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EXPERT FORUM

The metabolic syndrome
and obesity

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Arya M. Sharma, editor



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Cover photo: Scanning electron microscopy image of glomerulus in moderately hypertensive patient.

Over the past decade, the Metabolic Syndrome (also referred to as insulin resistance syndrome, Syndrome X or cardiometabolic syndrome) has become increasingly important in cardiovascular medicine. Diagnostic criteria for the metabolic syndrome have been established by the World Health Organization (1998), the Third Report of the Adult Treatment Panel (ATP III) of the National Cholesterol Education Program (2001), and, more recently, the International Diabetes Foundation (IDF, 2005). Although the WHO and ATP III criteria both include abdominal obesity, it is a necessary requirement in the IDF definition. This reflects the IDF position that while the pathogenesis of the metabolic syndrome and its components are complex, abdominal obesity is a key causative factor.¹

The metabolic syndrome and obesity

Proceedings of An Expert Forum

The following is a brief overview of the presentations made during a recent Expert Forum organized by the Center for Cardiovascular Obesity Research and Management at McMaster University, Hamilton, Ontario, Canada. Participants in the forum, entitled *Total Cardiovascular Risk: The Metabolic Syndrome and Obesity*, discussed the biological and social determinants of the current obesity pandemic and its impact on metabolic syndrome and cardiovascular disease (CVD), incorporating learnings from the areas of adipose and muscle tissue biology, clinical research and epidemiology.

Environmental and biological determinants of obesity

Arya M. Sharma

An unprecedented increase in the prevalence of overweight and obesity is underway, affecting more than 500 million people worldwide.² As a consequence, obesity-related health problems, including type 2 diabetes, hypertension and cardiovascular disease, are increasing. In an analysis of cardiac rehabilitation patients in Hamilton (n = 3542), the prevalence of metabolic syndrome increased with weight, from 14% of non-obese males and 18% of non-obese females to 64% and 66%, respectively, among those with Class III morbid obesity.

Obesity has occurred throughout history but a number of factors are involved in the current global pandemic. These factors can be divided into broad categories, such as lifestyle (physical inactivity, consumption of energy-dense foods), characteristics of the built environment (motorized transportation and the elimination of physical labour from the workplace), and food production and distribution policies and practices. There is an urgent need to address these factors to curtail the obesity pandemic.³ Total energy homeostasis is now recognized as a complex biological process involving an intricate and finely tuned cross-talk between peripheral organs and the central nervous system. Recent years have led to the elucidation of numerous pathways that have a profound influence on all aspects of energy regulation, including appetite, hunger, satiety, thermogenesis, food partitioning, and other complex aspects of energy metabolism. Not surprisingly, these complex, biological processes underlie tight genetic control, with a large number of genes playing roles in energy regulation.⁴ To date, 300 genes have been identified as being involved in obesity-related phenotypes.

The other part of the equation is energy expenditure, which includes both non-exercise thermogenesis (unconscious activity/fidgeting)

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Arya M. Sharma, editor

and conscious exercise. Observational research in Atlanta⁵ suggests that conscious physical activity is not only an important determinant of weight, but is itself heavily influenced by the built environment. 'Fixing' the weight problem will not be easy, as it consists of a complicated interlinking between individuals and the engineered environments (work, school and home) at both the micro- and macro level (local, regional, national and international).

The current obesity pandemic calls for action at all levels: prevention, treatment and secondary prevention. Recent progress in our understanding of the underlying biological processes will potentially lead to the development of more effective and safer pharmacological approaches for treating patients challenged by excess body weight.⁶ These developments should not distract from the continuing need to develop and implement preventive strategies for both individual and whole populations.

Ethnic variations

Salim Yusuf

Over the last 100 years, average life expectancy has increased greatly in western nations. As part of this transition, CVD has changed from being primarily an infectious disease of childhood (e.g., rheumatic fever) to a degenerative disease of later life (e.g., coronary heart disease). With the decline in childhood and infectious diseases and increases in tobacco use and urbanization (with its consequential impact on physical activity, psychosocial stress,⁷ and diet), CVD is undergoing a similar epidemiologic transition in non-western and developing countries.

Data from the INTERHEART study, a case control study of myocardial infarction (MI) risk

factors globally and in the major ethnic groups of the world, show that in all populations nine risk factors (smoking, hypertension, diabetes, waist/hip ratio, dietary patterns, physical activity, consumption of alcohol, blood apolipoproteins, and psychosocial factors) explained 90% of the population attributable risk (PAR).⁸ Globally, central or abdominal obesity accounted for 30-35% of the PAR for MI.

In order to understand the societal factors that lead to the development of obesity, we have established the Prospective Urban Rural Epidemiological study (PURE Study), a prospective cohort study tracking lifestyles, risk factors and chronic diseases in rural and urban areas of 15 non-western countries. Preliminary data from the pilot study conducted in India (n = 5000) has found important behavioural and biological differences between urban and rural populations. Compared to those living in rural areas, those in the urban centres ate more calories, more calories from fat, and because of greater use of television, motorized two-wheelers and kitchen appliances, had reduced energy expenditures. Not surprisingly, half (53%) of those in the urban centre were overweight, compared to 5% in the rural setting. There was a tenfold difference between urban and rural participants in the rates of diabetes (19% vs. 2%), a three-fold difference in hypertension (30% vs. 9%), and a two-fold difference in coronary heart disease (9% vs 5%). These findings suggest that maladaptation to societal transitions such as urbanization may be the root cause of obesity and, as a consequence, the development of related risk factors such as dyslipidemia, dysglycemia and hypertension.

In INTERHEART, the standard definition of the metabolic syndrome did not have more predictive power than several of the individual risk factors, such as apolipoprotein (Apo) A/B or diabetes. The concept of the metabolic syndrome has been useful, however, in bringing attention to the need for managing such risk factors for CVD prevention. At the same time, it must be emphasized that the ATP III definition of metabolic syndrome is based upon Framingham study data and may not be appropriate for other populations. For example, INTERHEART suggests that BMI is not only a less reliable indicator of CVD risk than the waist to hip ratio, but that the standard cutoff of 30 kg/m² for the diagnosis of obesity may be too high in some non-Caucasian populations.

Metabolically healthy but obese

Rémi Rabasa-L'Horet of the Research Centre of the University Hospital of Montréal described his study of inflammation in obese, post-menopausal women displaying the 'metabolically healthy but obese' (MHO) phenotype. Eighty-eight subjects were classified as MHO (n = 22) or 'at risk' (n = 22) based on the upper and lower quartile of insulin sensitivity, as measured by the hyperinsulinemic-euglycemic clamp technique. Despite comparable total body fatness between groups, MHO individuals had significantly lower levels of visceral fat, fasting insulin, plasma triglycerides, high-sensitivity C-reactive protein (CRP), and α -1 antitrypsin levels, as well as higher levels of HDL, than at-risk individuals. Stepwise regression analysis showed that CRP, fasting triglycerides and lean body mass index explained 19.5%, 8.5% and 4.0%, respectively, of the variance observed in glucose disposal (total $r^2 = 0.320$, $p < 0.001$). These results suggest that in women displaying the MHO phenotype, lower inflammation state, as attested by low CRP levels, could have a protective role and may be associated metabolically with a lower risk for CVD. Future studies will replicate the study among men and look at the effect of weight loss interventions.

Case study in ethnic variations: the six nations of the grand river treaty

Sonia Anand

The SHARE study compared Canadians of European, Chinese and South Asian descent with people from the Six Nations of the Grand River Treaty (a First Nations or Aboriginal population in southern Ontario). Compared to European-Canadians and Canadians of Chinese and South Asian descent, people of the Six Nations had high rates of obesity, abdominal obesity, diabetes, glucose intolerance, cardiovascular disease (CVD) and atherosclerosis. Overall, non-Caucasian populations appeared to experience insulin resistance at much lower Body Mass Index (BMI) than Caucasians. The following table, taken from our 2005 publication, illustrates some of the differences between the different populations⁹ (Table 1).

Environmental and lifestyle factors play an important role in risk factor prevalence and are the subject of ongoing research by the McMaster team. A nutrition food frequency questionnaire validated by a seven day diet record has shown that Six Nations people tend to consume more calories than European-Canadians and more of their calories come from saturated and trans fatty acids. Fruit drinks and colas were common sources of carbohydrates, and may reflect community concerns with the quality of their drinking water. Compared to European-Canadians, Six Nations people were less likely to report leisure time physical activity and more likely to report smoking. There was a strong inverse relationship between income and the prevalence of CVD.

Studies of healthy, normal people show that daily variation of blood glucose is usually within a narrow range (e.g., between 2 and 8 mmol/L).

Mean (standard deviation)	European Canadians (n = 321)	South Asian Canadians (n = 328)	Chinese Canadians (n = 306)	Aboriginal Canadians (n = 296)
Income <\$20,000 Cdn/yr (%)	8.1	12.3	15.1	36.3
Fasting glucose (mmol/l)				
• Age and sex adjusted	5.3 (1.4)	5.8 (1.7)	5.3 (1.0)	6.6 (2.8)
• Excluding subjects with established diabetes	5.2 (0.8)	5.5 (1.4)	5.2 (0.9)	5.6 (1.2)
Total cholesterol/HDL				
• Age and sex adjusted	4.7 (1.5)	5.3 (1.6)	4.7 (1.6)	5.2 (1.6)
• Excluding subjects with established dyslipidemia	4.6 (1.6)	5.4 (1.7)	4.7 (1.8)	5.1 (1.)
Systolic blood pressure (mmHg)				
• Age and sex adjusted	118.9 (14.6)	119.7 (15.3)	119.3 (16.9)	117.9 (18.6)
• Excluding subjects with established hypertension	117.8 (15.8)	116.1 (15.4)	113.8 (16.1)	115.5 (16.5)
Metabolic syndrome (%) (age and sex adjusted)	21.4	25.3	12.0	43.8
BMI (age adjusted)				
• Female	26.6 (4.9)	26.6 (3.8)	22.9 (3.4)	31.1 (6.7)
• Males	28.3 (3.9)	26.0 (3.6)	25.2 (3.4)	32.2 (6.0)
Waist circumference (cm) (age adjusted)				
• Female	84.6 (12.1)	86.7 (10.4)	76.3 (8.0)	99.0 (15.5)
• Male	100.6 (11.3)	94.6 (9.1)	89.9 (9.4)	109.3 (13.8)
Waist to hip ratio (age adjusted)				
• Female	0.80 (0.06)	0.84 (0.07)	0.81 (0.06)	0.88 (0.07)
• Male	0.94 (0.06)	0.93 (0.05)	0.90 (0.05)	0.99 (0.06)

From Razak et al. Int J Obesity. 2005

Table 1: Ethnic differences in the SHARE and SHARE-AP studies.

Prevalence of metabolic syndrome: research results from Europe

Ada Dormi and Maddalena Veronesi of the University of Bologna gave an overview of results from the Brisighella Heart Study, a prospective, population-based longitudinal cohort of 2939 Italians 14 to 84 years of age, free of CVD at enrollment. In 2004, prevalence of the metabolic syndrome was 21.9% among males and 20.2% in women, increasing with age for both genders. Although Italy is considered a lower risk region in terms of CVD, analysis of the population aged 40 and over suggested a doubling in the prevalence of metabolic syndrome over time (from approximately 10% in 1996 to 20% in 2004). The rise may reflect the increasing prevalence of obesity and other disadvantageous lifestyle changes during the study period.

Guy Amah reported on his research looking at metabolic syndrome in 100 consecutive African (n = 48) and Caucasian (n = 52) outpatients seen in the hypertension unit of a Paris hospital. Using the ATP III criteria, metabolic syndrome was diagnosed in 30% of the African and 18% of the Caucasian patients. Blood pressure, BMI, waist circumference and blood glucose were significantly higher in the African subjects, with the differences being more pronounced in African women compared with both Caucasian men and women.

The cut-offs used to define diabetes (plasma glucose levels 7 mmol/L or greater (≥ 126 mg/dL) or a 2-hour plasma glucose level after a 75-g glucose load of 11.1 mmol/L or greater (≥ 200 mg/dL) are substantially higher than 'normal' fasting and 2-hour mean glucose levels. However, these cut-offs were chosen because they effectively differentiate individuals at high and low risk for retinopathy and do reflect the relationship of glucose to CVD risk – the most common and deadly of the health consequences of diabetes. Over 70% of people with diabetes die from cardiovascular causes.

More evidence on dysglycemia and the metabolic syndrome

As reported by Katuhiro Higashiura, researchers at the Sapporo University School of Medicine have evaluated insulin sensitivity and lipid profiles in patients with essential hypertension, with and without insulin resistance (EHT-R vs ENT-N). Glucose, insulin, triglycerides and free fatty acids did not vary significantly between EHT-N and normotensives, but were significantly higher in EHT-R. When coronary angiographic findings were evaluated in patients with coronary artery disease (CAD), the severity was highest in CAD with diabetes mellitus (DM); even in CAD without DM, the severity of coronary angiographic findings was greater in those demonstrating insulin resistance. Eight-year follow-up of the rural participants showed the incidence of CVD was higher in subjects with insulin resistance than those without.

Guiseppe Penno described results from the Italian Cohort of the EURODIAB IDDM Complications Study. The prevalence of metabolic syndrome among type 1 diabetics was 14.9% (13.9% in males and 15.9% in females). Besides hyperglycemia, common components of the metabolic syndrome included hypertension (40% males, 32% females, $p = 0.01$), high triglycerides (12% males, 8% females), low HDL (16% males, 21% females, $p = 0.03$) and abdominal obesity (3% males and 13% females, $p < 0.0001$). The prevalence of metabolic syndrome increased with age and deterioration of glycemic control. Compared to those without the metabolic syndrome, diabetics with the syndrome had a 5.32-fold (85% CI 3.13-9.04) increased odds ratio for overt nephropathy and a 4.45-fold (85% CI 2.63-7.51) increased risk for proliferative retinopathy.

A recent meta-analysis of prospective epidemiologic studies in people with type 2 diabetes reported the risk of CVD rises 18% and the risk of peripheral vascular disease 28% for every 1% rise in glycosylated hemoglobin A1C (HbA1c).¹⁰ Possible explanations for the CVD risk associated with diabetes include, but are limited to, diabetes-associated dyslipidemia, hypertension, high oxidative stress, antecedent 'insulin resistant' state, genetic or environmental predisposition, abdominal obesity, and physical inactivity (sedentary lifestyle).

A growing body of epidemiologic research shows that the link between glucose and CVD risk extends below glucose levels that are in the diabetes range. A meta-regression analysis of prospective studies of mainly nondiabetic people reported that a post-load glucose of 7.8 mmol/l increases the risk of a CV event by 58% compared to a level of 4.2 mmol/l, even after excluding those with diabetes.¹¹ A six year study of more than 10,000 men and women (only 243 with diabetes) found that a 1% rise in HbA1c predicted a 20-30% rise in the risk of incident CVD.¹² Indeed, in this study it was the HbA1c level, and not the presence or absence of diabetes *per se*, that was an independent predictor of CV death. The relationship between CV events and glucose or HbA1c is similar to that between CV events and blood pressure or lipids: no clear 'safe' threshold is apparent.

Whether targeting glucose elevation in either nondiabetic or diabetic individuals prevents cardiovascular events remains unknown. It is, however, being tested in several large international clinical trials that should be completed within the next six years (e.g., ACCORD, PROACTIVE, DREAM, ORIGIN, LOOKAHEAD).

The societal burden of diabetes and the evidence that the pandemic is being fueled by our current lifestyle means that diabetes has become an urgent public health problem.^{13,14} Public health approaches are needed to facilitate the sort of lifestyle changes that would reduce the burden of diabetes, and, as a result, the risk of associated CVD. We also need new and better agents and tools to lower glucose and manage those already diabetic. New agents are in development, many of which reflect our evolving understanding of the mechanisms underlying diabetes and obesity. Obesity plays a central role in many of the problems of the metabolic syndrome and is the strongest risk factor for the development of type 2 diabetes. Adipose tissue is an endocrine organ and expresses all components of the renin angiotensin system (RAS), with the excep-

tion of Angiotensin II.¹⁵ It has been observed that RAS blockade, either by inhibiting the angiotensin-converting enzyme (ACE inhibitors) or blocking the angiotensin type 1 receptor (ARBs), may substantially lower the risk for type 2 diabetes.¹⁶ It is important to note that none of the 12 studies that show this effect had diabetes prevention as a primary endpoint and in many cases the measures were crude (e.g. self-report of new diagnosis of diabetes as opposed to fasting glucose measures).¹⁷ Despite this, the data have been consistent and have been confirmed by meta-analysis. It can be argued that in the treatment of the obese hypertensive, ARBs, particularly telmartsartan, may be more advantageous than ACE inhibitors.

What is the mechanism by which RAS blockade by ARBS prevents diabetes? A number of mechanisms have been studied. It has been observed that by increasing adiponectin and binding to the nuclear transcription factor peroxisome proliferators-activated receptor gamma (PPAR γ , a major regulator of lipid and glucose metabolism), ARBs induce preadipocyte differentiation and enhance insulin sensitivity. RAS inhibition also increases the lipid storage capacity of the liver and muscle, as well as blood flow to the pancreas and skeletal muscle.

More information about the effects of RAS blockade should come from The Telmisartan in Reduction of Intra-Myocellular lipids (TRIM) study. A randomized 2x2 factorial study, it is looking at the effect of telmisartan and a low-glycemic index diet on myocellular lipids in overweight and obese individuals with impaired glucose tolerance. The study should be completed by the end of 2006.

This presentation dealt with the potential role of endoplasmic reticulum (ER) stress as an underlying mechanism in the metabolic syndrome. In eukaryotic cells, the ER is the principal site for folding and maturation of transmembrane, secretory and ER-resident proteins. Disruption in ER function can lead to ER proteotoxicity (ER stress) and activation of the unfolded protein response (UPR), resulting in increased expression of the ER stress response gene and a general decrease in protein translation (Figure 1).

ER stress is a central feature of peripheral insulin resistance and type 2 diabetes¹⁸ at the molecular, cellular and organismal level. In addition, ER stress triggers three fundamental processes that contribute to atherothrombosis:

1. enhanced tissue factor (TF) procoagulant activity;

More insights into RAS blockade

Mathias Goebel of the Center for Cardiovascular Research, Berlin, described his lab's recent research on the potential of two ARBS (telmisartan and irbesartan) to act as selective PPAR modulators (SPPARMs). Compared to a glitazone, telmisartan directly interacted with the receptor, producing a distinct PPAR γ protein conformation, with attenuated release of nuclear receptor corepressor (NCoR) and the absence of tumour inhibitory factor-2 (TIF-2) recruitment. Telmisartan improved insulin sensitivity in diet-induced obese mice even in the absence of weight gain. Modulation of PPAR γ activation by ARBS could provide a new therapeutic option for better cardiovascular risk management in metabolic diseases.

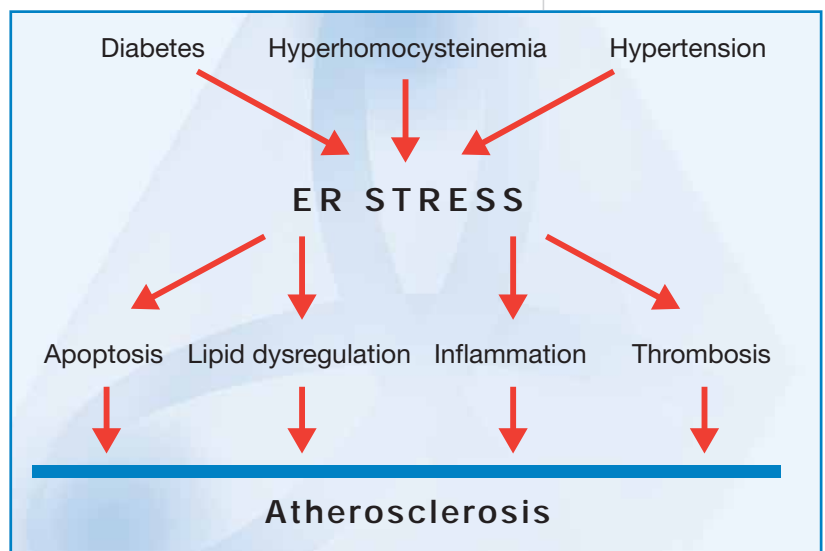
Adiponectin, an adipocyte-derived protein, is reduced in hypertensive patients with insulin resistance and is negatively associated with CVD morbidity and mortality. Takafumi Okura of Ehime University Hospital described his research on the influence of RAS blockers on adiponectin concentration in 40 essential hypertensive patients (21 men and 19 women, with a mean age of 64 years) without renal damage or macroproteinuria. Patients were treated with an ARB (lorsartan) or a calcium channel blocker (CCB) (amlodipine). Compared to the CCB, treatment with the ARB significantly decreased U-Alb/r and uric acid values and increased the adiponectin concentration (9.56 ± 6.75 vs. 10.36 ± 6.94 ng/mL, $p = 0.0381$). It was speculated that this effect may be due to adiponectin-associated improvement of insulin resistance.

2. lipid dysregulation; and
3. if ER stress is severe or prolonged, increased apoptotic cell death.

It is well established that many of the acute clinical manifestations of atherothrombotic disease such as unstable angina, myocardial infarction and stroke result from lesion rupture, triggering thrombus formation and vessel occlusion. Although previous studies have reported that an increase in plasma lipid levels, oxidative stress and inflammation contribute to CVD, they do not completely explain the atherothrombotic process.

Obesity, diabetes, and hypertension are among the many factors that can induce ER stress and UPR. The role of hyperhomocysteinemia

Figure 1: CVD risk factors, ER stress and atherosclerosis.



Reducing atherothrombotic damage

Inflammation plays an important role in CVD, and nuclear factors, growth factors and cell adhesion molecules are critical for the development of inflammation. Jun-ichi Suzuki, of the Tokyo Medical and Dental University discussed new treatments utilizing IκB and hepatocyte growth factor (HGF) being developed in Japan. In animal models, an inhibitor of nuclear factor κB (NFκB) phosphorylation (IMD0354) and direct injection into the myocardium of human HGF genes have been shown to improve cardiac function and reduce apoptosis in cardiomyocytes.

At the University of Valencia, Vincent Giner Galvan is studying oxidative stress as a determinant of left ventricular mass (LVM) and shape in essential hypertension. He has found that relative wall thickness but not LVM is significantly related to malondialdehyde and mitochondrial 8-oxo-2'-deoxyguanosine (8-oxo-dG) values, independent of age, sex, BMI and average of 24-hour mean blood pressure. Because remodeling is the initial mechanism in the development of target organ damage, oxidative stress assessment in peripheral mononuclear cells may have clinical relevance in the early detection of high cardiovascular risk in hypertensive patients.

in ER stress and endothelial dysfunction and the resulting relationship to atherothrombotic disease has been a focus of much research.¹⁹

Both muscular strength and cardiorespiratory (aerobic) fitness has been found to be inversely associated with the metabolic syndrome. It has been suggested that lack of physical activity (i.e., a sedentary lifestyle) should be added to the definition of the metabolic syndrome. Conversely, a number of studies have demonstrated that exercise training results in improvements in insulin resistance²⁰ and reductions in the risk of developing type 2 diabetes^{21,22} and the metabolic syndrome.²³

What type of exercise is needed to reduce metabolic syndrome risk? It has been suggested that cardiorespiratory and muscular fitness may have different and interacting effects on cardiovascular risk variables such as waist girth, glucose, triglycerides, total and high density lipoprotein (HDL) cholesterol, and systolic and diastolic blood pressure. In one study of women who trained for 16 weeks, compared to controls or those who were assigned to only aerobic exercise, those who combined aerobic exercise and weight lifting had the greatest adipose tissue and weight loss and the greatest improvements in peak maximal oxygen consumption (VO_2), muscle mass and glucose disposal.

Is the effect of exercise on metabolic syndrome dependent upon weight loss? Recently, we looked at metabolic syndrome indicators at baseline and at completion of a 24-week program with a supervised exercise program in a population of over 1000 patients referred to Hamilton's cardiac rehabilitation program. At baseline only 19% of the individuals were not

obese. At endpoint, even though none of the participants lost weight a number of metabolic risk factors decreased. Thus, we suspect that although losing weight is beneficial and should be encouraged in all high risk patients, positive changes can occur independently.

Practical issues faced by physicians trying to treat the metabolic syndrome patient include determining the amount, type and intensity of exercise required to be beneficial. Generally, for most people moderate to high intensity exercise is required to produce significant and beneficial changes. Amount can vary according to the patient's baseline, and in the very obese even a small amount of moderate walking may be beneficial. For our population of cardiac rehab patients, we recommend approximately 30 minutes of vigorous or brisk walking, preferably every day.

Exercise, nutrition and muscle metabolism in the metabolic syndrome

Mark Tarnopolsky

One of the greatest challenges of the metabolic syndrome is understanding the pathophysiology underlying the clustering of obesity, insulin resistance, dyslipidemia, hypertension and other abnormalities.²⁴ Skeletal muscle metabolism in response to exercise and nutrition may be of key relevance for the development of the metabolic syndrome.

Skeletal muscle must adapt to a large range of metabolic insults from diet and exercise.²⁵ In response to an acute bout of exercise, for example, the metabolic rate of muscle can increase 20-fold. Skeletal muscle is a store for carbohydrate (glycogen, around 400 g), lipids (intramyocellular triacylglycerol [IMCL], about 125 g) and protein (contractile and regulatory proteins, 4000 g). Most of the fuel for muscle metabolism in the fasted resting state comes from blood-derived free fatty acids from lipolysis of peripheral adipose tissue. The proportion of carbohydrate used as energy is a function of exercise training status and antecedent carbohydrate intake. Protein represents at most 10% of the resting energy metabolism, but can increase during periods of prolonged starvation (hence, the concern for maintenance of skeletal muscle mass during very low energy diets).

The proportion of fuel that is utilized during exercise is dependent upon many factors including:

- antecedent diet (increased carbohydrate use with carbohydrate loading);^{26,27}
- gender (women oxidize more lipid and less carbohydrate and protein, as compared to men);^{28,29,30,31}

- duration (increased lipid and protein use with longer duration);^{32,33}
- intensity (increased carbohydrate use with higher intensities);^{34,35}
- pre- and during-exercise carbohydrate feeding (increased carbohydrate use);³⁶ and
- training status (increased lipid and lower protein use).³⁷

After a period of endurance exercise training in healthy humans, there is an increase in lipid (IMCL), glycogen and total mitochondrial content in skeletal muscle.³⁸ These changes are associated with the shift towards increased reliance on lipid utilization during exercise and an increased ability to take up glucose from the plasma at rest but not during exercise.³⁹ The increase in glycogen stores and improved insulin sensitivity are strongly related to an increase in the total number of glucose transporters (GLUT-4), which facilitate glucose movement into muscle in response to insulin and muscle contraction.

An apparent paradox is found in obese individuals, in that they also show an increase in IMCL accumulation with a decrease in glycogen. According to the 'lipotoxicity' theory, the excess accumulation of non-metabolized free fatty acids (FFA) mobilized from peripheral stores (subcutaneous and intra-abdominal adipose stores) is deposited in both skeletal muscle (IMCL) and fatty liver disease. The excess IMCL accumulation is well correlated with insulin resistance and this is felt to be due to an accumulation of acyl-CoA species, ceramides and other lipid byproducts that appear to inhibit insulin signaling pathways at the level of insulin receptor substrate-1 (i.e., inhibiting GLUT-4 activation and glucose disposal into skeletal muscle, the largest site of glucose disposal).^{40,41} At least one study has shown that immobilization results in down regulation of mitochondrial activity and of GLUT-4.

Part of the inability to oxidize the IMCL in skeletal muscle in obese individuals may relate to smaller and less efficient mitochondria, the site of lipid oxidation (β -oxidation).⁴² Aerobic (endurance) training is known to increase mitochondria size and the proportion of mitochondria in direct contact with IMCL. However there is now evidence in older adults that resistance training may also stimulate mitochondria activity. Studies to demonstrate the effects of endurance exercise training on mitochondrial function and IMCL content in obese men and women are underway.

Sympathetic function in the metabolic syndrome

Previous studies have shown that alterations in vascular, metabolic, inflammatory and hemocoagulative function character metabolic syndrome. Gino Seravalle, San Luca Hospital, Milan, is exploring the role of sympathetic function in healthy controls and age-matched subjects with metabolic syndrome. He has found that muscle sympathetic nerve traffic directly and significantly correlates with waist circumference and is inversely related to baroreflex sensitivity, which is impaired in metabolic syndrome. These data provide the first direct evidence that metabolic syndrome is characterized by sympathetic activation. Moreover, it suggests that this abnormality depends on insulin resistance, as well as reflex alterations, and is detectable even when the metabolic syndrome is not accompanied by hypertension.

Lipoprotein metabolism and atherosclerosis: reverse cholesterol transport and beyond

Bernardo Trigatti

The criteria of metabolic criteria include low levels of high density lipoprotein cholesterol (HDL-C). Both clinical and basic research, using model systems at the cellular and model organism levels, have supported the notion that HDL protects against the development of atherosclerosis. It is not the amount of HDL or the size of the particles that is critical, as much as the flux of cholesterol through the liver. Altering HDL cholesterol in ways that enhance this flux may be helpful, and is the object of some new and emerging HDL therapies (ApoA1-mimetic peptides, CETP inhibitors and recombinant therapy with the ApoA1-Milano gene). However, there is still a lot to learn about the basic biology of HDL clearance.

A critical player in the pathways by which HDL protects against cardiovascular disease is an HDL receptor called scavenger receptor class B type 1 (SR-B1). SR-B1 is a multiligand receptor that binds to a variety of ligands, including native lipoproteins such as HDL, low density lipoprotein (LDL) and very low density lipoprotein (VLDL), although most studies have focused on its activity as a cell-surface HDL receptor. In mice, knock out of SR-B1 blocks clearance of cholesterol through the liver and results in an increase in the amount of atherosclerosis.^{43,44} SR-B1 overexpression is associated with a decrease in HDL and total cholesterol, but protection against atherosclerosis because of increased liver clearance.

SR-B1 levels are regulated by several factors, including insulin and insulin-like growth factors. In obese subjects there is an increase in CETP inhibitors from liver and adipose tissue, increased production of triglycerides and the blockage of VLDL. In mouse model, leptin knock-out mice are not only obese but have reduced liver SR-B1 and, as a result of decrease in the flux of cholesterol in the liver, increased HDL levels. As

Renal disease in the metabolic syndrome

A number of forum participants focused upon the renal implications of the metabolic syndrome. Josep Maria Galceran Gui, of Palamos Hospital, Girona, noted that it has been estimated that the prevalence of chronic kidney disease (CKD) is increasing 10% per year in western countries. At the same time, he feels the problem is seriously underestimated, as most studies use serum creatinine as a renal function marker and creatinine does not increase until a significant amount of renal function has been lost. In certain populations (women and the elderly), creatinine may be low even in the presence of moderate to severe renal failure. Using a computerized database to estimate glomerular filtration rate with the MDRD formula, the prevalence of CKD was estimated to be 8.8% among Spanish primary care patients age 18 and over. CKD was associated with age, pulse pressure, low HDL cholesterol, female gender, and cigarette smoking.

Fernando de Alvaro, reports that even CKD patients followed by nephrology clinics have low rates of control and high rates of co-morbidities, particularly in diabetes. In the MERENA study, compared to nephrology outpatients without diabetes, those with diabetes were found to be older, presented with higher BMI, glomerular filtration rate (GFR), proteinuria and serum potassium (all $p < 0.001$), higher systolic blood pressure (145 ± 19 vs. 139 ± 19 mmHg, $p < 0.001$), pulse pressure ($p < 0.001$), heart rate ($p = 0.039$), Cornell product in EKG ($p = 0.045$), and had more comorbid conditions (CVD 48% vs 31% for non-diabetes; ischemic heart disease 20% vs. 14%; peripheral vascular disease 30% vs 11%; and heart failure 48% vs. 31%, $p < 0.05$). Target blood pressure objectives were achieved only in 25% of the patients (21% in diabetics vs. 27% in non-diabetics) and LDL cholesterol was ≤ 100 mg/dl in 35% (28% in non-diabetics and 47% in diabetes, $p < 0.001$).

Serum aldosterone levels have been found to correlate with the incidence of hypertension, and primary aldosteronism (high aldosterone) occurs in 5 to 10% of diagnosed hypertensives. Accurate localization of aldosterone-secreting adenoma (APA) is essential for the treatment of primary aldosteronism (PA). Fumitoshi Satoh, Tohoku University Hospital described work showing that adrenal venous sampling with adrenocorticotrophic hormone (ACTH) simulation may be a viable method for localizing an APA.

leptin is given, SR-B1 levels increase, but only up to a point. Both too little and too much leptin reduces HDL. In humans, inhibition of hepatic HDL clearance may lead to large atherogenic HDL and possible increased triglycerides.

There is good evidence that exercise leads to a decrease in the metabolism of HDL, thus preserving Apo in the blood stream.

Conclusions

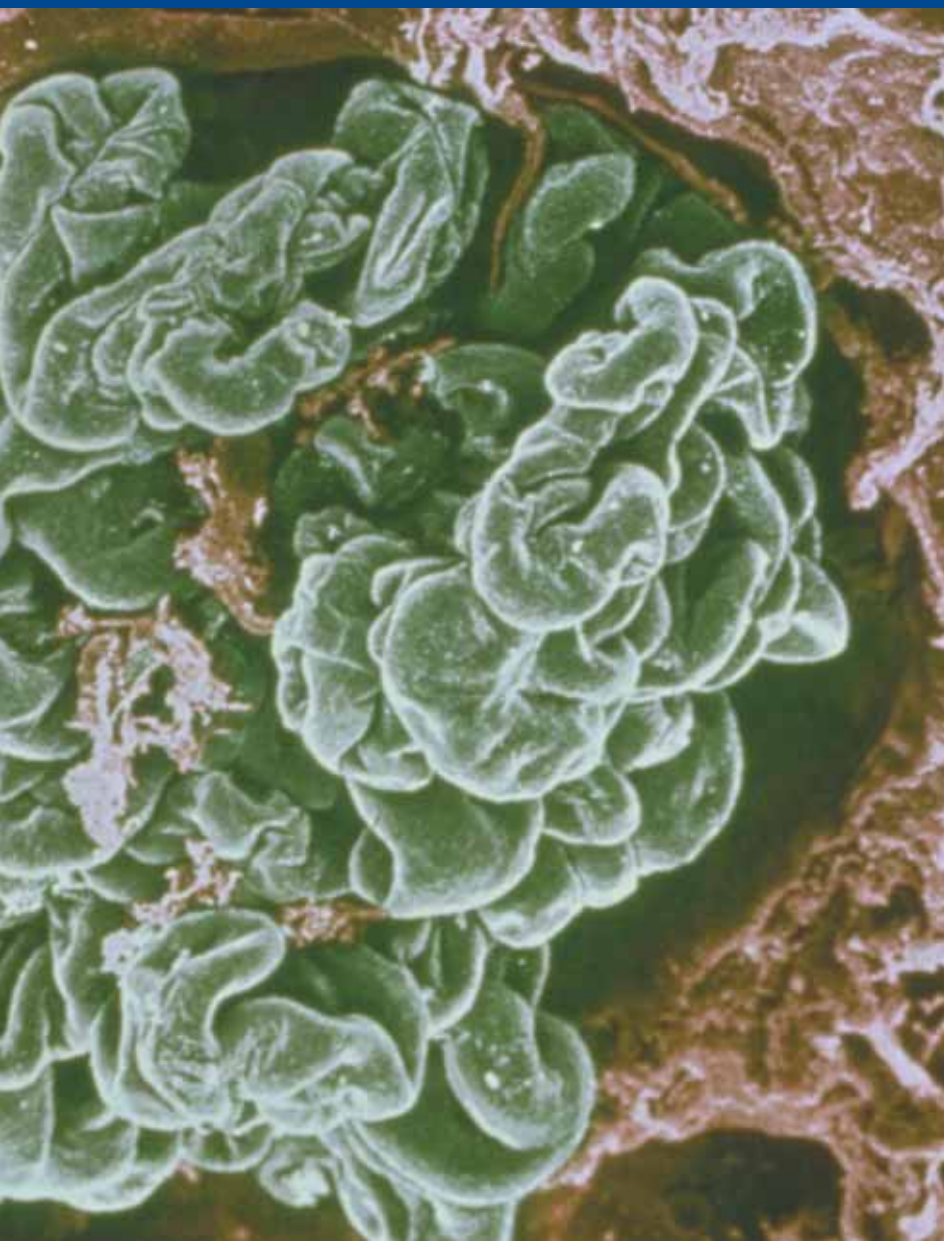
Arya M. Sharma

Recently, criticisms of the existence and utility of the metabolic syndrome have received high profile.⁴⁵ It is true that the WHO and ATP-III definitions are not without flaws, a fact which the IDF has attempted to address with its new definition.⁴⁶ Moreover, the criticism that the metabolic syndrome is unnecessary, and one should just treat the independent risk factors, clearly requires further discussion.⁴⁷ CVD risk factors do not exist in silos, and one of the more helpful aspects of the metabolic syndrome has been its ability to highlight how risk factors interact to impact global risk.

Mounting evidence that abdominal obesity is common to each of the components of the metabolic syndrome led to the IDF establishing increased waist circumference is a necessary requirement for diagnosis. In this forum, we looked at a number of epidemiologic, clinical and physiologic factors and processes involved in abdominal obesity that affect blood pressure, glucose and lipid metabolism and, ultimately, CVD risk. Given the global pandemic of obesity, a better understanding of its role in the metabolic syndrome is essential for all those concerned with CVD prevention and treatment.

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