Lipid disorders

1

THE YEAR IN LIPID DISORDERS

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VOLUME 1

EDITED BY

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CLINICAL PUBLISHING
OXFORD

Clinical Publishing

an imprint of Atlas Medical Publishing Ltd

Oxford Centre for Innovation
Mill Street, Oxford OX2 0JX, UK

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Email: info@clinicalpublishing.co.uk
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Distributed in USA and Canada by:
Clinical Publishing
30 Amberwood Parkway
Ashland, OH 44805, USA
Tel: 800-247-6553 (toll-free within US and Canada)
Fax: 419-281-6883
Email: order@bookmasters.com

Distributed in UK and Rest of World by:
Marston Book Services Ltd
PO Box 269
Abingdon
Oxon OX14 4YN, UK
Tel: +44 1235 465500
Fax: +44 1235 465555
Email: trade.orders@marston.co.uk

First published 2007

A catalogue record for this book is available from the British Library

ISBN-13 978 1 904392 96 5
ISBN-10 1 904392 96 2
ISSN 1751-3782

Project Manager: Rosemary Osmond, Helimetrics Ltd, Chipping Norton, Oxon, UK
Typeset by Hope Services (Abingdon) Ltd, Abingdon, Oxon, UK
Printed by T G Hostench SA, Barcelona, Spain

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VOLUME 1

Contents

Part III

Prevention and treatment strategies

Part IV

Infection, inflammation and secondary causes of atherosclerosis

Part I

Clinical aspects in coronary artery disease

1

Metabolic syndrome, diabetes and cardiovascular risk

MOHAMED AHMED, CHRISTOPHER BYRNE

Introduction

The last year has seen a vast amount of interest, controversy, debate and published work on metabolic syndrome. This chapter is not intended to be a comprehensive review of the subjects of the title, but will focus on:

- defining the syndrome and recent controversy;
- new developments in epidemiology;
- pathogenesis and new developments;
- links between non-alcoholic fatty liver disease and cardiovascular disease;
- treatments and recent clinical trials.

Definitions of the metabolic syndrome and recent controversies

Medical science usually defines a syndrome as an 'aggregate of symptoms and signs associated with any morbid process, and constituting together the picture of the disease' (*Stedman's Medical Dictionary*) [1]. Reaven defined a syndrome (syndrome X) as a cluster of insulin resistance, dysglycaemia, dyslipidaemia and hypertension [2]. Definitions of the metabolic syndrome that now also include a measure of central obesity were developed between 1999 and 2001 by the World Health Organization (WHO Consultation, 1999 [3]), the European Group for the Study of Insulin Resistance (EGIR) and the National Cholesterol Education Program (NCEP) (Table 1.1). The International Diabetes Federation produced a consensus worldwide definition of the metabolic syndrome in 2005. The criteria for this definition are a waist circumference of ≥94 cm for European men and ≥80 cm for European women (with lower cut-off points for some other ethnic groups) and two or more of the following: blood pressure, triglyceride and high-density lipoprotein (HDL) cholesterol cut-off points as for the Adult Treatment Panel-III (ATP-III) definitions, and fasting plasma glucose ≥5.6 mmol/l (Table 1.1). The application of

Table 1.1 Features of the World Health Organization (WHO), European Group for study of Insulin Resistance (EGIR), National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (ATP-III) and International Diabetes Federation (IDF)

Definition	WHO	EGIR	NCEP ATP-III (NCEP Expert Panel on Detection, 2001, revised in 2005)	IDF
	Impaired glucose tolerance or diabetes and/or insulin resistance and two of the other factors		Three or more of the following factors (triglyceride and HDL counted separately) [5]	Waist circumference is required in addition to two or more of the following factors
Central obesity	WHR ≥0.9 cm (men), ≥0.85 (women) and/or BMI >30 kg/m^2	Waist ≥94 cm (men), ≥80 cm (women)	Waist ≥102 cm (men), ≥88 cm (women)	Waist ≥94 cm for European men and waist ≥80 cm for European women (lower cut-points for some other ethnic groups)
Blood pressure (mmHg)	≥140/90	≥140/90 or treated for hypertension	≥130/85 or treated for hypertension	Same as ATP-III
Dyslipidaemia (mmol/l)	Triglyceride ≥1.7 or HDL <0.9 (men), <1.0 (women)	Triglyceride ≥2 or HDL <0.1 or treated for dyslipidaemia	Triglyceride ≥1.7 or HDL <1 (men), <1.3 (women)	Same as ATP-III
Dysglycaemia (mmol/l)	Fasting plasma glucose ≥6.1 and/or 2 h post-challenge glucose ≥7.8 on diabetes	Fasting plasma glucose ≥6.1 but non-diabetic	Fasting plasma glucose ≥5.6	Fasting plasma glucose ≥5.6
Insulin resistance	Glucose uptake during hyper-insulinaemic euglycaemic clamp in lowest quartile for population	Presence of fasting hyper-insulinaemia (i.e. among the highest 25% of non-diabetic population)	Not applicable	Not applicable
Other factors	Microalbuminuria	None	Not applicable	Not applicable

BMI, body mass index; WHR, waist:hip ratio.

this definition will increase the prevalence of metabolic syndrome and potentially increase the usefulness of these criteria as a screening test. The major difference between criteria is that the WHO and the EGIR criteria include a measure of insulin resistance as one of the components. The WHO criteria also require the result of a glucose tolerance test, which reduces the utility of these criteria in large epidemiological or clinical studies in which often only the fasting glucose level is measured [3]. Recently, the American Diabetes Association and European Association for the Study of Diabetes released a statement addressing some of the concerns about the definition of the metabolic syndrome [4]. Concerns about the definitions are summarized in Table 1.2.

Importantly, the metabolic syndrome is not only of concern to diabetologists but also needs the attention of primary care physicians, cardiologists, hepatologists, epidemiologists and pathologists. It is clear that a multidisciplinary approach is needed (Fig. 1.1). Therefore, the lack of an agreed definition for the metabolic syndrome may necessitate the need for a concerted, global research initiative on the subject. However, we consider that the criteria for metabolic syndrome are continuing to evolve and will be refined in the future.

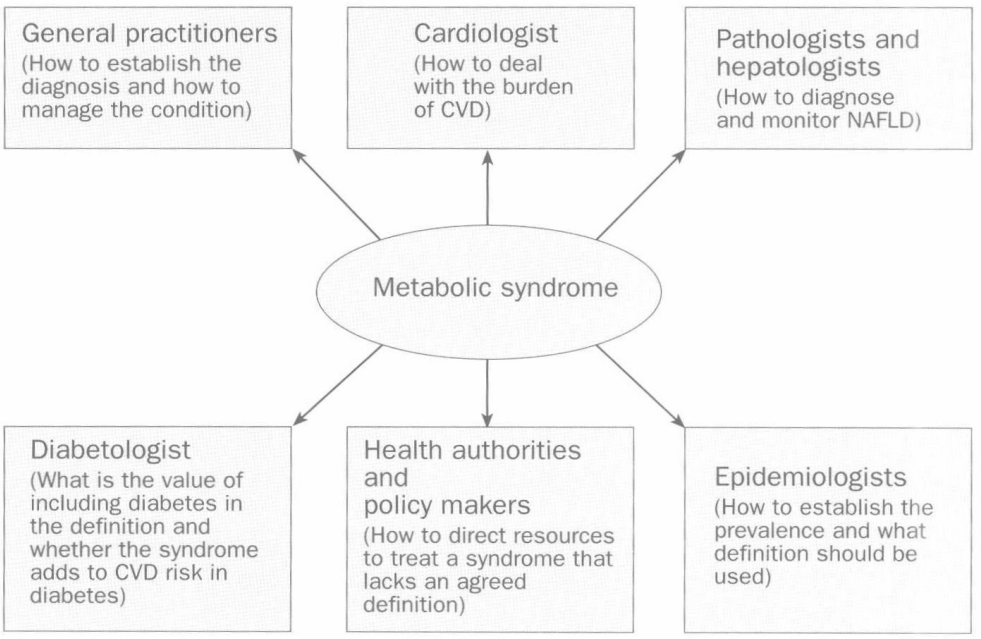

Fig 1.1 Schematic figure showing how metabolic syndrome presents different challenges that require a multidisciplinary approach to diagnosis and management.

Table 1.2 Summary of American Diabetes Association and European Association for the Study of Diabetes concerns about the definition of the metabolic syndrome

Concern	Example
Some criteria used are ambiguous or incomplete	Systolic blood pressure >130 or ≥130; no agreement on methods of measurement of BP and waist circumference
Difference in criteria used	Microalbuminuria listed in WHO but not in ATP-III or IDF
The main rationale for criteria is insulin resistance which is not present in all patients with metabolic syndrome	Recent definition by IDF (2005) established waist circumference as major criterion
No clear basis for including/excluding CVD risk factors	Cut-off points have never been established; for instance, reducing the threshold for fasting glucose from 6.1 to 5.6 mmol/l did not change the hazard ratio for CHD. There is no evidence to establish the sex-specific cut-off points for CVD risk factors

New developments in the epidemiology of metabolic syndrome

The present secular trends show a decline in the prevalence of hypertension, in average low-density lipoprotein (LDL) cholesterol and smoking prevalence. In parallel with these improvements in recognized risk factors for cardiovascular disease (CVD), there has been a decrease in age-standardized rates for CVD in developed nations. Although these three risk factors have improved, there is an epidemic of type 2 diabetes and the prevalence of diabetes is expected to double between 2000 and 2030. Many patients with type 2 diabetes are overweight with metabolic syndrome and, given the marked increase in obesity worldwide, it is expected that the increased global prevalence of metabolic syndrome may reverse the present secular decrease in age-standardized rates of CVD.

Trend in the prevalence of the metabolic syndrome and its impact on cardiovascular disease incidence: the San Antonio Heart Study

Lorenzo C, Williams K, Hunt KJ, Haffner SM. *Diabetes Care* 2006; **29**: 625–30

BACKGROUND. The recent results from the San Antonio Heart Study investigators show an increase in the prevalence of metabolic syndrome over time and the investigators have addressed whether a change in the prevalence of metabolic syndrome in two separate cohorts is associated with a change in CVD prevalence. The

San Antonio Heart Study was a cross-sectional population-based study of 5158 subjects aged between 25 and 64 years from diverse backgrounds and ethnic groups. These individuals were assigned to two cohorts: 1979–1982 and 1984–1988. Re-examination of 71.4% of these individuals took place in 1987–1990 (cohort 1) and 1991–1996 (cohort 2) and assessed a 7.5-year incidence of CVD of 90% of participants. Metabolic syndrome was defined according to the criteria of the National Cholesterol Education Program–ATP-III.

INTERPRETATION. At baseline, the metabolic syndrome was more frequent in cohort 2 than in cohort 1. This difference was statistically significant in men and women from both ethnic groups and in most of the age-groups considered in both men (30–39 years, $P = 0.474$; 40–49 years, $P = 0.028$; 50–59 years, $P < 0.001$) and women (30–39 years, $P = 0.032$; 40–49 years, $P < 0.001$; 50–59 years, $P < 0.001$). The prevalence of metabolic syndrome was higher at follow-up than at baseline in both cohorts. A total of 269 (5.8%) individuals developed incident CVD. In a multiple logistic regression analysis, there were more incident CVD events in cohort 2 relative to cohort 1 (odds ratio [OR] 1.37; 95% confidence interval [CI] 1.02–1.84) after adjustment for age, sex, ethnic origin, socio-economic status, history of CVD, diabetes, total cholesterol, smoking and family history of heart attack. This difference was no longer statistically significant after the addition of metabolic syndrome as a covariate (OR 1.26; 95% CI 0.93–1.71) and the presence of the metabolic syndrome was an independent predictor of new cases of CVD. In 4524 non-diabetic participants there were 170 individuals who developed incident CVD. Further adjustment for the metabolic syndrome reduced this difference and demonstrated that metabolic syndrome predicted incident CVD. The main finding of this study was that the increase in prevalence of metabolic syndrome had an adverse impact on CVD risk.

Comment

The limitations of this study as discussed by the authors need to be considered in interpreting this result. Repeated measurements in the same individuals are used for analysis and there was no waist circumference available in cohort 1 at baseline. In addition, it is not known whether CVD occurred at an older age within the second cohort. Given that there was an increase in prevalence of metabolic syndrome, perhaps the most important message from this study is that an increase in the prevalence of metabolic syndrome may reverse the secular decline in age-standardized rates of CVD in developed and also perhaps developing nations.

Pathogenesis of metabolic syndrome and new developments

There is no central unifying mechanism that explains all features of the metabolic syndrome, but it is quite likely that there may be multiple causes or pathogeneses that result in the same final phenotype. Although obesity, in particular central obesity, is a key component, it is still uncertain why obesity contributes to the

features of the syndrome. It is known that central obesity is associated with a high concentration of non-esterified fatty acids and low levels of physical activity and that relatively high dietary calorie intake can decrease the free fatty acid concentration and glucose oxidation in skeletal and cardiac muscles, which leads to an increase in total body fat. Adipose tissue can secrete tumour necrosis factor-α (TNF-α), interleukin (IL)-6 and IL-1β, which are associated with insulin resistance. TNF-α is known to be associated with decreased insulin-induced suppression of hepatic glucose production, increased free fatty acid and cholesterol synthesis, increased hepatic very low-density lipoprotein (VLDL) production and increased adipocyte lipolysis, which leads *per se* to increased production of non-esterified fatty acids (NEFAs). Both NEFAs and TNF-α indirectly produce low HDL concentration and high triglyceride and cholesterol concentrations [3] (Fig. 1.2).

The interest in the pathogenesis of metabolic syndrome is largely due to the associated link with increased risk of diabetes and coronary heart disease (CHD). These risks vary with the criteria for the metabolic syndrome. In summary, the relative risk of diabetes is at least 3-fold higher among people with metabolic syndrome than among those without the syndrome and relative risks are generally highest for coronary heart disease mortality, intermediate for cardiovascular disease mortality and lowest for all-cause mortality [3]. On the basis of data from the Framingham Offspring Study of 3323 men and women (mean age 52 years) with an 8-year follow-up, it has been estimated that the metabolic syndrome contributes to almost half of the population-attributable risk of diabetes and approximately a quarter of all incident cardiovascular disease [6]. Interestingly, fatty liver, which is considered to be the hepatic component of the metabolic syndrome, is thought to be associated with an increased risk of CHD [7–8].

The following section focuses on recent articles that contribute to our understanding of the pathogenesis of the metabolic syndrome.

The FFA receptor GPR40 links hyperinsulinemia, hepatic steatosis, and impaired glucose homeostasis in mouse

Steneberg P, Rubins N, Bartoov-Shifman R, Walker MD, Edlund H. *Cell Metab* 2005; **1**: 245–58

BACKGROUND. Overweight and obese individuals have markedly increased fasting NEFA concentrations compared with slightly overweight subjects and obesity is associated with impaired suppression of plasma NEFA concentrations. Recently, we have demonstrated that NEFAs are independently associated with hepatic steatosis in obese subjects [9]. This work by Steneberg *et al.* suggests that the NEFA receptor GPR40 links hyperinsulinaemia, hepatic steatosis and impaired glucose homeostasis in the mouse. GPR40 is a G-protein-coupled receptor expressed mainly in pancreatic beta cells but also in the central neurons system. GPR40, a fatty acid-activated receptor, mediates the ability of fatty acids to promote glucose-induced insulin secretion. Activation of GPR40 leads to symptoms of metabolic syndrome.