, Sinkey CA, Mark AL. Hyperinsulinemia produces both sympathetic neural activation and vasodilation in normal humans. *J Clin Invest*. 1991; 87:2246–2252.
15. Berne C, Fagius J, Pollare T, Hjemdahl P. The sympathetic response to euglycaemic hyperinsulinaemia. Evidence from microelectrode nerve recordings in healthy subjects. *Diabetologia*. 1992;35:873–879.
16. Rowe JW, Young JB, Minaker KL, Stevens AL, Pallotta J, Landsberg L. Effect of insulin and glucose infusions on sympathetic nervous system activity in normal man. *Diabetes*. 1981;30:219–225.
17. Sowers JR. Treatment of hypertension in patients with diabetes. *Arch Intern Med*. 2004;164:1850–1857.
18. Raji A, Seely EW, Bekins SA, Williams GH, Simonson DC. Rosiglitazone improves insulin sensitivity and lowers blood pressure in hypertensive patients. *Diabetes Care*. 2003;26: 172–178.
19. Dengel DR, Hagberg JM, Pratley RE, Rogus EM, Goldberg AP. Improvements in blood pressure, glucose metabolism, and lipoprotein lipids after aerobic exercise plus weight loss in obese, hypertensive middle-aged men. *Metabolism*. 1998;47: 1075–1082.
20. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes*. 1988;37:1595–1607.
21. Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA*. 2002;288:2709–2716.
22. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care*. 2001;24:683–689.
23. Malik S, Wong ND, Franklin SS, et al. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation*. 2004;110:1245–1250.
24. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C, for the Conference P. Definition of Metabolic Syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition. *Circulation*. 2004;109:433–438.
25. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus: provisional report of a WHO consultation. *Diabet Med*. 1998;15:539–553.
26. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002; 106:3143–3421.
27. Ferrannini E, Mari A. How to measure insulin sensitivity. *J Hypertens*. 1998;16:895–906.
28. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28: 412–419.
29. Chen H, Sullivan G, Quon MJ. Assessing the predictive accuracy of QUICKI as a surrogate index for insulin sensitivity using a calibration model. *Diabetes*. 2005;54:1914–1925.

Featured research

Abstracts and commentaries

Obesity, insulin resistance, and the metabolic syndrome: determinants of endothelial dysfunction in Whites and Blacks

Lteif AA, Han K, Mather KJ. *Circulation*. 2005;112:32–38.

Insulin resistance is strongly associated with obesity and other components of the metabolic syndrome (MS). The relative importance of these components in the determination of endothelial function is unknown. Furthermore, there is conflicting evidence about whether ethnic differences exist in the relative importance of these components in regard to other cardiovascular outcomes. We evaluated the contributions of insulin resistance, obesity, and the other components of the MS to impaired endothelial function. The relationships of the MS components (as defined according the National Cholesterol Education Program) and insulin resistance (estimated using the homeostasis model) with endothelium-dependent vasodilatation were examined in 42 white and 55 black individuals. Endothelium-dependent vasodilatation was assessed as the increment in leg blood flow (measured by thermodilution) after exposure to methacholine chloride. Waist circumference, glucose, blood pressure, and insulin resistance distributions did not differ between ethnic groups; in our sample the black individuals had greater high-density lipoprotein cholesterol (1.31 compared with 1.09 mmol/L; $P < 0.001$) and lower triglyceride concentrations (1.01 compared with 1.37 mmol/L; $P < 0.005$) than white individuals. In the absence of the MS, black individuals exhibited reduced endothelium-dependent vasodilatation compared with white individuals ($P < 0.005$), and both groups demonstrated significantly worse endothelial function when the MS was present (maximal increase in leg blood flow: black individuals $107 \pm 9\%$ MS absent, $53 \pm 16\%$ MS present; white individuals $163 \pm 16\%$ MS present, $54 \pm 18\%$ MS absent; $P < 0.007$, MS absent compared with present; $P =$ NS for interaction of ethnicity and MS). Multivariable regression analysis examining relationships of endothelial function with the five MS components (analyzed as continuous variables) revealed independent relationships only with waist circumference ($P < 0.01$) and systolic blood pressure (SBP, $P < 0.02$). Waist circumference was no longer independently associated after insulin resistance had been added to the modeling ($P < 0.02$ for log of homeostasis model index of insulin resistance; $P < 0.02$ for SBP). Ethnicity still exerted an independent effect on endothelial function after the above components had been accounted for ($P < 0.04$ for an additional effect of ethnic status on endothelial function), with an ethnic difference in the effect of insulin resistance on endothelial function ($P < 0.046$ for interaction of ethnicity and log of homeostasis model index of insulin resistance). These findings suggest that insulin resistance and SBP are the principal determinants of endothelial dysfunction in the MS and that there are ethnic differences in the relative importance of these factors. These differences may imply different benefits from treatments targeting blood pressure or insulin resistance in different ethnic groups.

Commentary

Obesity and metabolic syndrome are associated with impaired endothelium-dependent vasodilatation. Insulin has a specific and physiological action to vasodilate skeletal muscle vasculature in humans; this action appears to be important both for the maintenance of vascular tone and the modulation of uptake of substrates. Insulin resistance has been reported to be associated with both defective insulin-mediated and endothelium-dependent vasodilatation; these findings suggest the possibility that the endothelium may also exhibit resistance to the action of insulin in modulating the endothelium-derived nitric oxide system. Obesity and the metabolic syndrome are associated with impaired endothelium-dependent vasodilatation. Insulin resistance is considered to be the pathogenic link between the components of

metabolic syndrome and endothelial dysfunction. This suggests that, in clinical practice, it would be important to measure insulin resistance in the metabolic syndrome state. Little information is available about ethnic differences between the presence of insulin resistance and cardiovascular outcomes. This study investigated the contribution of clinical variables associated with metabolic syndrome to the development of endothelial dysfunction. The study population included 42 white and 55 black individuals. At baseline, high-density lipoprotein cholesterol concentrations were higher and triglyceride concentrations were lower among black individuals; there were no statistical differences in insulin, glucose, or insulin resistance between the two groups. The endothelium-dependent vasodilatation was impaired in black individuals compared with their white counterparts, and both demonstrated a worse endothelial function in the presence of metabolic syndrome. The addition of the homeostasis model index (to calculate insulin resistance) removed the independent contribution of waist circumference in the determination of endothelial dysfunction, suggesting that, in obesity, the effects are mediated by insulin resistance.

Mario Marzilli

Impaired coronary blood flow in patients with metabolic syndrome: documented by Thrombolysis in Myocardial Infarction (TIMI) frame count method

Turhan H, Erbay AR, Yasar AS, Bicer A, Sasmaz H, Yetkin E. *Am Heart J*. 2004;148:789–794.

Endothelium plays an important part in regulating coronary vascular tone. In addition, several of the cardiovascular risk factors that are associated with the metabolic syndrome have been reported to be associated with endothelial dysfunction. In the present study we aimed to evaluate the coronary blood flow in patients with metabolic syndrome by means of the Thrombolysis in Myocardial Infarction (TIMI) frame count. Forty-two patients with metabolic syndrome (group I) and 42 control individuals without the syndrome (group II) were included in the study. All had angiographically proven normal coronary arteries. Diagnosis of metabolic syndrome was based on the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines published in 2001. Coronary flow rates of all participants were documented by TIMI frame count. TIMI frame counts for each of the major epicardial coronary arteries were found to be significantly greater in patients with metabolic syndrome than in controls (corrected TIMI frame count for left anterior descending coronary artery: 35 ± 7 compared with 25 ± 7, respectively; left circumflex coronary artery: 32 ± 9 compared with 25 ± 7, respectively; right coronary artery: 31 ± 9 compared with 24 ± 5, respectively; $P < 0.001$ for all). Statistically significant independent relationships were found between TIMI frame count and body mass index ($R^2 = 0.480$, $P < 0.009$), waist circumference ($R^2 = 0.551$, $P < 0.001$), and triglyceride concentration ($R^2 = 0.434$, $P < 0.036$). We have shown for the first time that patients with metabolic syndrome and angiographically normal coronary arteries have greater TIMI frame counts for all three coronary vessels, indicating impaired coronary blood flow, compared with control individuals without metabolic syndrome.

Commentary

Patients with metabolic syndrome and typical angina pectoris (group I) have been compared with control individuals without metabolic syndrome and atypical chest pain (group II). The study shows for the first time that patients with metabolic syndrome and angiographically normal coronary arteries have greater TIMI frame counts for all three coronary vessels, indicating impaired coronary blood flow, compared with control individuals without metabolic syndrome. Given the absence of epicardial obstructions, greater TIMI frame counts are likely to reflect a microvascular dysfunction. Because of the important role of endothelium in the control of coronary blood flow (by regulating coronary vascular resistance) and because of the association of the insulin resistance with endothelial dysfunction, metabolic syndrome and impaired coronary blood flow could be ascribed, at least in part, to an absolute or relative deficiency in the action of insulin on the vessel wall. Furthermore, the significant positive correlations between mean TIMI frame count and body mass index, waist circumference, triglyceride concentration (the most frequent components of metabolic syndrome in group I), and fasting plasma glucose is intriguing. Body mass index and central fat distribution are inversely related to the endothelium-dependent vasodilatation. The increased concentrations of free fatty acid, resulting from increased lipolysis, indirectly increase the release of vasoconstrictor substances (such as endothelin-1), have a direct effect on the endothelial nitric oxide system, and may also induce the formation of reactive oxygen species that could quench nitric oxide and thus result in decreased nitric oxidation at the level of vascular smooth muscle.

Mario Mazilli

Postconditioning the human heart

Patrick Staat, Gilles Rioufol, Christophe Piot, et al. *Circulation*. 2005;112:2143–2148

In animal models, brief periods of ischemia performed just at the time of reperfusion can reduce infarct size, a phenomenon called postconditioning. In this prospective, randomized, controlled, multicenter study, we investigated whether postconditioning may protect the human heart during coronary angioplasty for acute myocardial infarction.

Thirty patients, submitted to coronary angioplasty for ongoing acute myocardial infarction, contributed to the study. Patients were randomly assigned to either a control or a postconditioning group. After reperfusion by direct stenting, control individuals underwent no further intervention, whereas postconditioning was performed within 1 min of reflow by four episodes of 1 min of inflation and 1 min of deflation of the angioplasty balloon. Infarct size was assessed by measuring total creatine kinase release over 72 h. Area at risk and collateral blood flow were estimated on left ventricular and coronary angiograms. No adverse events occurred in the postconditioning group. Determinants of infarct size, including ischemia time, size of the area at risk, and collateral flow, were comparable between the two groups. Area under the curve of creatine kinase release was significantly reduced in the postconditioning group, averaging 208 984 ± 26 576 arbitrary units, compared with 326 095 ± 48 779 in control individuals – a 36% reduction in infarct size. Blush grade, a marker of myocardial reperfusion, was significantly increased in postconditioned compared with control individuals: 2.44 ± 0.17 and 1.95 ± 0.27, respectively ($P < 0.05$).

These findings suggest that postconditioning by coronary angioplasty protects the human heart during acute myocardial infarction.

Commentary

Many have heard of ischemic preconditioning but, I suspect, fewer of ischemic postconditioning. Ischemic preconditioning was described, about two decades ago, as a way of protecting the heart against infarction by subjecting it to prior, repeated, short episodes of ischemia. In contrast, ischemic postconditioning was described only as recently as 2003 [1]. As the name suggests, it describes a method of reducing infarction by subjecting the heart to repeated short episodes of ischemia after the event. In other words, interrupting the reperfusion that follows the prolonged period of ischemia that causes infarction. Those with long memories will realize that this is really a modified form of reperfusion. Studies many years ago showed an attenuation of injury by curtailing reperfusion, especially the reactive hyperemic phase that occurs immediately after ischemia. This has caused some to question whether postconditioning really is a new phenomenon, or merely 'old wine in new bottle' [2]; I would tend to agree with the wine analogy. Nonetheless, the new bottle is attractive and has done an excellent job at promoting the old wine. Consequently, the field of reperfusion injury has become revitalised. One manifestation of its vitality is the above manuscript.

Staat and his fellow collaborators with Ovize have been quick off the mark in performing a small 'proof of principle' study in the setting of primary percutaneous coronary intervention for ST-segment elevation myocardial infarction (STEMI). The attraction of postconditioning, in contrast to preconditioning, is that it can be applied after occlusion of the infarct-related artery. There is therefore no longer the need to predict this arbitrary event. Furthermore, primary percutaneous coronary intervention is an increasingly common mode of reperfusion that allows postconditioning with relative ease.

Patients with STEMI resulting from occlusion of either the left anterior descending or right coronary artery, and in whom direct stenting restored at least Thrombolysis In Myocardial Infarction grade 2 flow, were allocated randomly to groups to undergo either unhampered reperfusion (control) or 60 s of reperfusion followed by four 60-s episodes of intracoronary balloon inflation to prevent antegrade flow (postconditioned). Each of these inflations was separated by four periods of 60 s of balloon deflation, or interspersed reperfusion. Compared with the 14 controls, the 16 postconditioned patients had significant reductions in creatine kinase-derived infarction size and improved myocardial blush grade measured at minute 8 of reperfusion in both groups.

There are several minor criticisms that can be levelled at this study. The main concern is that this is a chance finding attributable to small group size and possible differences between the groups. However, Staat et al went to appreciable lengths to ensure that the main determinants of infarct size – duration of ischemia, myocardial risk volume, and depth of ischemia, or collateral flow – were adequately matched. However, the techniques used to measure these determinants were not contemporary. Other possible criticisms are that the principal endpoints of injury, creatine kinase release and blush grade, can be influenced by the postconditioning process, independent of a true reduction in infarct size. For example, blush grade was determined at minute 8 after balloon deflation; this equated to 8 min of reperfusion in the control group and only 4 min in the postconditioned group. Thus the postconditioned risk zone could have been inadequately reperfused and relatively hyperemic. Similarly, the postconditioning process

could conceivably alter the dynamics of creatine kinase release or reduce infarction at the expense of increased apoptosis.

Despite a number of possible minor criticisms, this is an important study that, if verified in a larger cohort, could alter the practice of primary percutaneous coronary intervention for STEMI, to the benefit of very many patients. The authors should be congratulated for their foresight and efficiency.

REFERENCES

1. Zhao ZQ, Corvera JS, Halkos ME, et al. Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. *Am J Physiol Heart Circ Physiol*. 2003;285:H579–H588.
2. Heusch G. Postconditioning: old wine in a new bottle? *J Am Coll Cardiol*. 2004;44:1111–1112.

Michael Marber

Glossary

Gary D. Lopaschuk

Lipoprotein lipase

Lipoprotein lipase is an enzyme that cleaves fatty acids from triacylglycerol contained within lipoproteins. It is an important enzyme involved in the delivery of fatty acids to tissues such as muscle and heart.

Leptin

Leptin is a peptide hormone synthesized by adipocytes that plays a key role in the regulation of appetite and energy expenditure. This can occur through direct actions of leptin on the hypothalamus or via direct actions on peripheral lipid and glucose metabolism.

Diabetic db/db mouse

The genetic leptin-resistant (db/db) mouse possesses a mutation in the leptin-receptor, resulting in a defective leptin-receptor. This leptin-receptor deficiency induces a hyperglycemic-hyperinsulinemic endometabolic environment that results in the development of type 2 diabetes.

Ob/ob mouse

The leptin-deficient (ob/ob) mouse is a genetically mutated mouse in which a leptin deficiency occurs. This leptin deficiency results in the development of a marked obesity, glucose intolerance and insulin-resistance. It is a very common experimental model in which to examine the consequences of leptin deficiency on obesity and insulin-resistance.

Serine/threonine kinase

Kinases are proteins that phosphorylate other proteins, usually resulting in a modification of that protein's function. Serine/threonine kinases are protein kinases that phosphorylate proteins on serine or threonine amino acids.

Acyl-CoA synthetase (MHC-ACS)

Long chain acyl-CoA synthetase is one of the first enzymes in the fatty acid metabolic pathway. It converts long chain fatty acids to long chain acyl-CoA within the cell. Long chain acyl-CoA is then either metabolized by the mitochondria to produce energy, or is used to produce membrane and cellular lipids. MHC-ACS refers to an experimental approach to selectively express acyl-CoA synthetase (ACS) in muscle. This is achieved by linking the ACS gene to the myosin heavy chain (MHC) promoter. The production of transgenic mice from embryonic stem cells that contain the MHC-ACS gene will result in mice that overexpress ACS targeted to muscle.

Peroxisome proliferator-activated receptor alpha (MHC-PPARα)

Peroxisome proliferator-activated receptor (PPARα) is a nuclear receptor involved in transcriptional regulation of proteins. PPA0052α has many functions, including regulating enzymes involved in the control of fatty acid oxidation in the heart. MHC-PPARα refers to an experimental approach that is used to selectively express Peroxisome proliferator-activated receptor alpha in muscle. This is achieved by linking the Peroxisome proliferator-activated receptor α gene to the myosin heavy chain (MHC) promoter. The production of transgenic mice from embryonic stem cells that contain the MHC- PPARα gene will result in mice that overexpress PPARα targeted to muscle.

Glycophosphatidylinositol-linked lipoprotein lipase

One type of post-translational modification of protein involves the addition of a glycophosphatidylinositol (GPI) anchor that facilitates anchoring of proteins to cell membrane. A glycophosphatidylinositol-linkage on lipoprotein lipase is one way of linking lipoprotein lipase to the cell membrane.

Ectonucleotide pyrophosphatase/phosphodiesterase 1

Ectonucleotide pyrophosphatase/phosphodiesterase is a plasma cell membrane glycoprotein that functions to release nucleoside 5′-monophosphates from

various nucleotides (such as ATP). There has been interest in the ectonucleotide pyrophosphatase/phosphodiesterase since a K121Q polymorphism in the enzyme has been shown to be associated with obesity, glucose intolerance and insulin resistance.

A number of variants of ectonucleotide pyrophosphatase/phosphodiesterase have now been identified to have a primary role in mediating insulin resistance and the development of obesity and type 2 diabetes.

Protein kinase (AMPK) pathway

AMP-activated protein kinase (AMPK) is a widely distributed cellular kinase that is activated during times of metabolic stress. It has been termed a cellular ''fuel gauge'', and primarily functions to turn off energy-consuming pathways and turn on energy-producing pathways during metabolic stress.

Leukotriene B

Leukotriene B is an eicosanoid that is synthesized from arachidonic acid by the 5-lipoxygenase pathway. Leukotrines are involved in the inflammatory process, as well as in vasoconstriction and vascular permeability.

Endothelin-1 (ET-1)

Endothelin-1 is a vasoactive peptide produced by endothelial cells. Endothelin-1 is a potent vasoconstrictor that acts by binding to endothelin-1 receptors on vascular smooth muscle cells.