Metabolic syndrome: A marker of patients at high cardiovascular risk

David CW Lau MD PhD FRCPC, Hongyun Yan MD PhD, Bikramjit Dhillon BSc

DCW Lau, H Yan, B Dhillon. Metabolic syndrome: A marker of patients at high cardiovascular risk. *Can J Cardiol* 2006;22(Suppl B):85B-90B.

The metabolic syndrome is a constellation of metabolic abnormalities associated with an increased risk for cardiovascular disease (CVD). It is present in one of four adults, and its prevalence is markedly increased in obese adults and adolescents. The plasma concentration of C-reactive protein (CRP), a marker of inflammation, is elevated in obese patients, is correlated with the metabolic syndrome and decreases with weight loss. CRP is produced by mature adipocytes in adipose tissue, and may contribute to the elevated circulating plasma CRP concentrations present in obese patients and people with the metabolic syndrome. Treatment of the metabolic syndrome is aimed at improving insulin resistance through lifestyle changes, namely weight loss and regular physical activity. In patients with abnormal glucose concentrations, dyslipidemia or hypertension, treatment of the individual components of the syndrome may result in greater impact on reducing overall CVD risks. Given the prevalence of the metabolic syndrome and the exaggerated CVD risks, innovative therapeutic approaches continue to evolve.

Key Words: *Adipokines; Cardiovascular disease; C-reactive protein; Insulin resistance; Metabolic syndrome; Obesity*

The metabolic syndrome has rapidly become a household name since its introduction a few years ago by the World Health Organization (WHO), and later the United States National Cholesterol Education Program (NCEP), as an operational clinical entity associated with increased cardiovascular risk (1,2). It refers to a constellation of metabolic abnormalities associated with increased risk for type II diabetes and cardiovascular disease (CVD) (2,3). Insulin resistance and compensatory hyperinsulinemia appear to be the common conditions that predispose to the development of the various clinical conditions clustered in the same patient. This concept was first proposed by Reaven (4) in 1988 and the clinical syndrome was termed Syndrome X. As our understanding of the pathophysiology of insulin resistance expands, so have the clinical features ascribed to the metabolic syndrome (3). The creation of a new *International Classification of Diseases* diagnostic code of 277.7 not only makes it possible for reimbursement of treating the metabolic syndrome, but also gives it legitimacy as a real disease entity.

Departments of Medicine, Biochemistry and Molecular Biology

Correspondence and reprints: Dr David CW Lau, Julia McFarlane Diabetes Research Centre, 2521 – 3330 Hospital Drive Northwest, Calgary, Alberta T2N 4N1. Telephone 403-220-2261, fax 403-210-8113, e-mail dcwlau@ucalgary.ca

Syndrome métabolique : Marqueur chez les patients à haut risque cardiovasculaire

Le syndrome métabolique regroupe une constellation d'anomalies métaboliques associées à un risque accru de maladie cardiovasculaire (MCV). On observe ce syndrome chez un adulte sur quatre et sa prévalence est nettement en hausse chez les adultes et adolescents obèses. Le taux plasmatique de protéine C réactive (PCR), un marqueur de l'inflammation, est élevé chez les patients obèses, il est en corrélation avec le syndrome métabolique et diminue avec la perte de poids. La PCR est fabriquée par les adipocytes à maturité dans les tissus adipeux, ce qui contribuerait à l'augmentation des taux de PCR circulants chez les patients obèses et chez ceux qui souffrent du syndrome métabolique. Le traitement du syndrome métabolique vise à améliorer l'insulinorésistance par le biais d'une meilleure hygiène de vie, notamment par la perte de poids et la pratique régulière d'exercices physiques. Chez les patients dont la glycémie est anormale, qui souffrent de dyslipidémie ou d'hypertension, le traitement de chaque composante individuelle du syndrome peut exercer un impact plus grand sur la réduction globale des risques de MCV. Compte tenu de la prévalence du syndrome métabolique et des importants risques de MCV qui lui sont associés, les nouvelles approches thérapeutiques doivent continuer d'évoluer.

CLINICAL FEATURES OF THE METABOLIC SYNDROME

In addition to hyperglycemia, dyslipidemia and hypertension, as originally described by Reaven (4), abdominal obesity, proinflammatory and prothrombotic states have now been included as key features of the metabolic syndrome. The key features of the metabolic syndrome along with novel risk factors, such as elevated plasma concentrations of C-reactive protein (CRP), plasminogen activator inhibitor-1 and fibrinogen, are listed in Figure 1. Not all patients develop the full spectrum of the metabolic syndrome; however, the majority of adults have one or more of these components. Other clinical conditions linked to the metabolic syndrome include nonalcoholic fatty liver disease, sleep apnea, acanthosis nigricans and, in women, polycystic ovary disease (3).

DIAGNOSIS OF THE METABOLIC SYNDROME

At present, the metabolic syndrome cannot be diagnosed with a single test. Several classification schemes based on various

Figure 1) Current concept of the metabolic syndrome. Central obesity is the principal abnormality that predisposes to the development of the metabolic syndrome, which also includes insulin resistance (hyperglycemia and/or type II diabetes), atherogenic dyslipidemia characterized by hypertriglyceridemia and decreased high density lipoprotein cholesterol concentrations, hypertension, along with proinflammatory and prothrombotic states (increased circulating plasma concentrations of plasminogen activator inhibitor-1, fibrinogen and C-reactive protein). CVD Cardiovascular disease

cardiovascular risk factors have been proposed for the identification of the metabolic syndrome (Table 1) (1,3,5,6). The most widely used is the NCEP Adult Treatment Panel III (ATP III) criteria (2). A diagnosis of the metabolic syndrome requires three or more of five criteria (Table 1).

The WHO definition of the metabolic syndrome, in contrast to the NCEP ATP III criteria, is more etiologically oriented and

requires insulin resistance and/or impaired glucose tolerance (IGT) as a prerequisite criterion, along with two of the following: obesity; hypertriglyceridemia; low high density lipoprotein (HDL) cholesterol; hypertension; or microalbuminuria (Table 1) (1).

PREVALENCE OF THE METABOLIC SYNDROME

Using the NCEP ATP III criteria, the prevalence of the metabolic syndrome is common among adults. According to the Third United States National Health And Nutrition Examination Survey (NHANES III), a cross-sectional health survey of a representative sample of the United States population conducted between 1988 and 1994, one of four adult men or women has the metabolic syndrome (7). The prevalence is similar in men (24%) and women (23.4%). The prevalence increases markedly with age from approximately 7% in adults 20 to 29 years to over 40% in people older than 60 years.

The metabolic syndrome is more common in Mexican Americans (32%), and in patients with lower socioeconomic status and sedentary lifestyles, but is less common in African Americans (21.6%) (7,8). According to the Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) studies, the prevalence of the metabolic syndrome studies appears to be somewhat lower in Europe, affecting 15% of nondiabetic adults, with little difference between men and women (9). The prevalence of the metabolic syndrome increases sharply with age, reaching a peak in the 60- to 69-year-old group in both sexes, a finding similar to the United States data.

It should be noted that the WHO criteria for the metabolic syndrome rely more heavily on insulin resistance as the underlying abnormality, and as such, the prevalence of the syndrome may be lower than that in the NCEP ATP III criteria (1,3,5).

TABLE 1
Criteria for the identification of the metabolic syndrome

International Diabetes Federation		National Cholesterol Education Program Adult Treatment Panel III	World Health Organization	American Association of Clinical Endocrinologists
Risk factors		At least ≥ 3 of the following:	One of the following:	1 risk factor + 2 parameters
Central obesity	Waist circumference			
	Europeids, Middle East, Africans			
	≥94 cm			
	≥80 cm			
	South Asians, Chinese, South/Central Americans			
	≥90 cm			
	≥80 cm			
	Japanese			
	≥85 cm			
	≥90 cm			
And ≥ 2 of the following:				
Insulin resistance and/or fasting glucose	≥5.6 mmol/L	≥5.6 mmol/L	Insulin resistance, impaired glucose tolerance, type II diabetes	2 h post challenge ≥7.8 mmol/L 6.1 mmol/L to 6.9 mmol/L
Obesity		Waist circumference	BMI ≥30 kg/m ² or waist-to-hip ratio	BMI ≥25 kg/m ² or waist circumference
Men		>102 cm	Men >0.90	Men >102 cm
Women		>88 cm	Women >0.85	Women > 88 cm
Triglycerides	≥1.7 mmol/L	≥1.7 mmol/L	≥1.7 mmol/L	≥1.7 mmol/L
HDL-cholesterol				
Men	<1.04 mmol/L	<1.04 mmol/L	<0.90 mmol/L	<1.04 mmol/L
Women	<1.33 mmol/L	<1.33 mmol/L	<1.00 mmol/L	<1.33 mmol/L
Blood pressure	≥130/85 mmHg	≥130/85 mmHg	≥140/90 mmHg	≥135/≥85 mmHg
Microalbuminuria	Not required	Not required	Albumin/creatinine ratio ≥30 mg/g or albumin excretion rate ≥20 µg/min	Not required
				Age >40 years, non-Caucasian ethnicity, sedentary lifestyle, history of hypertension, dyslipidemia, CVD, PCOD, nonalcoholic liver disease, acanthosis nigricans, obesity-related cancer, or family history of CVD, type 2 diabetes, hypertension

BMI Body mass index; CVD Cardiovascular disease; HDL High density lipoprotein; PCOD Polycystic ovary disease. Data from references 1, 6, 7 and 8

TABLE 2
Prevalence and adjusted ORs of the metabolic syndrome according to body mass index (BMI)

BMI (kg/m ²)	Normal (18.5–24.9)	Overweight (25–29.9)		Obese (30–34.9)		Severe obesity (≥ 35)	
		Men	Women	Men	Women	Men	Women
Prevalence (%)	6	22	28	60	50	72	65
OR (95% CI)	1	5.2 (3.9 to 6.9)	5.4 (3.7 to 7.9)	25.2 (19.3 to 32.9)	14.0 (9.1 to 21.4)	67.7 (40.5 to 113.3)	34.5 (22.6 to 52.7)

Data from reference 8

When the NHANES III data comparing the NCEP ATP III and WHO criteria were reanalyzed, the age-adjusted prevalence among 8608 patients older than 20 years was 23.9% using the NCEP ATP III definition, and 25.1% using the WHO definition (10). Among all patients, 86.2% were classified as either having or not having the metabolic syndrome under both definitions. Estimates differed substantially for some subgroups (10). Nonetheless, the prevalence using either the NCEP ATP III or the WHO criteria appeared to be similar among Caucasians in the Framingham Offspring Study (24% in both NCEP ATP III and WHO) and the San Antonio Heart Study (23% and 21%, respectively, for NCEP ATP III and WHO) (11).

Recent data in adolescents and youth suggested that the metabolic syndrome is increasingly common, especially in overweight and obese people. The overall prevalence among adolescents aged 12 to 19 years was 4.2%, with 6.1% in male and 2.1% in female patients in the NHANES III survey (12). The syndrome was present in 6.8% of overweight (body mass index [BMI] 85th percentile or above) and 28.7% of obese (BMI 95th percentile or above) adolescents. It has been estimated that close to 900,000 adolescents in the United States have the metabolic syndrome (12).

A more recent study in 439 obese and 31 overweight adolescents demonstrated that the prevalence of the metabolic syndrome increased dramatically with the severity of obesity, reaching 50% in severely obese children (13). Of 77 patients who underwent a second assessment after a 21-month follow-up, 24 of 34 patients who had met the criteria for the metabolic syndrome initially continued to meet the criteria. The metabolic syndrome developed in 16 of 43 children who did not have the condition initially. Eight children who previously had the metabolic syndrome and IGT developed type II diabetes during follow-up (13). Emerging data also suggest that the metabolic syndrome persists into adulthood if left untreated.

COMPONENTS OF THE METABOLIC SYNDROME

Obesity, especially abdominal obesity, appears to be a major underlying abnormality frequently present in the metabolic syndrome. Indeed, the emerging obesity epidemic is widely viewed as the principal driver for the rising prevalence of the metabolic syndrome. The metabolic syndrome is present in less than 6% of normal-weight adults, but a steep rise in its prevalence is seen in overweight and obese men (22% and 60%, respectively), and a similar distribution is also seen in women (Table 2) (8). The prevalence of the metabolic syndrome rises sharply with increasing adiposity, with an OR of 34.5 in women and 67.7 in men with BMI 35 kg/m² or greater (Table 2) (8). Abdominal obesity is also thought to be closely correlated with the metabolic syndrome (14), cardiovascular risk and diabetes, and can be attributed to excessive release by visceral fat of free fatty acids (FFAs), proinflammatory cytokines,

thrombotic and atherogenic factors. CRP, a marker of chronic inflammation that has emerged to become a predictor of CVD and type II diabetes, is correlated with adiposity. Its circulating concentrations increase with obesity and decrease with weight loss induced by lifestyle modification or surgery (15–17).

Abdominal or visceral obesity is associated with insulin resistance and abnormal lipoprotein and remnant lipoprotein metabolism, and can lead to atherogenic dyslipidemia. The latter is characterized by hypertriglyceridemia, decreased HDL cholesterol, increased small, dense low density lipoprotein (LDL) particles and increased apolipoprotein B concentrations, which are hallmarks of the dyslipidemia of metabolic syndrome. It appears that the excessive release of FFAs and adipocytokines by the metabolically active visceral fat might be responsible for the deranged lipoprotein metabolism.

The excessive release of proinflammatory cytokines and prothrombotic factors in obesity, and notably abdominal obesity, is well documented. The higher plasma CRP and plasminogen activator inhibitor-1 and fibrinogen concentrations in obese states are due to increased production from hepatic and possibly adipose tissue. Recent evidence suggests that CRP is not a mere marker of inflammation, but that it may directly contribute to insulin resistance and atherogenesis. Indeed, CRP has emerged to become a strong predictor of future CVD events and the development of type II diabetes (18,19).

Hypertension is by far the most prevalent of the individual components of the metabolic syndrome, and is found in as many as 50% to 76% of patients. Both obesity and insulin resistance are known to be associated with increased blood pressure, but the etiology of hypertension is likely multifactorial. The compensatory hyperinsulinemia may induce hypertension by a number of mechanisms, including chronic stimulation of the sympathetic and vascular tone, and antinatriuresis.

METABOLIC SYNDROME AND CARDIOVASCULAR RISK

While each of the individual components of the metabolic syndrome is clearly associated with increased CVD risks, the presence of the metabolic syndrome greatly augments CVD morbidity and mortality. A number of large population and prospective studies have demonstrated significantly increased risk of all-cause mortality, and CVD mortality and morbidity, in association with the presence of the metabolic syndrome. Data from the United States NHANES III participants 50 years and older demonstrated a mean OR of 2.07 for CVD (14% with the metabolic syndrome versus 9% in those without) (20). Approximately 85% of the patients with diabetes have the metabolic syndrome, whereas the 15% of the patients with diabetes but not the metabolic syndrome have a lower prevalence of coronary artery disease (CAD). This finding could be attributed to the lower prevalence of hypertriglyceridemia, low HDL cholesterol concentrations and lower rates of hypertension

TABLE 3
Metabolic syndrome and cardiovascular disease risks according to various studies

	United States NHANES III	WOSCOP	Kuopio	DECODE
OR	2.07	2.75	2.9 to 4.2	Men 2.26 Women 2.78

DECODE Diabetes Epidemiology: Collaborative Analysis Of Diagnostic Criteria in Europe; NHANES III National Health And Nutrition Examination Survey III; Kuopio Ischemic Heart Disease Risk Factor Study; WOSCOP West Of Scotland COronary Prevention. Data from references 9, 20, 21 and 23

among this unusual group of patients with diabetes (20). The West Of Scotland COronary Prevention Study (WOSCOPS) also yielded similar results. The CVD hazard ratio rose with increasing numbers of components of the metabolic syndrome, and was 2.75 in the presence of the metabolic syndrome and a high CRP concentration (21). In the Framingham cohort, the metabolic syndrome predicted approximately 25% of all cases of newly onset CVD. The 10-year CAD risk in men with the metabolic syndrome fell into the moderate category, and ranged from 10% to 20% (22). Although women with the metabolic syndrome also had higher CAD risks, the 10-year risk was less than 10%, which is attributable to the fact that they were younger with fewer CVD events.

In the prospective Finnish Kuopio Ischemic Heart Disease Risk Factor Study, both CVD and all-cause mortality were significantly increased in men with the metabolic syndrome, even in the absence of baseline CVD and diabetes (23). Middle-aged men with the metabolic syndrome had 2.9- to 4.2-fold higher CVD mortality rates after adjustment for conventional CVD risk factors (23).

A study based on 11 prospective European cohort studies comprised of 6156 men and 5356 women without diabetes who were between 30 and 89 years of age also confirmed that non-diabetic people with the metabolic syndrome have an increased risk of death from all causes as well as CVD (9). Of 1119 deaths recorded during a median follow-up period of 8.8 years, 432 were caused by CVD. The overall hazard ratios for all-cause and cardiovascular mortality in persons with the metabolic syndrome were similar in men and women; they were, respectively, 1.44 (95% CI 1.17 to 1.84) and 2.26 (95% CI 1.61 to 3.17) in men, and 1.38 (95% CI 1.02 to 1.87) and 2.78 (95% CI 1.57 to 4.94) in women (compared with controls and after adjustment for age, blood cholesterol concentrations and smoking) (9).

It follows from the above review of population and prospective studies that the metabolic syndrome is associated with markedly increased CVD risk, with significantly increased OR (Table 3). Whether treatment of the metabolic syndrome reduces the CVD risk is the focus of several ongoing and future clinical trials. A better understanding of the pathophysiology of the metabolic syndrome will provide additional and new insights into therapy and prevention of this prevalent condition.

CRP AND THE METABOLIC SYNDROME

Circulating plasma CRP and adipokine concentrations are elevated, whereas plasma adiponectin concentrations are decreased in obese patients and in people with the metabolic syndrome. Plasma CRP concentrations are also directly correlated with the amount of body fat, as assessed anthropometrically

by BMI and notably by visceral obesity (assessed by the presence of a large waist circumference). Weight loss by hypocaloric diets or surgical intervention reduced CRP concentrations in healthy, middle-aged and postmenopausal obese women and obese men (16,24). Emerging evidence suggests that elevated plasma concentrations of CRP have become one of the strongest independent predictors of CAD. High plasma CRP concentrations have been correlated with CAD in several large, cross-sectional, prospective population studies, including the United States Physicians Health Study, the MONItoring of trends and determinants in CArdiovascular disease (MONICA) Augsburg cohort study, the Multiple Risk Factor Intervention Trial (MRFIT) and the Women's Health Study (25,26). CRP is not merely a marker of inflammation, but appears to be an active participant in endothelial dysfunction, an early abnormality that ultimately leads to the development of atherosclerosis (27).

The relationships between circulating CRP concentrations, the metabolic syndrome and incident CVD have been explored in a large cohort of 14,719 healthy women (19). Plasma CRP concentrations appeared to correlate with individual components of the metabolic syndrome; higher CRP concentrations were seen in women with increasing numbers of features of the syndrome. Interestingly, the predictive value of plasma CRP concentrations greater than 3 mg/L in the development of CVD was similar to that of the metabolic syndrome (19). Hence, CRP adds prognostic information to the metabolic syndrome, and further studies will help to elucidate whether CRP can be used as a surrogate marker of the metabolic syndrome, as well as its predictive value for CVD events.

ADIPOSE TISSUE-DERIVED ADIPOKINES AND CRP AS THE CELLULAR LINKS BETWEEN THE METABOLIC SYNDROME AND CVD

Adiposity, and notably abdominal obesity, is by far the most consistent and easily recognizable phenotype of the metabolic syndrome. The dramatic increase in obesity rates in both adults and adolescents largely accounts for the increasing prevalence of the metabolic syndrome in North America and Europe. Adipose tissue is no longer viewed as a passive repository for triacylglycerol storage and a source of FFAs (28-30). As developing preadipocytes differentiate to become mature adipocytes, they acquire the ability to synthesize over hundreds of proteins, including enzymes, cytokines, growth factors and hormones, that are involved in overall energy homeostasis (30). Mature adipocytes are active endocrine and paracrine cells secreting an ever-increasing number of mediators that participate in diverse metabolic processes (28,29). More recently, adipose tissue was also deemed to be a rich source of proinflammatory mediators, many of which are cytokines, growth factors and hormones, that directly contribute to the proinflammatory milieu mediating vascular injury and insulin resistance, ultimately impacting on cardiovascular health (27). These proinflammatory adipocytokines, or adipokines, include tumour necrosis factor- α , interleukin-6 (IL-6), leptin, plasminogen activator inhibitor-1, angiotensinogen, resistin and, more recently, CRP (27).

The close correlation between the degree of obesity and CRP concentrations in cross-sectional and prospective epidemiological studies have led us to hypothesize that adipose tissue is a potential source of CRP. We first reported CRP expression by real-time polymerase chain reaction, and confirmed

by DNA sequencing that CRP was expressed in rat, mouse, as well as human adipose tissue, and mature and developing fat cells (27,31,32). CRP messenger RNA expression was not only present in rodent and human adipose tissue, but could be localized largely to mature adipocytes and endothelial cells, and to a much lower extent, preadipocytes (32,33). CRP messenger RNA expression was exaggerated in mature adipocytes derived from obese patients. The increased circulating CRP concentrations observed in obese people and metabolic syndrome may be attributed to augmented CRP production by adipose tissue (32,33). Ongoing and future studies will help to affirm the role of adipokines, and notably CRP, as cellular and molecular links between obesity, the metabolic syndrome and atherosclerosis (27).

TREATMENT APPROACHES TO THE METABOLIC SYNDROME

Because the metabolic syndrome is associated with increased CVD risk, making a diagnosis is prudent to identify and treat those patients who harbour this condition. Lifestyle modification is the cornerstone treatment for the metabolic syndrome, because excess adiposity and physical inactivity are the major lifestyle variables that have an untoward effect on insulin action and insulin resistance. Weight loss and increased physical activity, when appropriately initiated, enhance insulin sensitivity and also decrease the associated CVD risk factors. Two landmark clinical trials in overweight and obese patients with IGT have proven that modest weight loss (5% to 7%), along with regular physical activity (150 min of moderately intense activity per week) are highly beneficial in reducing the risk of type II diabetes by 59% (34,35). In addition, a modest 5% to 7% reduction in body weight can result in improvement in lipid profile, blood pressure and CRP concentrations (15-17,36).

In very obese patients with the metabolic syndrome, weight loss results in the attenuation of circulating CRP and IL-6 by as much as 80% and 23%, respectively, while no significant change in tumour necrosis factor- α concentrations was observed (15). CRP, but not IL-6, lowering, however, is correlated with body fat loss (15), suggesting that changes in IL-6 and CRP, respectively, have differential effects on insulin resistance and, by extension, cardiovascular health. Further, the data are in keeping with the proposed concept of adipose tissue as a modulator of circulating CRP concentrations.

Normalizing postprandial hyperglycemia in patients with IGT with an alpha-glucosidase inhibitor, acarbose, reduced diabetes risk by 25% in the Canadian-led Study TO Prevent NonInsulin Dependent Diabetes Mellitus (STOP-NIDDM) multicentre trial (37). Further, the STOP-NIDDM was the first study to demonstrate that in IGT patients, who likely have the metabolic syndrome, reducing postprandial glucose and insulin resistance resulted in a 49% decrease in CVD events and 34% reduction in new cases of hypertension (38).

Medical therapy for insulin resistance is now an emerging therapeutic area. Metformin and more recently the thiazolidinedione (TZD) insulin-sensitizing agents are used to treat diabetes either as mono- or combination therapy (39). TZDs act as ligands for the peroxisome proliferator-activated receptor- γ nuclear receptors found mainly in adipose tissue. In addition to improving peripheral insulin sensitivity, TZDs exhibit other metabolic and CVD benefits, such as lowering triglycerides and raising HDL cholesterol, reducing proinflammatory cytokines, like CRP, and improving endothelial function,

an early abnormality in atherosclerosis. Ongoing clinical trials are investigating the effect of TZDs and angiotensin-converting enzyme inhibitor (ACEI) on the prevention of type II diabetes (Diabetes REduction Assessment with ramipril and rosiglitazone Medication [DREAM]) and the reduction of CVD events in people with type II diabetes by improving hyperglycemia, lipid profile and hypertension (Action to Control Cardiovascular Risk in Diabetes [ACCORD] trial).

With respect to treatment of the specific risk factors, it is important to recognize that an aggressive multifactorial approach is beneficial in reducing overall CVD risk. Treating to reach target glucose, lipid and blood pressure values are desirable, even though evidence for the improvement of CVD end points in the metabolic syndrome is lacking.

Statins are effective in lowering total and LDL cholesterol concentrations, although they are less effective in reducing very low density lipoprotein, triglycerides and atherogenic remnant lipoprotein particles. Fibrates may be useful in modifying the atherogenic dyslipidemia and should be considered in appropriate patients.

Treatment of hypertension should adhere to the recommended clinical practice guidelines and efforts should be directed at increasing adherence. The United Kingdom Prospective Diabetes Study has provided irrefutable evidence that treating hypertension in people with diabetes not only improves macro- but also microvascular diabetes related end points (40).

Compelling evidence from the landmark Heart Outcomes Prevention Evaluation (HOPE) study, and more recently the EUROpean trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease (EUROPA) trial, indicate that patients with CVD or at CVD risk can greatly benefit from vascular protection by taking an ACEI (41,42). The CVD benefits appear to be independent of the blood pressure-lowering effects of ACEIs. Whether angiotensin receptor blockers confer similar benefits as ACEIs on vascular protection remains unknown.

Acetylsalicylic acid is recommended to reduce the prothrombotic state, and ongoing studies will detail the potential benefits of reducing the proinflammatory states by the use of ACEIs or statins.

CONCLUSION

The metabolic syndrome and its cluster of associated abnormalities are important CVD and diabetes risk factors. The formal recognition of this multisystem disorder with its distinct diagnostic code lends further support to the need to recognize and treat people with the metabolic syndrome. Targeting the individual components of the syndrome for treatment may result in greater impact on reducing overall CVD and diabetes risks. Given the prevalence and magnitude of the clinical problem, new therapeutic approaches for the management of the metabolic syndrome continue to evolve. While awaiting the results of ongoing and future clinical trials, it makes imminent common sense to treat the sum rather than dealing with the parts.

ACKNOWLEDGEMENTS: The present work was supported in part by grants from the Heart and Stroke Foundation of Alberta and the Diabetes Association (Brooks and District Chapters). The expert technical assistance of Cecil Liu, Lucia Ma and Yangfei Wang is gratefully acknowledged.

REFERENCES

- 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: World Health Organization, 1999.
- 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;285:2486-97.
- Grundy SM, Brewer HB, Jr, Cleeman JI, Smith SC, Jr, Lenfant C. 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;109:433-8.
- Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 1988;37:1595-607.
- Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part I: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998;15:539-53.
- Einhorn D, Reaven GM, Cobin RH, et al. American College of Endocrinology position statement on the insulin resistance syndrome. *Endocr Pract* 2003;9:237-52.
- 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;287:356-9.
- Park YW, Zhu S, Palaniappan L, Heshka S, Carnethon MR, Heymsfield SB. The metabolic syndrome: Prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988-1994. *Arch Intern Med* 2003;163:427-36.
- Hu G, Qiao Q, Tuomilehto J, Balkau B, Borch-Johnsen K, Pyorala K. Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women. *Arch Intern Med* 2004;164:1066-76.
- Ford ES, Giles WH. A comparison of the prevalence of the metabolic syndrome using two proposed definitions. *Diabetes Care* 2003;26:575-81.
- Meigs JB, Wilson PW, Nathan DM, D'Agostino RB Sr, Williams K, Haffner SM. Prevalence and characteristics of the metabolic syndrome in the San Antonio Heart and Framingham Offspring Studies. *Diabetes* 2003;52:2160-7.
- Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: Findings from the third National Health and Nutrition Examination Survey, 1988-1994. *Arch Pediatr Adolesc Med* 2003;157:821-7.
- Weiss R, Dziura J, Burgert TS, et al. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med* 2004;350:2362-74.
- Lorenzo C, Serrano-Rios M, Martinez-Larrad MT, et al. Central adiposity determines prevalence differences of the metabolic syndrome. *Obes Res* 2003;11:1480-7.
- Kopp HP, Kopp CW, Festa A, et al. Impact of weight loss on inflammatory proteins and their association with the insulin resistance syndrome in morbidly obese patients. *Arterioscler Thromb Vasc Biol* 2003;23:1042-7.
- Esposito K, Pontillo A, Di Palo C, et al. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: A randomized trial. *JAMA* 2003;289:1799-804.
- Tchernof A, Nolan A, Sites CK, Ades PA, Poehlman ET. Weight loss reduces C-reactive protein levels in obese postmenopausal women. *Circulation* 2002;105:564-9.
- Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 2001;286:327-34.
- Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: An 8-year follow-up of 14,719 initially healthy American women. *Circulation* 2003;107:391-7.
- Alexander CM, Landsman PB, Teutsch SM, Haffner SM. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes* 2003;52:1210-4.
- Sattar N, Gaw A, Scherbakova O. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation* 2003;108:414-9.
- Wilson PW, Kannel WB, Silbershatz H, D'Agostino RB. Clustering of metabolic factors and coronary heart disease. *Arch Intern Med* 1999;159:1104-9.
- Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002;288:2709-16.
- Heilbronn LK, Noakes M, Clifton PM. Energy restriction and weight loss on very-low-fat diets reduce C-reactive protein concentrations in obese, healthy women. *Arterioscler Thromb Vasc Biol* 2001;21:968-70.
- Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. *JAMA* 1999;282:2131-5.
- Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation* 2003;107:363-9.
- Lau DC, Dhillon B, Yan H, Szmitko PE, Verma S. Adipokines: Molecular links between obesity and atherosclerosis. *Am J Physiol Heart Circ Physiol* 2005;288:H2031-41.
- Lau DC, Schillabeer G, Li ZH, Wong KL, Varzaneh FE, Tough SC. Paracrine interactions in adipose tissue development and growth. *Int J Obes Relat Metab Disord* 1996;20(Suppl 3):S16-25.
- Lau DC. Adipose tissue growth and differentiation: View from the chair. *Int J Obes Relat Metab Disord* 2000;24(Suppl 4):S20-2.
- Ahima R, Flier JS. Adipose tissue as an endocrine organ. *Trends Endocrinol Metab* 2000;11:327-32.
- Lau D, Yan H, Abdel-Hafez M, Kermouni A. Adipokines and the paracrine control of their production in obesity and diabetes. *Int J Obes Relat Metab Disord* 2002;26(Suppl 1):S111.
- Dhillon B, Yan H, Wang Y, et al. Adipose tissue is a source and modulator of C-reactive protein expression. *Can J Diabetes* 2004;28:252.
- Dhillon B, Yan H, Wang Y, et al. Characterization of C-reactive protein mRNA levels in lean and obese human adipose tissue. *Obesity Res* 2004;12(Suppl):A21.
- Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001;344:1343-50.
- Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393-403.
- Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: A meta-analysis. *Am J Clin Nutr* 1992;56:320-8.
- Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose for prevention of type 2 diabetes mellitus: The STOP-NIDDM randomised trial. *Lancet* 2002;359:2072-7.
- Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: The STOP-NIDDM trial. *JAMA* 2003;290:486-94.
- Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Can J Diabetes* 2003;27(Suppl 2):S37-42.
- Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 1998;317:703-13. (Erratum in 1999;318:29).
- Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000;355:253-9. (Erratum 2000;356:860).
- Fox KM; EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: Randomised double-blind, placebo-controlled, multicentre trial (the EUROPA Study). *Lancet* 2003;362:782-8.