HOSPITAL CHRONICLES 2006, SUPPLEMENT: 201–208

Metabolic Syndrome and Cardiovascular Risk: The Nurse's Role

Dimitra Agelidou, RN

A´ Departmetn of Cardiology, Evagelismos General Hospital of Athens, Athens, Greece

List of Abbreviations:
MS= metabolic syndrome
BMI= body mass index
HDL= high density lipoprotein
LDL= low density lipoprotein

KEY WORDS: *metabolic syndrome; diabetes mellitus; obesity; hyperlipidemia; hypertension; nursing intervention*

Address for correspondence:
Dimitra Agelidou, RN
A´ Cardiology Department
Evagelismos Hospital
Ipsilantou 45-47
Athens, Greece
Tel: 210-7201490
Fax: 210-7201456

ABSTRACT

Metabolic Syndrome (MS) is characterized by dysglycemia, arterial hypertension, atherogenic dyslipidemia and central obesity. Its presence has been associated with increased risk for the development of diabetes mellitus and cardiovascular disease. The main treatment goal is to lower the incidence of both MS and its cardiovascular sequelae and includes diet, exercise, weight loss, control of blood glucose and pharmacological therapy of hypertension and dyslipidemia. Nursing care focuses in the development of a concise treatment plan based upon patient's education, psychosocial support and close follow-up. Nurses should have a wide knowledge of MS pathophysiology which will facilitate their active participation in both diagnosis and treatment processes. The final goal is to assure the long-term compliance of patients with both the proposed lifestyle changes and the medical treatment in order to achieve a significant reduction in their cardiovascular morbidity and mortality.

INTRODUCTION - HISTORY

The clustering of cardiovascular risk factors like obesity, type 2 diabetes, hyperlipidemia and hypertension in the same person was initially described several decades ago [1,2]. On the other hand, insulin resistance has been the earliest described characteristic of type 2 diabetes mellitus [3]. The association of diabetes with hyperinsulinemia, hyperlipidemia, obesity and hypertension were subsequently reported. Thus, it became clear that the majority of patients suffering from type 2 diabetes had also high incidence of several other cardiovascular risk factors [4]. This risk factor clustering and its association with insulin resistance was attributed to a distinct pathophysiologic entity named initially as "insulin resistance syndrome" [5,6].

Reaven in his hallmark lecture in 1988 [7] unified and expanded these aspects by introducing the term "syndrome X" to describe the combination of these cardiovascular risk factors (hypertension, hyperglycemia, dyslipidemia). He developed the hypothesis that insulin resistance resulting in compensatory increased insulin plasma levels, predisposed to the development of hypertension, hyperlipidemia and diabetes. Obesity was not included in Reaven's list of insulin resistance derived abnormalities although he accepted the existence of an association between obesity and insulin resistance. Subsequently, other investigators underlined the pivotal role of obesity as a causal factor of Reaven's syndrome X and used instead the term "Metabolic Syndrome" (MS) which finally prevailed in the literature and in clinical practice [8].

DEFINITION AND PATHOPHYSIOLOGY OF THE METABOLIC SYNDROME

Metabolic Syndrome is a combination of interrelated metabolic abnormalities (metabolic risk factors) that increase the risk of atherosclerotic cardiovascular disease. Patients with MS are prone to the development of diabetes mellitus type 2, coronary artery disease and cerebrovascular disease. Another cluster of pathophysiologic conditions (underlying risk factors) are thought to be the cause of the metabolic risk factors. Dyslipidemia, high blood pressure and high blood glucose are the principal metabolic risk factors. Patients with these abnormalities are also frequently in a pro-thrombotic and pro-inflammatory state [9-11]

The most important underlying risk factors are central obesity and insulin resistance, whereas associated conditions are sedentary life, age and hormonal abnormalities leading to increased androgen production (e.g. polycystic ovary syndrome) (Figure 1) [12-14]. Although the cause of MS has not been clearly defined, most experts agree that insulin resistance is the primary underlying abnormality [15]. Insulin resistance is responsible for the hyperglycemia observed in diabetes mellitus. Multiple metabolic pathways have been proposed as the link between insulin resistance, compensatory hyperinsulinemia and the other metabolic risk factors [16]. On the other hand, insulin resistance is closely related to the development of abdominal or central obesity which is thought to be responsible for the increased prevalence of the MS noted during the last few years. Individuals with insulin resistance are not necessarily overweight. They exhibit however an abnormal distribution of adipose tissue mainly in the upper part of their body (central obesity) [17]. This type of obesity highly correlates with insulin resistance [18]. Interestingly, upper body fat distribution leads to an increased release of non-esterified fatty acids from the adipose tissue in the circulation which subsequently accumulate in other tissues [19,20]. This ectopic fat accumulation into the muscles [21] and the liver [22] –the two main target organs of insulin- predispose to insulin resistance. Moreover, the abnormal production of fatty tissue hormones (adipokines) also affect insulin sensitivity and modifies atherosclerosis risk factors like inflammatory cytokines and tissue plasminogen activator inhibitor [23,24]. Based on these findings some investigators believe that a low-grade inflammation may be either the underlying cause or simply the aggravating factor of the MS [25,26]. Finally some genetic predisposition to the development of the MS is also thought to exist. This genetic background seems to influence the phenotypic expression of the syndrome after exposure in different environments. This seems to explain the ethnic variations in the clinical expression of metabolic risk factors in obese individuals with insulin resistance [27].

Several terms, other than MS, have been proposed in the literature, such as Dysmetabolic or Polymetabolic Syndrome, Insulin Resistance Syndrome, or Syndrome X. Three definitions of the MS are currently in common use. According to the World Health Organization's (WHO) [28] diagnostic criteria, dysglycemia (diabetes, glucose intolerance) along with two of the following, increased body mass index (BMI), dyslipidemia, high blood pressure and microalbuminuria, are required to define the MS (Figure 2). The National Cholesterol Education Program Adult Treatment Program III (NCEP ATP III) [29] criteria are more suitable for clinical use although based upon the same principle (Figure 3). At least three of the following criteria have to be present: central obesity, dyslipidemia, hypertension, and fasting glucose ≥110 mg/dl. In the most recent definition of MS published by the International Diabetes Federation (IDF) [30] (Figure 4), fasting glucose cut-off point have been lowered to 100 mg/dl. Central obesity

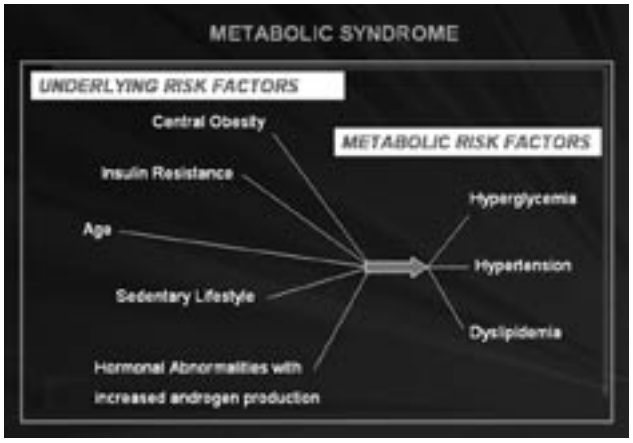

FIGURE 1. Metabolic risk factors and their underlying abnormalities in the metabolic syndrome.

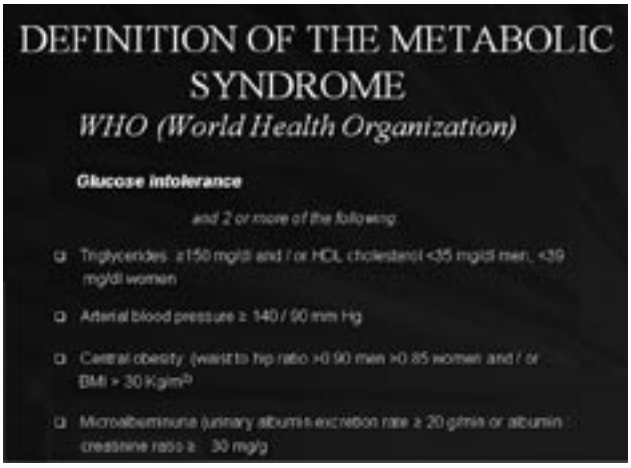

FIGURE 2. Definition of the metabolic syndrome (MS) according to the World Health Organization (WHO) criteria.

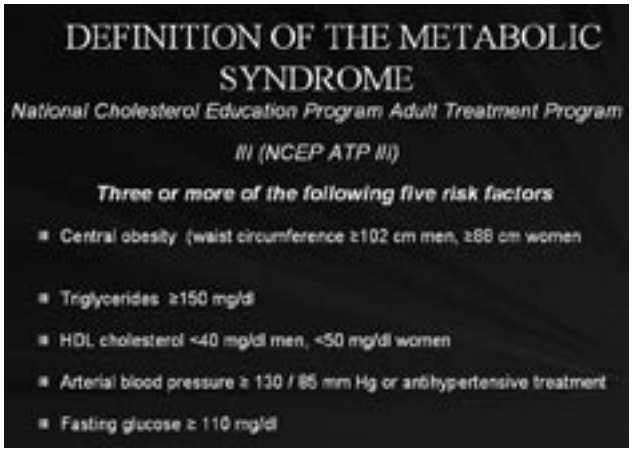

FIGURE 3. Definition of the metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Program III (NCEP ATP III) criteria.

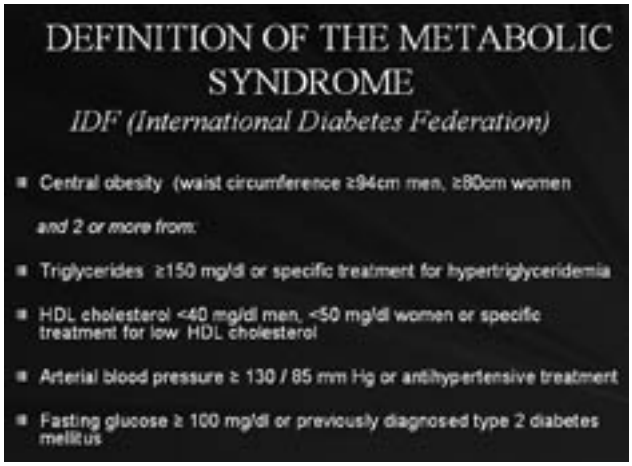

FIGURE 4. Definition of the metabolic syndrome according to the International Diabetes Federation (IDF) criteria.

in addition to two of the other classic criteria is required for the diagnosis.

METABOLIC SYNDROME AND CARDIOVASCULAR RISK – PREVALENCE OF THE METABOLIC SYNDROME

Every single component of the MS increases cardiovascular risk [31-33], while their combination has been associated with an exponential increase of cardiovascular morbidity and mortality [34-36]. Many studies have shown that patients with MS have an increased incidence of cardiovascular disease. In these studies, the risk excess varies from 30-400%. This high variability could be attributed to differences in the populations studied, in the definition criteria used and in the follow-up time. From a pathophysiologic point of view, insulin resistance has been related to endothelial dysfunction [37] and to a delayed clearance of atherogenic lipoproteins in the postprandial state [38] promoting this way the development of the atherosclerotic plaque. Obesity, on the other hand, has been associated with increased production of inflammatory cytokines and pro-thrombotic factors [9] which promote atherosclerotic plaque rupture. Finally, MS has been associated with an increased concentration of the highly atherogenic small dense LDL cholesterol particles.

The metabolic syndrome is extremely common. According to the WHO definition, 25% of the USA adult population has the syndrome while 23,9% fit the NCEP ATP III criteria [40]. The results of the INTERHEART study, a large trial conducted in 52 countries, 26% of the control group had the MS [41]. Men and black individuals are at higher risk to develop the syndrome, the prevalence of which increases also with age [40]. Based on data form the National Health and Nutrition Examination Survey (NHANES) the prevalence of the MS is 6.7% in persons less than 30 years old but goes up to 40% in those older than 60 years [40].

DIAGNOSIS-PREVENTION-TREATMENT OF THE METABOLIC SYNDROME: THE NURSE'S ROLE

Given the high prevalence of the MS (approximately 47 million in the USA) and its well established relationship with the increasing incidence of diabetes mellitus, coronary artery disease and stroke, prevention, diagnosis and treatment of this poly-metabolic abnormality should become a high priority goal. The coordinated work of various health care professionals is essential to achieve high success rates in diagnosis and treatment. Among these health providers, the nurse has a very important role given her or his close relationship with the patient and her or his holistic approach to health problems. This latter approach facilitates the implementation of the integrated type of intervention required for "reversing the tide" of this major health crisis.

NURSE'S ROLE IN THE DIAGNOSIS OF THE MS

To establish the diagnosis of MS is mandatory to recognize its individual components through their clinical characteristics. Obesity is the most important and also the most clinically obvious abnormality of the MS. Generalized obesity refers to increased weight in relation to an individual's height and can be determined by calculating the body mass index (BMI) defined as weight in kilograms divided by height in meters square (Kg/m^2). This parameter is one of the defining criteria

according to the WHO's definition of the MS. It is the nurse's responsibility to accurately measure BMI. However, central obesity defined as the excess adipose tissue residing mainly in the upper body within the abdominal region, is thought to be a better diagnostic indicator of the MS. This index can be calculated either as waist to hip circumference ratio or simply as waist circumference in centimeters. Individuals with this type of obesity even if they do not fulfill any other criteria of the MS, have a high risk to develop it in the future. Obtaining of a waist circumference measurement with use of a measuring tape, no matter what the patient's overall body habitus is, should be part of the nurse's clinical routine. These measurements must be based on standard guidelines (Table 1) [42].

Insulin resistance along with its accompanying hyperinsulinemia is the second major pathophysiologic component of the MS. Although fasting blood glucose levels may reflect the degree of hyperinsulinemia, it should be remembered that normal blood glucose levels (<100 mg/dl) do not exclude the existence of an insulin resistance state. Thus, even though fasting blood glucose should be measured in every patient with the clinical suspicion of MS and a history of anti-diabetic medication use should always be taken, the nurse must be aware that this information is usually not enough. Two other clinical signs suggesting hyperinsulinemia must be sought and identified. These signs are: acanthosis nigrans and hirsutism [43] Acanthosis nigrans is characterized by hyperpigmentation, or velvety plaques of body folds (back of the neck, axillae, elbows, knee etc). The exact etiology of this cutaneous abnormality is unknown but is thought to be caused by hyperinsulinemia.

Hirsutism, an excessive growth of hair in locations where hair growth is atypical for women and more common for men, could be caused by insulin-mediated overstimulation of the ovaries to produce androgens. In that case, hirsutism may be part of the polycystic ovary syndrome, which is a common cause of hyperinsulinemia and is characterized also by menstrual irregularities, glucose intolerance and alopecia.

Regarding hyperlipidemia, the nurse must be aware of the lipid values considered abnormal and used as criteria for the diagnosis of the MS (triglycerides ≥150 mg/dl, HDL-cholesterol ≤40 mg/dl in men and ≤50 mg/dl in women).

Finally, regarding hypertension, although it is unclear how it is caused within the MS, we are certain that its simultaneous presence even with only one other component of the MS significantly increases cardiovascular risk. Blood pressure measurements should be part of the initial assessment of every patient with the clinical suspicion of the MS. Accurate and reproducible measurements of blood pressure are not only a medical but a nursing duty as well, and to achieve these measurements the use of standard practicing guidelines is necessary [44] (Table 2). On the other hand, the use of anti-hypertensive medications confirms the diagnosis of hypertension without any further assessment and such a history must always be obtained.

TABLE 1. Guidelines for accurate patient's waist measurement

NURSING GUIDELINES FOR WAIST MEASUREMENT
• First have the patient face away from you and put his hands at the top of his hip bones or iliac crests. Mark this spot on each of his hip with a felt-tip pen
• Put the measuring tape around your patient at the level of the iliac crest
• Make sure that the measuring tape is parallel to the floor and that it is snug but not so tight that dents the skin
• Wait until the patient exhales normally, then take the measurement and record it

NURSE'S ROLE IN THE PREVENTION AND TREATMENT OF THE METABOLIC SYNDROME

The final step after identifying somebody being at risk for the development of MS, is to implement measures for preventing its full clinical expression while at a later stage in a patient who has the MS, health care providers should treat all its metabolic abnormalities. The final goal is common in both situations: cardiovascular risk reduction. At any stage, patient management requires an integrated approach with the involvement of various health care provides, i.e. physicians, nurses, dietitians, pharmacists and social workers. Among them the nurse plays a pivotal role in implementing a patient-oriented therapeutic strategy with realistic goals and expectations. Cornerstones of therapy include 1) lifestyle modifications, 2) judicious pharmacologic management, and 3) collaborative provider/patient partnership aiming at patient's active par-

TABLE 2. Guidelines for accurate patient's blood pressure measurement

NURSING GUIDELINES FOR BLOOD PRESSURE MEASUREMENT
• Make sure that the patient hasn't had any caffeine or tobacco in the past 30 minutes
• Place the patient in a comfortable sitting or lying position for at least 5 minutes prior to blood pressure measurement
• Choose an appropriate size cuff (it should cover two-thirds of the area between his axilla and elbow, and 80% of the bladder should encircle his arm
• Take one reading, then another 2 minutes later. If the pressure differ by 5 mmHg or more, take additional readings at least 2 minutes apart and record the average

ticipation in the achievement of the final goal [45].

Lifestyle modification is the most important but also the most difficult to achieve and sustain. It has two basic components: dietary changes [46] and regular exersise [47]. Both diet and exercise have a beneficial effect on all the abnormalities of the MS and especially on obesity. Obese patients should be encouraged to lose weight to achieve and sustain a BMI <25 kg/m2. This can be done by restricting daily calorie intake (to 1200 calories for women and 1600 calories for men), reducing saturated fat in the meals and by engaging in a regular aerobic exercise program for 30 minutes daily, 5 days a week. Beyond obesity treatment, lifestyle modifications have been proven to prevent the development of diabetes and cardiovascular disease. Moreover, its contribution to the prevention of MS in adult life by reducing the childhood obesity rates seems to be of critical importance [48]. Lifestyle modifications contribute also to the dyslipidemia and hypertension treatment. Dietary guidelines suggest: total cholesterol intake less than 200 mg/day; fat intake 25% to 35% of total calories per day; saturated fats less than 7% of total fat intake; and soluble fiber 20 to 30 grams/day. Restricting carbohydrate intake to 45% to 50% of total daily caloric requirements can also help patients achieve the goal of lowering triglyceride levels. Trans-fatty acids should be less than 2% of total calories since a higher intake has been associated with increased LDL cholesterol levels. Finally, salt intake should be restricted to 2-4 gr/day [49] (Table 3). Finally, enrollment in a smoking-cessation program is essential. Nicotine is a potent vasoconstrictor and has been identified as the primary cause of heart disease.

Pharmacological therapy is required for patients who are unable to achieve target levels of metabolic and blood pressure parameters with lifestyle changes alone. For dyslipidemia treatment statins are the drugs of choice [50]. Even though they do have a major impact upon triglyceride and HDL cholesterol levels they have been shown to decrease LDL cholesterol levels substantially. Of note, high LDL cholesterol significantly increases cardiovascular risk in patients with MS and reduction to <70 mg/dl has been proposed for these patients. Statins can be administered concomitantly with fibric acid derivatives, nicotinic acid, bile acid sequestrants or ezetimibe to effectively reduce all lipid parameters. The statin dosage should be reduced, however, when combined with fibric acid derivatives, to avoid the potential complication of rabdomyolysis.

Treatment of hypertension is also a very important component of the treatment strategy. All classes of antihypertensive medications can be used. However, some of those seem more appropriate for the patients with MS. For example, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers are effective in blood pressure management without affecting carbohydrate metabolism or aggravating lipid levels. They have been found to maintain renal function and are renal protective. Moreover, studies have shown that they prevent diabetes development in 23% of the patients [51].

TABLE 3. Lifestyle modification guidelines for the patients with Metabolic Syndrome

NUTRIENT	RECOMMENDED INTAKE
Saturated fat	<7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Trans-polyunsaturated fat	<2% of total calories
Total fat	25-35% of total calories
Carbohydrate	50-60% of total calories
Proteins	~15% of total calories
Fiber	20-30 gm/day
Cholesterol	< 200 mg/day
Total calories	Balance energy intake and expenditure to maintain desirable body weight/prevent weight gain
Salt	2-4 gm/day
WEIGHT LOSS TO THE DESIRABLE LEVEL	
EXERCISE	

Regarding hyperglycemia treatment, it has been shown that its aggressive management reduces cardiovascular risk by approximately 20% [52]. Patients with MS are by definition insulin-resistant and may benefit from the administration of a new category of hypoglycemic agents, thiazolidinediones. These drugs, rosiglitazone and pioglitazone, are essentialy insulin sensitizers since they work at the cellular level to increase insulin recognition by the receptors. Thiazolidinediones along with some older antidiabetic medications, acarboze and metformin, may also prevent the development of diabetes in patients with MS [53].

Complementary pharmacological and non-pharmacological measures include the administration of low-dose aspirin (81-325 mg/day) in men >45 years old and in postmenopausal women. Folic acid and vitamin B6 decrease homocysteine levels and are also beneficial to cardiovascular health of these patients. Garlic may reduce total cholesterol by 5% to 10% in patients with moderately elevated cholesterol (around 220 mg/dl). The recommendation is to eat 7 grams of garlic (a few cloves) per day. Large doses of omega-3 fatty acids (6 grams/day) may lower total cholesterol and triglyceride levels. Fish oil supplements are acceptable, but eating fish, such as cold water salmon, daily is preferred [54].

For all the above lifestyle modifications and pharmacological interventions to have a high success rate, the patient

himself has to become an active participant of his treatment plan. Several studies have clearly shown that a very low percentage of patients with MS achieve their treatment goals. In the United Kingdom Prospective Diabetes Study (UKPDS), the proportion of patients achieving the target of glycocylated hemoglobin HbA1c <7% after 9 years of follow –up was low (ranging from 9 to 18% depending upon treatment group) [55]. The situation is similar in the USA. The third National Health and Nutrition Examination Survey (NHANES III) showed that only half of the hypertensive and another half of the hyperlipidemic patients were well controlled. Of great concern, fewer than 3.6% of the patients with both hypertension and dyslipidemia were at both therapeutic goals [56].

This huge gap between "what we know and what we have to do" for the MS can be attributed at least partially to the following patient barriers:

- Lack of awareness and understanding of the problem.
- Low level of compliance due to medication adverse effects or due to reluctance to take life-long treatment.
- Lack of adherence to lifestyle modifications.

Dealing with this major limitation, nursing intervention can be of great importance. Basic aspects of this type of intervention are:

- Patient education in understanding the increased cardiovascular risk assoc iated with the MS and the contribution of the various treatment modalities in risk reduction.
- Psychosocial support of the patient encouraging compliance with diet changes, with increased physical activity and with any other risk factor modifications.
- Support of the patient's family, encouraging their active involvement in the implementation of a successful treatment strategy.
- Involvement of the patient in his care (self-monitoring, tailoring doses based on a treatment schedule).
- Participation along with the medical personnel in the long-term follow-up of the patient, recording his compliance and assessing treatment efficacy [57].

CONCLUSIONS

Metabolic Syndrome is a particularly common clinical entity characterized by a constellation of various risk factors associated with the development of type 2 diabetes mellitus and cardiovascular disease. Its hallmarks are dysglycemia, hypertension, atherogenic dyslipidemia and central obesity. Because MS is a constellation of disease processes, treating it requires an integrated approach with the involvement of various health care providers. Among them, the nurse can play a role of vital significance by actively participating a) in the identification of patients with MS and of individuals who are at risk to develop it and b) preventing the development of the syndrome and its cardiovascular sequelae through the implementation of a treatment plan featuring an integrated problem management approach. This plan should be developed along with the patient and has to be based upon patient's education, psychosocial support and close follow-up. The final goal is to assure the long-term compliance of the patients with both the proposed lifestyle changes and the medical treatment in order to achieve a significant reduction in their cardiovascular morbidity and mortality.

REFERENCES

1. Avogaro P, Crepaldi G, Enzi G, Tiengo A. Associazione di iperlidemia, diabete mellito e obesita di medio grado. *Acto Diabetol Lat* 1967; 4:36–41.
2. Haller H. Epidemiology and associated risk factors of hyperlipoproteinemia. *Z Gesamte Inn Med* 1977; 32:124–128.
3. Himsworth H: Diabetes mellitus: a differentiation into insulin-sensitive and insulin-insensitive types. *Lancet* 1936; 1:127-130.
4. Wingard DL, Barrett-Connor E, Criqui MH, Suarez L. Clustering of heart disease risk factors in diabetic compared to non-diabetic adults. *Am J Epidemiol* 1983; 117:19–26.
5. Singer P: Diagnosis of primary hyperlipoproteinemias. *Z Gesamte Inn Med* 1977; 32: 129–133.
6. Stern MP, Haffner SM. Body fat distribution and hyperinsulinemia as risk factors for diabetes and cardiovascular disease. *Arteriosclerosis* 1986; 6:123–130.
7. Reaven GM. Banting lecture 1988: Role of insulin resistance in human disease. *Diabetes* 1988; 37:1595-1607.
8. Alberti G. Introduction to the metabolic syndrome. *Eur Heart J* 2005; 7(Suppl D):D3-D5.
9. Grundy SM. Obesity, metabolic syndrome, and coronary atherosclerosis. *Circulation* 2002; 105:2696-2698.
10. Isomaa B. A major health hazard: The metabolic syndrome. *Life Sci* 2003; 3:2395-2411.
11. Scott M, Grundy MS, Cleeman JI, Daniels SR et al. Diagnosis and Management of the Metabolic Syndrome. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005; 112:2735-52.
12. Lemieux I, Pascot A, Couillard C, Lamarche B, et al. Hypertriglyceridemic waist: a marker of the atherogenic metabolic triad (hyperinsulinemia; hyperlipolipoprotein B; small, dense LDL) in men? *Circulation* 2000; 102:179–184.
13. Ferrannini E, Haffner SM, Mitchell BD, Stern MP. Hyperinsulinemia: the key feature of a cardiovascular and metabolic syndrome. *Diabetologia* 1991; 34:416–422.
14. Apridonidze T, Essah PA, Iuorno MJ, Nestler JE. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2004; 90: 1929–1935.
15. Reaven G. The metabolic syndrome or the insulin resistance syndrome? Different names, different concepts, and different goals. *Endocrinol Metab Clin North Am* 2004; 33:283–303.
16. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005; 365:1415–1428.
17. Brunzell JD, Shofer JB, Fish BE, Knopp RH, et al. Intra-ab-

dominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. *Diabetes* 2004; 53:2087–2094.
18. Hayashi T, Boyko EJ, Leonetti DL, McNeely MJ, et al. Visceral adiposity and the risk of impaired glucose tolerance: a prospective study among Japanese Americans. *Diabetes Care* 2003; 26:650–655.
19. Goodpaster BH, Thaete FL, Simoneau JA, Kelley DE. Subcutaneous abdominal fat and thigh muscle composition predict insulin sensitivity independently of visceral fat. *Diabetes* 1997; 46:1579 –1585.
20. Jensen MD, Haymond MW, Rizza RA, Cryer PE, et al. Influence of body fat distribution on free fatty acid metabolism in obesity. *J Clin Invest* 1989; 83:1168 –1173.
21. Petersen KF, Shulman GI. Pathogenesis of skeletal muscle insulin resistance type 2 diabetes mellitus. *Am J Cardiol* 2002; 90:11G–18G.
22. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology* 2004; 40: 1387–1395.
23. Trayhurn P, Wood IS. Adipokines: inflammation and the pleiotropic role of white adipose tissue. *Br J Nutr* 2004; 92:347–355.
24. Juhan-Vague I, Alessi MC, Mavri A, Morange PE. Plasminogen activator inhibitor-1, inflammation, obesity, insulin resistance and vascular risk. *J Thromb Haemost* 2003; 1:1575–1579.
25. Hanley AJ, Festa A, D'Agostino RB Jr, Wagenknecht LE, et al. Metabolic and inflammation variable clusters and prediction of type 2 diabetes: factor analysis using directly measured insulin sensitivity. *Diabetes* 2004; 53:1773–1781.
26. Chandalia M, Cabo-Chan AV Jr, Devaraj S, Jialal I, et al. Elevated plasma high-sensitivity C-reactive protein concentrations in Asian Indians living in the United States. *J Clin Endocrinol Metab* 2003; 88:3773–3776.
27. Martin LJ, North KE, Dyer T, Blangero J, et al. Phenotypic, genetic, and genome-wide structure in the metabolic syndrome. *BMC Genet* 2003; 4(suppl):S95.
28. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. *Diab Med* 1999; 16:442-443.
29. NCEP. Expert panel on detection, evaluation and treatment of high blood pressure in adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection and evaluation and treatment of high blood cholesterol in adults. (Adult Treatment Panel III). *JAMA* 2001; 285:2486-2497.
30. Zimmet P, Alberti G, Shaw J. A new IDF worldwide definition of the metabolic syndrome: the rationale and the results. *Diabetes Voice* 2005; 50:31-33.
31. McGill HC, McMahan A, Herderick EE, Zieske AW, et al. Obesity accelerates the progression of coronary atherosclerosis in young men. *Circulation* 2002; 105:2712–2718.
32. The DECODE Study Group Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular diseases? *Diabetes Care* 2003; 26: 688–696.
33. Eberly LE, Stamler J, Neaton JD, Multiple Risk Factor Intervention Trial Research Group. Relation of triglyceride levels, fasting and nonfasting, to fatal and nonfatal coronary heart disease. *Arch Intern Med* 2003; 163:1077–1083.
34. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002; 288:2709–2716.
35. Isomaa B, Almgren P, Tuomi T, Forsen B, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001; 24:683–689.
36. Trevisan M, Liu J, Bahsas FB, Mentotti A. Syndrome X and mortality: a population-based study. Risk factor and life expectancy research group. *Am J Epidemiol* 1998; 148:958–966.
37. Deedwania PC. Clinical significance of cardiovascular dysmetabolic syndrome. *Curr Control Trials Cardiovasc Med* 2002; 3:1-5.
38. Reaven GM. Diet and Syndrome X. *Curr Atheroscler Rep* 2000; 2:403-507.
39. Lamarche B, Tchernhof A, Moorjani S, Cantin B, et al. Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men: Prospective results from the Quebec Cardiovascular Study. *Circulation* 1997; 95:69-75.
40. Ford ES, Giles WH, Dietz WH. Prevalence of metabolic syndrome among US adults. Findings from the third National Health and Nutrition Examination Survey. *JAMA* 2002; 87: 356-359.
41. Rosengren A, Hawken S, Ounpuu S, Sliwa K, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet* 2004; 364:953–962.
42. Appel SJ. Sizing up patients for metabolic syndrome. *Nursing* 2005; 35:20-21.
43. Appel SJ, Jones ED, Kennedy-Malone L. Central obesity and the metabolic syndrome: Implications for primary care providers. *J Am Acad Nurse Pract* 2004; 16:335-342.
44. Woods AD. Improving the odds against hypertension. *Nurs Manage* 2002; 33:28-33.
45. Fowler SB, Moussouttas M, Mancini B. Metabolic syndrome: contributing factors and treatment strategies. *J Neurosci Nurs* 2005; 37:220-223.
46. Franz MJ, Bantle JP, Beebe CA, Brunzell JD, et al. Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care* 2002; 25:148-198.
47. Rennie KL, McCarthy N, Yazdgerdi S, Marmot M, et al. Association of the metabolic syndrome with both vigorous and moderate leisure physical activity. *Int J Epidemiol* 2003; 32: 600-606.
48. Mooney B. Syndrome X. Advance for Nurses 2004; 6:36-37.
49. Bray GA, Champagne CM. Obesity and the metabolic syndrome: Implications for dietetics practitioners. *J Am Diet Assoc* 2004; 104:86-89.
50. Tuomilehto J, Lindstrom J, Quiao Q. Strategies for the prevention of type 2 diabetes and cardiovascular disease. *Eur Heart J*

2005; 7 (Suppl D):D18-D22.
51. Julius S, Kjeldsen SE, Weber M, Brunner HR, et al. for the VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomized trial. *Lancet* 2004; 363: 2222-2231.
52. Gaede P, Vedel P, Larsen N, Jensen JV, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *New Engl J Med* 2003; 348:383-393.
53. Buchanan TA, Xiang AH, Peters RK, Kjos SL, et al. Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk hipanic women. *Diabetes* 2002; 51:2796-2803.
54. Ginsberg HN. Treatment for patients with metabolic syndrome. *Am J Cardiol* 2003; 91: 29E-39E.
55. Turner RC, Cull CA, Frighi V, Holman RR. UKPDS 49 Glycemic control with diet, sulphonylurea, metformin and insulin therapy in patients with type 2 diabetes: progressive requirement for multiple therapies. *JAMA* 1999; 281:2005-2012.
56. Erhardt LR. Managing cardiovascular risk:reality vs. perception. *Eur Heart J* 2005; 7(suppl L):L11-L15.
57. Fletcher B, Lamendola C. Insulin resistance syndrome. *J Cardiovasc Nurs* 2004; 19:339-345.