Metabolic syndrome and ethnic groups

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Abstract

Metabolic syndrome is defined as the co-occurrence of metabolic risk factors for both type 2 diabetes and cardiovascular disease (i.e. abdominal obesity, hyperglycemia, dyslipidemia, and hypertension). Indeed, metabolic syndrome is an important risk factor for subsequent development of type 2 diabetes and/or CVD. Thus, the key clinical implication of a diagnosis of metabolic syndrome is the identification of a patient who needs aggressive lifestyle modification focused on weight reduction and increased physical activity. Multiple different phenotypes and ethnic-specific values for waist circumference are included within metabolic syndrome, with indications for differing treatment strategies. This book covers several aspects of metabolic syndrome, including its definition, diagnostic criteria, preventive measures, and treatment, as well as the possible association between ethnicity and the occurrence of metabolic syndrome.

1. Introduction

Obesity, particularly abdominal obesity, is associated with resistance to the effects of insulin on peripheral glucose and fatty acid utilization, often leading to type 2 diabetes mellitus. Insulin resistance, the associated hyperinsulinemia and hyperglycemia, and adipocyte cytokines (adipokines) may also lead to vascular endothelial dysfunction, an abnormal lipid profile, hypertension, and vascular inflammation, all of which promote the development of atherosclerotic cardiovascular disease (CVD) (1-4). A similar profile can be seen in individuals who have abdominal obesity but are not overweight (5-8). The co-occurrence of metabolic risk factors for both type 2 diabetes and CVD, i.e., abdominal obesity, hyperglycemia, dyslipidemia, and hypertension, suggests the existence of a "metabolic syndrome" (1, 9-11). Other names applied to this constellation of findings have included syndrome X, the insulin resistance syndrome, the deadly quartet, or the obesity dyslipidemia syndrome (12). Genetic predisposition, lack of exercise, and body fat distribution affect the likelihood that a given obese subject will become overtly diabetic or develop

CVD. It should be noted that questions have been raised as to whether the metabolic syndrome, as currently defined, captures any unique pathophysiology implied by calling it a "syndrome" and whether metabolic syndrome confers risk beyond its individual components. These questions raise uncertainty about the value of diagnosing metabolic syndrome in individual patients (13, 14). Regardless of whether the metabolic syndrome is considered a unique entity, there is no question about the need to identify and manage its individual components to decrease morbidity and mortality associated with diabetes and cardiovascular disease (15, 16).

2. Definition and diagnostic criteria

A complex accumulation of metabolic abnormalities, including hyperinsulinism, impaired glucose tolerance, hypertension, low HDL cholesterol, and hypertriglyceridemia, were given the name 'syndrome X' by Raven two decades ago (1). These non-communicable risk factors, which were later termed "metabolic syndrome," have an obscure etiology and a variety of clinical presentations. Therefore, metabolic syndrome has not been defined on the basis of etiology and pathology, but it has been defined with respect to phenotype. Various definitions of metabolic syndrome have been provided by the World Health Organization (WHO) (17), the Adult Treatment Panel (ATP) III, (18), the International Diabetes Federation (IDF) (19), the American Heart Association

(AHA), and the National Heart, Lung, and Blood Institute (NHLBI) (20). Because the traits of metabolic syndrome usually occur simultaneously, patients identified with one or just a few traits are likely to have other traits, as well as insulin resistance (21). It is uncertain whether it is valuable to assess insulin resistance in addition to more readily-measured traits of the syndrome. There are several definitions for the metabolic syndrome, leading to some difficulty in comparing data from studies using different criteria, as described below:

2.1. 2001 National Cholesterol Education Program / ATPIII

Guidelines developed by the 2001 National Cholesterol Education Program focused explicitly on the risk of cardiovascular disease and did not require evidence of insulin or glucose abnormalities even though abnormal glycemia is one of the criteria (18). The criteria for ATPIII metabolic syndrome were updated in 2005 in a statement from the American Heart Association /National Heart, Lung, and Blood Institute (AHA/NHLBI) (20). The updates included the following:

- Lowering the threshold for abnormal fasting glucose to 100 mg/dL, corresponding to the ADA criterion for impaired fasting glucose
- Explicitly including diabetes in the trait definition of hyperglycemia

- Explicitly including use of drugs for lipid control or blood pressure control in the definitions of the traits of dyslipidemia and hypertension, respectively

Current ATPIII criteria define metabolic syndrome as the presence of any three of the following five traits:

- Abdominal obesity, defined as a waist circumference in men ≥ 102 cm (40 in) and in women ≥ 88 cm (35 in)
- Serum triglycerides ≥ 150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides
- Serum HDL cholesterol < 40 mg/dL (1 mmol/L) in men and < 50 mg/dL (1.3 mmol/L) in women or drug treatment for low HDL-C
- Blood pressure $\geq 130/85$ mmHg or drug treatment for elevated blood pressure
- Fasting plasma glucose (FPG) ≥ 100 mg/dL (5.6 mmol/L) or drug treatment for elevated blood glucose

2.2. International Diabetes Federation

The International Diabetes Federation (IDF) updated its metabolic syndrome criteria in 2006 (19). Central obesity is an essential element in this definition, and different waist circumference thresholds were set for different race/ethnicity groups:

Increased waist circumference, with ethnic-specific waist circumference cut-points PLUS any two of the following:

- Triglycerides >150 mg/dL (1.7 mmol/L) or treatment for elevated triglycerides
- HDL cholesterol <40 mg/dL (1.03 mmol/L) in men or <50 mg/dL (1.29 mmol/L) in women, or treatment for low HDL
- Systolic blood pressure >130, diastolic blood pressure >85, or treatment for hypertension
- Fasting plasma glucose >100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes; an oral glucose tolerance test is recommended for patients with an elevated fasting plasma glucose, but not required

3. Comparing criteria in defining populations

Using data from the National Health and Nutrition Examination Survey's 1999 to 2002 database, 39% of adult participants in the U.S. met IDF criteria for the metabolic syndrome, whereas 34.5% met the ATPIII criteria (22). The two definitions overlapped for 93% of subjects in determining the presence or absence of the metabolic syndrome. When applied to an urban population in the U.S., the IDF criteria categorized 15 to 20% more adults with the metabolic syndrome than did the ATPIII criteria (23).

The relative value of the different definitions of metabolic syndrome appears to be similar in terms of prognosis and management (24-26), as indicated by the following examples:

- In a prospective cohort study of a random sample of British women (n = 3589) aged 60 to 79 years who were free of coronary heart disease (CHD) at baseline, all three definitions of metabolic syndrome were modestly and similarly associated with CHD risk (24). The age-adjusted hazard ratios for IDF, WHO, and NCEP syndromes were 1.32 (95% CI [confidence interval] 1.03-1.70), 1.45 (1.00-2.10), and 1.38 (1.00-1.93), respectively.
- Similarly, when data from the Framingham population were examined using ATPIII's, IDF's, and EGIR's definitions of metabolic syndrome, roughly equivalent associations were observed for the incidence of type 2 diabetes and for CVD (25). Thus, risk factor clustering defines increased risk for type 2 diabetes and CVD.

The WHO, ATPIII, and IDF definitions include type 2 diabetes as syndrome trait. All experts do not agree that type 2 diabetes should be part of the definition, since the importance of the syndrome is that it identifies patients at increased risk for the development of diabetes. Most patients with type 2 diabetes have features of the metabolic syndrome in that it identifies those at greater risk

of macrovascular complications but not those with microvascular complications (27).

Management of patients with type 2 diabetes should follow clinical guidelines, whether or not they also meet the criteria for metabolic syndrome. The AHA-NHLBI proposal was a revised definition of ATPIII with a reduction in fasting serum glucose from 110 to 100 mg/dL. Ethnic-specific values for waist circumference have been proposed for some populations, e.g., Europids and South Americans (4). The IDF definition stated that the ethnic-specific waist cut-off values should be considered rather than using a universal definition for central obesity when defining metabolic syndrome. It has been reported that the prevalence of metabolic syndrome in the Islamic Republic of Iran is one of the highest worldwide. In the adult population of the Tehran Lipid and Glucose Study (TLGS), metabolic syndrome was found in 42% of women and 24% of men with a total age-standardized prevalence of 33.7% (28). The prevalence increased by age, from 10% in individuals between 20 and 29 to 60% for those between 60 and 69. Moreover, the age-adjusted incidence of metabolic syndrome (defined by the ATPIII definition) was found to be 20.4% (95% CI, 19.6 – 21.2) in the TLGS adults (18.4% male vs. 23.1% female) after three years of follow-up (29).

The prevalence of metabolic syndrome has been reported to be 23% in Zanjan Province (30). A 2007 national survey of metabolic syndrome showed age

standardized prevalences of 34.7%, 37.4%, and 41.6% based on the ATPIII, IDF, and ATPIII/AHA/NHLBI definitions, respectively. The prevalence of metabolic syndrome was greater in women than in men, and it was greater in urban residents than in the rural population (31). Also, in the TLGS population, the prevalence of metabolic syndrome was 32.1% (95%CI, 31.2 – 33.0) by the IDF definition and 18.4% (17.6 –19.2) according to the WHO definition; it would be of note that the IDF definition has shown good agreement with the ATPIII definition and poor agreement with the WHO definition in this study (32). In September 2009, the Iranian Ministry of Health and Medical Education, in collaboration with the Research Institute of Endocrine Sciences, established the National Iranian Committee of Obesity, which included endocrinologists, biostatisticians, cardiologists, pediatricians, epidemiologists, nutritionists, and officials from the Iranian Center for Non-communicable Disease Control. The committee reviewed evidence-based studies on the indices of central obesity in Iran.

The cross-sectional studies reported waist circumference cut-off values with which to diagnose at least two other components of the cardiovascular disease (CVD) risk factors of IDF metabolic syndrome. The waist circumference cut-off values were 84 – 95 cm in women and 86 – 92 cm in men within various age groups (33); they were 89 cm for men and 91 cm for women of all ages (31). The third national survey found a cut-off of 90 cm for

waist circumference as the basis for diagnosing metabolic syndrome in both genders (34). The only prospective outcome-based cohort study in Iran found an identical waist circumference cut-off value of 94.5 cm for both men and women that could predict the incidence of CVD (35). Based on the above-mentioned evidence, the Iranian National Committee of Obesity announced a cut-off waist circumference of 90 cm for both genders at risk for CVD risk factors. The Committee also set a cut-off for waist circumference of 95 cm in both genders to be at high risk of CVD events requiring immediate preventive measures (36). A recent joint scientific statement of IDF, NHLBI, AHA, the World Heart Federation, the International Atherosclerosis Society, and the International Association for the Study of Obesity harmonized the definition of metabolic syndrome.

It suggested that none of the components is obligatory for metabolic syndrome; however three out of five components would indicate that a person has metabolic syndrome. It confirmed that waist circumference would continue to be a useful preliminary screening tool and that there should be national or regional cut-off points. For the remaining four components, a single set of cut-off points previously defined by all associations was suggested (37). The Iranian National Committee of Obesity considered the identical cut point of waist circumference for both genders in Iran (36) as well as the above-mentioned new harmonizing definition of metabolic syndrome (37) and

proposed a unified clinical and epidemiological study of metabolic syndrome among Iranians.

4. Other potential markers

The metabolic syndrome has been recognized as a pro-inflammatory, pro-thrombotic state that is associated with elevated levels of C-reactive protein, interleukin (IL)-6, and plasminogen activator inhibitor (PAI)-1 (4, 38). Inflammatory and pro-thrombotic markers are associated with an increased risk for subsequent CVD and type 2 diabetes, although one study indicated that adipokines and inflammatory markers can explain only a small part of the association between metabolic syndrome and CHD mortality. In addition, a causal association between elevated CRP and metabolic syndrome was not demonstrated in a study of phenotype patterns associated with metabolic syndrome and CRP levels (39). The value of measurement or treatment of inflammatory or vascular function markers in the setting of metabolic syndrome is unknown. Use of these markers should be considered for clinical purposes only relative to CVD risk assessment and reduction. AHA/CDC guidelines emphasize that CRP testing still should be optional and based on clinical judgment rather than being recommended routinely because the magnitude of its independent predictive power remains uncertain (40).

5. Prevalence and risk factors

The prevalence of metabolic syndrome, as defined by the 2001 ATPIII criteria, was evaluated in 8814 adults in the United States participating in the third National Health and Nutrition Examination Survey (NHANESIII, 1988 to 1994) (41). The overall prevalence was 22%, with age-dependent increases (6.7, 43.5, and 42.0% for ages 20 to 29, 60 to 69, and >70, respectively). Mexican-Americans had the highest age-adjusted prevalence (31.9 %). Among African-Americans and Mexican-Americans, the prevalence was higher in women than in men (57 and 26% higher, respectively). Data from NHANES 1999 to 2000 demonstrated that the prevalence has continued to increase, particularly in women (42). Metabolic syndrome is becoming increasingly common.

Using data from the National Health and Nutrition Examination Survey's 1999 to 2002 database, 34.5% of participants met ATPIII criteria for metabolic syndrome compared with 22% in NHANESIII (1988 to 1994) (22, 41). In addition, metabolic syndrome, defined by the 2005 revised ATPIII criteria, was assessed in 3323 participants in the Framingham Heart Study, ages 22 to 81, who did not have diabetes or cardiovascular disease at a baseline examination in the early 1990s. At baseline, the prevalence of metabolic syndrome was 26.8% in men and 16.6% in women. After eight years of follow-up, there was an age-adjusted 56 % increase in the prevalence among men and a 47% increase among women (43).

Increased body weight is a major risk factor for metabolic syndrome. In NHANESIII, the metabolic syndrome was present in 5% of those at normal weight, 22% of those who were overweight, and 60% of those who were obese (44). In the Framingham Heart Study, an increase in weight of 2.25 kg or more over 16 years was associated with a 21 to 45% increase in the risk for developing metabolic syndrome (45). A large circumference of the waist is sufficient, in and of itself, to identify up to 46% of individuals who will develop metabolic syndrome within five years (46). The rapidly increasing prevalence of obesity among adults in the United States is likely to lead to even higher rates of metabolic syndrome in the near future, highlighting the importance of preventing obesity and increasing the levels of physical activity (47).

In addition to age, race, and weight, other factors associated with an increased risk of metabolic syndrome in NHANESIII included postmenopausal status, smoking, low household income, high carbohydrate diet, no alcohol consumption, and physical inactivity (44). In the Framingham Heart Study, soft drink consumption also was associated with an increased risk of developing adverse metabolic traits and metabolic syndrome. Use of atypical antipsychotic medications, especially clozapine, significantly increases the risk of acquiring metabolic syndrome. In addition, poor cardiorespiratory fitness is an independent and strong predictor of metabolic syndrome in

both men and women. A parental history of metabolic syndrome increases risk, and genetic factors may account for as much as 50% of the variation in levels of metabolic syndrome traits in the offspring (48).

1. History of Iranian ethnicity and minorities

Iran occupies a pivotal geographical position within the southwestern Asian corridor, a natural passageway that has represented tri-continental crossroads for human migrations since the first expansions of humans out of Africa (49). Several studies have indeed proposed that sea level fluctuations in the Strait of Hormuz boosted the diffusion of *Homo sapien* populations from the Arabian Peninsula to the Iranian plateau and, ultimately, to Pakistan, India, and Eastern Asia during the early colonization of the Eurasian landmass (50-52). As a matter of fact, Paleolithic sites have been discovered recently in western Iran (53) and northern Iran (Central Alborz) (54), providing some of the first field evidence of early human settlements in this central area of the Middle East. Nevertheless, the Neolithic and Metal Ages seem to be the time windows that left the deepest imprint on the Iranian genetic landscape. Triggered by an abrupt shift towards warmer climate conditions following the Younger Dryas cold interval (55), new agricultural techniques appear to have been developed for the first time about 8,500 YBP in

the mid-level and lower valleys of the Zagros Mountains, especially in Elam (currently southwestern Iran).

Here, several local cultures speaking the Proto-Elamo-Dravidian language flourished in response to population increases (56), even maintaining smaller and more scattered family-scale organizations with respect to other geographical areas of agricultural development (i.e., Mesopotamia). A subsequent diffusion of these cultures eastwards occurred in parallel with the movement of farmers to the Indus Valley and the Indian subcontinent (57). Then, the Dravidian languages were almost completely replaced around 1,300 BC by the Indo-Iranian branch of the Indo-European language family at the arrival of the Aryans, nomadic tribes currently considered plausible ancestors of most of the present Iranians (58). Thus, Medes, Persians, Bactrians, and Parthians populated the Iranian plateau by the first millennium BC. One of these tribes, the Medes, succeeded in unifying territories and people to such an extent that, under Cyrus the Great and Darius the Great (559–486 BC), the Persian Empire became one of the largest empires in human history.

It has been speculated that, after the Persian apogee, other population movements that followed the invasions by the Macedonians (334 BC), the Arabs (7th century AD), the Turks (11th century AD), and the Mongols (13th – 15th centuries AD) only marginally affected the pre-existing genetic pool, even though they made

significant contributions to the ethno-linguistic heterogeneity of the region (59). According to this view, the Iranian corridor still hosts populations with very different backgrounds in terms of origins, languages, religions, and modes of subsistence, even though the genetic diversity of few Iranian ethnic groups has been investigated to date (59-64). In particular, mitochondrial diversity has been the object of either wide-ranging studies directed towards a generalized comparison between Western and Eastern Eurasian populations (59, 65) or of research for which the sampling criteria focused on the geographic origin rather than the ethnicity of the examined individuals (66-68). Therefore, an assessment of the overall Iranian mtDNA landscape has yet to be conducted.

Although Iranian people are mostly Muslims, an ethno-religious minority that follows Zoroastrianism is present in Iran, and they represent approximately 0.02-0.05% of the population. Zoroastrianism originated between the ninth and sixth centuries BC and was introduced by Sassanid as the official religion during the last pre-Islamic Persian Empire (52). In the last millennium, Zoroastrians have lived in a high level of isolation as well as endogamy, and this condition has been maintained vigorously to date. This enabled the survival of most of the indigenous Iranian ancestors' mtDNAs without foreign contributions to their gene pool in the recent past (53), thus providing an outstanding opportunity to study risk factors associated

with MS (metabolic syndrome) in a limited genetic-variability setting. Most of this population is distributed throughout the Tehran, Kerman, and Yazd Provinces.

2. Minorities and Metabolic syndrome

Observational studies around the world have identified profound disparities in cardiovascular disease (CVD) and its risk factors in ethnic minority groups. The genesis of the disparities in CVD and CVD risk factors is still not completely understood. Such disparities are undoubtedly multi-factorial, involving a complex interplay of behavioral, biological, and societal factors (69-70).

3. Metabolic syndrome within a minority ethnic group (adult Gypsy people) in Hungary

The occurrence of metabolic syndrome and glucose intolerance is high among adult Gypsy people in Hungary. Among the 77 individuals screened (35 men, 42 women, average age of 46.9 ± 10.6 years) 14 cases of diabetes mellitus were found (18.2%), and pre-diabetes (impaired fasting blood glucose (IFG) or impaired glucose tolerance (IGT) was diagnosed in an additional 14 cases (18.2%). Individual components of metabolic syndrome occurred as follows: hypertension in 47 subjects (61.0%), abnormal waist circumference in 40 individuals (51.9%), abnormal HDL-cholesterol in 39 cases (50.6%), abnormal triglycerides in 35 individuals (45.5%) and abnormal fasting blood glucose in 15 subjects (19.5%). Within the

cohort, metabolic syndrome was diagnosed in 39 individuals (50.6%) without a significant gender difference (males 20/35 = 57.1%; women: 19/42 = 45.2%, $P > 0.05$) (71).

4. Metabolic syndrome between two ethnic minority groups (Circassians and Chechens) and the original inhabitants of Jordan

The age-standardized prevalence rate of metabolic syndrome for Jordanians was 38.0%, Circassians 32.0%, and Chechens 33.7%. Compared to Jordanians, both minority groups had lower means of body mass index, total cholesterol, fasting blood glucose, and triglycerides. The means of high-density lipoprotein and low-density lipoprotein were significantly higher among Circassians than among Jordanians and Chechens. The odds of BMI being defined by overweight, obesity, and diabetes were less common among Circassians and Chechens than Jordanians. The prevalence of metabolic syndrome and the prevalence of its individual components were relatively high in the three ethnic groups compared to the rest of the world (72).

5. Metabolic Syndrome in Caribbean Hispanic Women Living in Northern Manhattan

Metabolic syndrome has the highest prevalence among Mexican-American women. Caribbean Hispanics are the largest and fastest-growing ethnic minority in the United

States. There were 204 women enrolled in a cross-sectional study, and their mean age was 58 ± 11 years. The women were Hispanic 44.1% (93% Caribbean), non-Hispanic white (NHW) 38.7%, and non-Hispanic black 9.8%. The women's educational levels were as follows: some high school (<HS) 33.7%, HS graduate 11.2%, some college 12.9%, college graduate 10.1%, and postgraduate 32%. Health insurance was Medicaid 47.8% and commercial 52.2%. Area of residence was urban 77.1% and suburban 22.9%. The frequency of metabolic syndrome was 42.4%, but it was 63.3% for the Hispanic women and 29.6% for the NHW women.

Based on educational levels, MS was present as follows: women with <HS (72.6%) and women with postgraduate education (32.1%), women with Medicaid (57.9% vs. 27.4%) and urban residence (47.5% vs. 27.2%). Education <HS was linked to increased risk of metabolic syndrome (odds ratio [OR] = 3.5, 95% CI, 1.2–10.0, $P = 0.02$). Hispanic women had the lowest level of education ($P < 0.001$) and the highest frequency of individual metabolic syndrome components ($P < 0.01$). In conclusion, there was an alarming rate of metabolic syndrome among the less-educated Caribbean Hispanic women, and the rate was independently associated with lower education level (73).

6. Prevalence of Metabolic Syndrome in Adult Zoroastrians of Yazd, Iran

In a community-based, cross-sectional study of Zoroastrians who live in Yazd, Iran, 512 participants aged ≥ 30 years were selected using systematic, random sampling. Patients with a history of chronic conditions, such as cardiac, pulmonary, renal, and thyroid diseases, were excluded, as were patients who took medications that influenced either glucose or lipid metabolism (such as non-steroidal, anti-inflammatory drugs and thyroid hormones) or blood pressure. The study also excluded people who had been hospitalized or had surgery in the past three months. After applying the inclusion and exclusion criteria, 403 eligible subjects were enrolled in the study. Of the 403 subjects, 153 (38%) were males (38%), and 250 (62%) were females. The mean age of the participants was 56.9 ± 12.8 (range: 30-88). The marital status of the subjects was as follows: 349 (86.6%) were married, 40 (9.9%) were widowed, and 14 (3.5%) were single. Among the married and widowed subjects, 152 (37.5%) were endogamous, and 239 (59.3%) were exogamous. The participants were mainly homemakers (44.2%). Seventy percent had an educational level of a high-school diploma or higher, while only 5.5% were illiterate. In addition, 35.7% of the subjects consumed alcohol. Personal and family history of diabetes mellitus was found in 18.6% and 43.2% of the participants, respectively. After biochemical evaluation, 30 additional

type 2 diabetes, 104 IGT, and 140 IFG cases were discovered.

History of hypertension and/or taking anti-hypertensive drugs was found in 125 (31%) subjects. A history of hyperlipidemia and/or taking anti-hyperlipidemic agents was found in 111 (27.5%) subjects. Based on both definitions, the prevalence of MS was significantly different by age group, marital status, job, educational level, and menopausal status, but this was not significant for gender, alcohol consumption, and family history of diabetes mellitus. The most prevalent abnormal parameters of MS according to ATPIII and JIS definitions were high WC (95%) and low HDL (87.9%), respectively. Mean values of known risk factors of MS were compared between the subjects with and without MS based on the application of both definitions. Mean serum levels of LDL and Cr were not different in subjects with and without MS based on the JIS definition. In addition, TC, LDL, urea, and Cr were not significantly different between the groups based on the ATPIII criteria. Mean values of LDL ($P = 0.005$), systolic BP ($P = 0.001$), WHR ($P < 0.001$), uric acid ($P < 0.001$), urea ($P = 0.004$), and Cr ($P < 0.001$) were different between men and women. These parameters also were evaluated for different age groups.

The difference between the age groups was statistically significant for BMI ($P = 0.011$), systolic BP ($P < 0.001$), diastolic BP ($P = 0.001$), TG ($P = 0.02$), WHR ($P < 0.001$), and urea ($P = 0.001$). The results of this study showed a

high prevalence of MS (i.e., 74.9% and 69.7% on the basis of ATPIII and JIS definitions, respectively) in the Zoroastrian population aged 30 years and older in Yazd. This study showed a higher prevalence of MS in women based on the ATPIII criteria, but MS was more prevalent in men based on the JIS definition, but the difference was not statistically significant. In a study conducted in the Fars Province (in southern Iran), the prevalence of MS in the adult population according to the ATPIII and IDF definitions was 26% and 30.5%, respectively. This was not statistically different between males and females (74). In a survey conducted by Ford et al., the prevalence of MS by ATPIII definition in Americans aged 60-69 and ≥ 70 years was 43.5% and 42%, respectively (75).

In a study on Turkish inhabitants with a mean age of 72, MS was more prevalent in women than in men (25.1% vs. 20.2% by the ATPIII definition) (76). The prevalence of MS in Caucasian people aged ≥ 65 who participated in the Cardiovascular Health Study was 20.8% and 27.6% based on ATPIII and WHO definitions, respectively (77). This is consistent with our findings. In the Chinese elderly population, the prevalence of MS was higher by the IDF definition than it was for the ATPIII definition, and the former was considered to be a more suitable definition for screening for MS risk (78). In another Iranian study, the prevalence of MS was 50.8% based on the ATPIII definition, and women were affected more than men (32), which is consistent with our study. Generally, Iranian

women have less physical activity and higher prevalence of overweight and obesity than men (2). In our study, the prevalence of MS based on the JIS definition was slightly lower than that based on the ATPIII definition, which seemed to be due to the presence of the central obesity trait in the JIS definition.

The CASPIAN study showed that the prevalence of MS in Iranian students ranging in age from 6 to 18 according to ATPIII definition was seven times greater than the prevalence based on NHANESIII. There was no significant difference between males and females. The most prevalent MS parameters were high TG and low HDL (79). In our study, the most frequent parameter of MS by the JIS definition was low HDL. This may be attributed to low mean HDL in the Iranian population (80), which might be, in turn, due to industrialization, unhealthy diets, lifestyle changes, obesity, and smoking (81). However, some studies have shown that gene polymorphism is responsible for a 40-60% variation in plasma levels of HDL in different individuals (82). Central obesity was the most prevalent parameter of MS based on the ATPIII definition in the current study. This may be related to the high prevalence of obesity as well as high WHR in Iran (83). Obesity is considered a principal factor in MS because it causes insulin resistance, hypertension, and various metabolic disorders (84). Björntorp suggested that an abnormal response to stress may cause neuroendocrine changes related to lipid and glucose metabolism. So,

abdominal obesity and MS may reflect changes in the subject's hormone function. MS was more common in subjects who consume alcohol than those who do not, but this was not statistically significant. Some studies have shown different results (85) that may be associated with age, gender, and amount of alcohol intake. Wakabayashi et al. showed that light drinking is associated with a lower risk of metabolic syndrome in Japanese men and women, while very heavy drinking is thought to increase the risk of metabolic syndrome in Japanese men (86).

This study showed a higher prevalence of MS in homemakers and self-employed subjects and the lowest prevalence in office workers, which may be due to the younger age of people in the latter group. There was an increasing prevalence of MS by age in the current study. This may be attributed to any of the parameters of MS. De Luis et al. showed steady decreasing prevalence of MS with decreasing age in age groups of 85-95 and >95 (87). A survey conducted on adults in the age range of 20 to 89 showed that the prevalence of MS was 25.9% and 29.6%, respectively, according to the ATP III and IDF definitions. Also, the prevalence increased with age up to 80-89 (84). In our study, although the prevalence was higher in subjects aged 70 and above than in the 30 to 39 group, it was lower than subjects who were 60 to 69. This may be related to malnutrition, insufficient care, higher mortality rate, and socioeconomic status of these subjects. These results agree with the results of Jalali et al.'s study (74).

Although not statistically significant, there was a higher prevalence of MS in subjects with a positive family history of diabetes mellitus in our study. Similarly, in a research study conducted by Chiti et al. regarding the prevalence of MS in children and adolescents, no significant associations were found (88).

The prevalence of MS in subjects with IFG was 43.7% and 45.6% according to the ATPIII and JIS definitions, respectively. For IGT, these values were 80% and 77%, respectively. A study conducted by Xiang et al. showed that, based on the ATPIII definition, in male subjects, MS was found in 65.6% with IFG/IGT, and MS was found 73.5% with type 2 diabetes mellitus. Female subjects with IFG/IGT and type 2 diabetes mellitus showed a MS prevalence of 51.0% and 75.4%, respectively (89). The parameters of MS are in association with increased risk of type 2 diabetes complications, and IGT also may progress to overt diabetes (26). There are some limitations for this study. The first was its cross-sectional design, which limited the causality relationships between the variables. The second limitation was the small number of subjects in the 30 to 39 age group, because this could lead to overestimation of the prevalence of MS due to healthier participants in this age group. In addition, our data was collected from the central part of Iran, and the results cannot be generalized to the entire country.

Finally, daily amount of alcohol consumption was not determined in this study. Strength of the study is that, to

our best knowledge, this is the first population-based study of Zoroastrians in which ATPIII and JIS criteria were used to estimate the prevalence of MS. Another strength of this study that we assessed MS according to the optimal cut-off points based on previous national studies. In conclusion, the results of this study showed a high prevalence of MS in the Zoroastrian population of Yazd, Iran.

1. Identification of patients at high metabolic risk

Metabolic syndrome is an important risk factor for subsequent development of type 2 diabetes and/or CVD. Thus, the key clinical implication of a diagnosis of metabolic syndrome is the identification of patients who need aggressive lifestyle modifications focused on weight reduction and increased physical activity (11). Healthcare providers should assess individuals for metabolic risk at their routine visits to clinics. The Endocrine Society's clinical guidelines suggest evaluation at three-year intervals in individuals with one or more risk factors (90). The assessment should include measurement of blood pressure, waist circumference, fasting lipid profile, and fasting glucose. In patients identified as having metabolic syndrome, aggressive lifestyle intervention (weight reduction, physical activity) is warranted to reduce the risks of type 2 diabetes and cardiovascular disease. Assessment of 10-year risk for cardiovascular disease, using a risk assessment algorithm, such as the Framingham Risk Score or SCORE, is useful in targeting individuals for medical intervention to lower blood pressure and cholesterol.

2. Risk of type 2 diabetes

Prospective observational studies demonstrate a strong association between metabolic syndrome and the risk for subsequent development of type 2 diabetes. In a meta-analysis of 16 multi-ethnic cohort studies, the relative risk of developing diabetes ranged from 3.53 to 5.17, depending upon the definition of metabolic syndrome and the population studied. As an example, in an analysis of 890 non-diabetic Pima Indians, 144 developed diabetes over four years of follow-up. Metabolic syndrome increased the relative risk (RR) for the development of diabetes by more than twofold with the ATPIII definition and by a factor of 3.6 using the WHO definition. This difference highlights the importance of insulin resistance (a required characteristic of the WHO definition) in the pathogenesis of type 2 diabetes (91, 92).

In several cohorts, the risk of diabetes increased with increasing number of components of metabolic syndrome (92). While metabolic syndrome predicts increased risk for diabetes, it is not clear whether this adds additional important information. In a prospective cohort study of 5842 Australian adults, metabolic syndrome (defined by WHO, ATPIII, EGIR, or IDF) was not superior to fasting plasma glucose or a published diabetes prediction model (including age, gender, ethnicity, fasting plasma glucose, systolic blood pressure, HDL cholesterol, BMI, and family history) in identifying individuals who developed diabetes (93).

3. Risk of CVD

Three meta-analyses, which included many of the same studies, found that metabolic syndrome increases the risk for incident cardiovascular disease (CVD) (RRs ranging from 1.53 to 2.18) and all cause mortality (RRs 1.27 to 1.60) (94-96). The increased risk appeared to be related to the clustering of risk factors or insulin resistance associated with metabolic syndrome rather than simply to obesity. This was illustrated by the following studies:

- In a study of the Framingham population, obese people without metabolic syndrome did not have a significantly increased risk of diabetes or CVD (97). Obese people with the metabolic syndrome had a 10-fold increased risk for diabetes and a twofold increased risk for CVD relative to normal weight people without metabolic syndrome. Normal weight people meeting revised the 2005 ATPIII criteria for metabolic syndrome had a fourfold increased risk for diabetes and a threefold increased risk for CVD.
- In a study of 211 moderately obese (BMI 30 to 35) men and women, insulin sensitivity varied by six fold, and those with the greatest degree of insulin resistance had the highest blood pressure, triglyceride concentrations, blood sugar levels when fasting or two hours after taking glucose orally, and the lowest HDL concentrations, despite equal levels of obesity (98).

Thus, not all moderately obese individuals have the same risk for developing cardiovascular disease or diabetes; risks differ as a function of insulin sensitivity, with individuals who are insulin-resistant and obese having the highest risk. The risk also may be related to underlying sub-clinical CVD (as measured by ECG, echocardiography, carotid ultrasound, and ankle-brachial blood pressure) in individuals with metabolic syndrome. In the Framingham Offspring study, 51% of 581 participants with metabolic syndrome had sub-clinical CVD, and the risk of overt CVD in these individuals was greater than in individuals with metabolic syndrome without sub-clinical CVD (HR 2.67 versus 1.59). Sub-clinical CVD also was predictive of overt CVD in subjects without metabolic syndrome (HR 1.93, 95% CI 1.15-3.24) (99).

4. Controversy in predicting risk factors

While metabolic syndrome predicts increased risk for CVD, it is not clear whether this adds additional important information (94). For example:

- In a prospective study of a population of patients with angiographically-determined coronary artery disease, elevated triglyceride and low HDL cholesterol levels were as effective at predicting vascular events as the presence of metabolic syndrome (by ATP III criteria) (100).
- The Framingham Risk Score was a better predictor of CHD and stroke than metabolic

syndrome (ATPIII criteria with obesity defined by an elevated BMI rather than waist circumference) in a prospective study of 5128 British men aged 40 to 59 followed for 20 years (101).

Low HDL cholesterol and high blood pressure were better predictors of CHD than the metabolic syndrome in a prospective study of 2737 men from the same cohort (102).

5. Other associations

Metabolic syndrome also has been associated with several obesity-related disorders including:

- Fatty liver disease with steatosis, fibrosis, and cirrhosis (103).
- Hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Chronic kidney disease (CKD), defined as a glomerular filtration rate less than 60 mL/min per 1.73 m²) and microalbuminuria. In a report from NHANESIII, the metabolic syndrome in multivariate analysis significantly increased the risk of both chronic kidney disease and microalbuminuria (adjusted odds ratios of 2.6 and 1.9, respectively) (104). The risk of both complications increased with the number of components of metabolic syndrome. In a prospective cohort study, 10% of individuals with metabolic syndrome at baseline subsequently developed CKD, whereas six percent among

those without metabolic syndrome developed CKD (105).

- Polycystic ovary syndrome, Sleep-disordered breathing, including obstructive sleep apnea, Hyperuricemia and gout. Several components of metabolic syndrome, including hyperlipidemia, hypertension, and diabetes, have been associated with an increased risk of cognitive decline and dementia. Metabolic syndrome (when associated with a high level of inflammation) also may be associated with cognitive decline in the elderly (106-110).

6. Treatment

In 2001, ATPIII recommended two major therapeutic goals in patients with metabolic syndrome (18). These goals were reinforced by a report from the American Heart Association and the National Institutes of Health and by clinical guidelines from The Endocrine Society (20):

- Treat underlying causes (overweight/obesity and physical inactivity) by intensifying weight management and increasing physical activity.
- Treat cardiovascular risk factors if they persist despite lifestyle modification.

There is no direct evidence that attempting to prevent type 2 diabetes and CVD by treating metabolic syndrome

is as effective as attaining the above goals. It is possible to treat insulin resistance with drugs that enhance insulin action (e.g., thiazolidinediones and metformin). However, the ability of such an approach to improve outcomes compared to weight reduction and exercise is not yet well supported by clinical trials (111, 112).

7. Lifestyle modification

Prevention or reduction of obesity, particularly abdominal obesity, is the main therapeutic goal in patients with metabolic syndrome (113). The importance of weight management in preventing the progression of the components of metabolic syndrome is illustrated by the study entitled 'The Coronary Artery Risk Development in Young Adults' (CARDIA) (114). In this observational study of 5115 young adults (ages 18 to 30), increasing BMI over 15 years was associated with adverse progression of the components of metabolic syndrome, whereas this progression either did not occur or was not as severe in young adults who maintained stable BMIs over the study period, regardless of their baseline BMIs. Weight reduction is optimally achieved with a multi-modality approach including diet, exercise, and possible pharmacologic therapy, e.g., orlistat (115, 116).

8. Diet

Several dietary approaches have been advocated for the treatment of metabolic syndrome. Most patients with

metabolic syndrome are overweight, and weight reduction, which improves insulin sensitivity, is an important goal of any diet. The following specific diet approaches have been recommended:

- The Mediterranean diet may be beneficial (117-120). In a study comparing the Mediterranean diet (high in fruits, vegetables, nuts, whole grains, and olive oil) with a prudent, low-fat diet, subjects in the Mediterranean diet group had greater weight loss, lower blood pressure, improved lipid profiles, improved insulin resistance, and lower levels of markers of inflammation and endothelial function (117). The dietary approaches to stop hypertension (DASH) diet (daily sodium intake limited to 2400 mg and higher in dairy intake than the Mediterranean diet), compared to a weight-reduction diet emphasizing healthy food choices, resulted in greater improvements in triglycerides, diastolic blood pressure, and fasting glucose, even after controlling for weight loss (121).
- Foods with low glycemic index may improve glycemia and dyslipidemia (122). A diet that is low in glycemic index/glycemic load; replacing refined grains with whole grains, fruits, and vegetables; and eliminating high-glycemic beverages may be particularly beneficial for patients with metabolic syndrome. The impact of the glycemic index itself versus the increase in high fiber foods that

accompanies a lower glycemic index diet is uncertain (123).

9. Exercise

Exercise may be beneficial beyond its effect on weight loss by more selectively removing abdominal fat, at least in women (124). Current guidelines for physical activity recommend practical, regular, and moderate regimens for exercise. The standard exercise recommendation is a daily minimum of 30 minutes of moderate-intensity (such as brisk walking) physical activity. Increasing the level of physical activity appears to further enhance the beneficial effect (125). Removal of abdominal adipose tissue with liposuction does not improve insulin sensitivity or risk factors for coronary heart disease, suggesting that the negative energy balance induced by diet and exercise are necessary for achieving the metabolic benefits of weight loss (126).

10. Prevention of type 2 diabetes

Although not strictly addressing the metabolic syndrome, clinical trials have shown that lifestyle modifications can substantially reduce the risk of development of type 2 diabetes and the levels of risk factors for CVD in patients at increased risk. Prevention of type 2 diabetes is discussed in detail elsewhere. In the Diabetes Prevention Program (DPP), 3234 obese subjects with impaired fasting glucose or impaired glucose

tolerance were randomly assigned to one of the following groups (112):

- Intensive lifestyle changes with the aim of reducing weight by seven percent through a low-fat diet and exercise for 150 minutes per week
- Treatment with metformin (850 mg twice daily) plus information on diet and exercise
- Placebo plus information on diet and exercise

At an average follow-up of three years, fewer patients in the intensive lifestyle group developed diabetes (14 versus 22 and 29% in the metformin and placebo groups, respectively). Metabolic syndrome (using ATPIII criteria) was present in 53% of DPP participants at baseline (127). In the remaining subjects ($n = 1523$), both intensive lifestyle intervention and metformin therapy reduced the risk of developing metabolic syndrome (three-year cumulative incidences of 51, 45, and 34% in the placebo, metformin, and lifestyle groups, respectively).

11. Oral hypoglycemic agents

Among the oral hypoglycemic agents used to treat type 2 diabetes, metformin and the thiazolidinediones (rosiglitazone and pioglitazone) improve glucose tolerance in part by enhancing insulin sensitivity. The role of these agents in patients with metabolic syndrome, i.e., to prevent diabetes, has not been established definitively, and,

furthermore, rosiglitazone has been removed from the market. As examples:

- Metformin may prevent or delay the development of diabetes in subjects with impaired glucose tolerance. In the Diabetes Prevention Program (DPP) trial described above, metformin therapy and instructions on diet and exercise were associated with a 31% reduction in the risk of developing diabetes compared to placebo (at three years, diabetes developed in 22 versus 29%); however, metformin was less effective than intensive lifestyle modification (diabetes developed in 22 versus 14%) (112). Both intensive lifestyle intervention and metformin therapy were effective for prevention of metabolic syndrome in patients who did not have the syndrome at baseline (127).
- Metformin may reduce the incidence of diabetes-related end points. In a sub-group analysis from the United Kingdom Prospective Diabetes Study (UKPDS), metformin was associated with significant reductions in any diabetes-related end point (sudden death, hypoglycemia or hyperglycemia causing death, MI, angina, heart failure, stroke, renal failure, amputation, retinopathy, monocular blindness, or cataract extraction), and all of these cause mortality compared to conventional therapy with diet (128).

There are no data on glycemic control goals in patients with the metabolic syndrome who are not diabetic. Current recommendations are to treat impaired fasting glucose and impaired glucose tolerance with weight loss of about 5 to 10% of the baseline weight; at least 30 minutes per day of moderately intense physical activity; and dietary therapy with a low intake of saturated fats, trans fats, cholesterol, and simple sugars, and increased intake of fruits, vegetables, and whole grains.

Routine pharmaco-prevention for diabetes with any agent is not recommended. However, metformin could be considered in certain individuals with both IFG and IGT. In addition, when patients cross the diabetic diagnostic threshold, immediate therapy with metformin is recommended (129).

12. Cardiovascular risk reduction

Reduction of risk factors for cardiovascular disease includes treatment of hypertension, cessation of smoking, glycemic control in patients with diabetes, and lowering of serum cholesterol according to recommended guidelines (130, 131).

12.1. Lipid-lowering

ATPIII recommended a goal for serum LDL cholesterol of less than 100 mg/dL (2.6 mmol/L) for secondary prevention in patients with type 2 diabetes (18), and subsequent studies have suggested a more aggressive

goal of less than 80 mg/dL (2.1 mmol/L) with a regimen that includes administration of a statin.

Current evidence does not support the metabolic syndrome as a coronary risk equivalent in terms of goals for lipid management (132). However, among patients with elevated serum LDL-cholesterol and established coronary disease in the 4S trial of lipid lowering with simvastatin, those with characteristics of metabolic syndrome (lowest quartile for HDL cholesterol and highest quartile for triglycerides) had both the highest risk of major coronary events and the greatest benefit (48% risk reduction) from statin therapy (133-134). Treatment of patients with known coronary disease and the metabolic syndrome with 80 mg of atorvastatin, compared to 10 mg, decreased the rate of major cardiovascular events at five years (9.5 versus 13%, HR 0.71, 95% CI 0.61-0.84) (135).

12.2. Antihypertensive therapy

There are conflicting data on whether angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB) used to treat hypertension in type 2 diabetes may also help to reduce insulin resistance. Hypertension control is important in patients with diabetes mellitus. The goal blood pressure may be somewhat lower than that in the general population, and it varies with the presence or absence of diabetic nephropathy with proteinuria. It is not clear if the lower goal applies to patients with metabolic syndrome, but it may be

reasonable to aim for such a goal. The value of ACE inhibitors and angiotensin II receptor blockers (ARBs) is not known in hypertensive patients with metabolic syndrome who do not have CVD or diabetes.

References

1. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes*. 1988 Dec; 37(12):1595-607. PubMed PMID: 3056758. Epub 1988/12/01. eng.
2. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 1991; 14:173.
3. Lindsay RS, Howard BV. Cardiovascular risk associated with the metabolic syndrome. *Curr Diab Rep* 2004; 4:63.
4. Koh KK, Han SH, Quon MJ. Inflammatory markers and the metabolic syndrome: insights from therapeutic interventions. *J Am Coll Cardiol* 2005; 46:1978.
5. Richelsen B, Pedersen SB. Associations between different anthropometric measurements of fatness and metabolic risk parameters in non-obese, healthy, middle-aged men. *Int J Obes Relat Metab Disord* 1995; 19:169.
6. Ruderman N, Chisholm D, Pi-Sunyer X, Schneider S. The metabolically obese, normal-weight individual revisited. *Diabetes* 1998; 47:699.
7. Conus F, Allison DB, Rabasa-Lhoret R, et al. Metabolic and behavioral characteristics of metabolically obese but normal-weight women. *J Clin Endocrinol Metab* 2004; 89:5013.
8. St-Onge MP, Janssen I, Heymsfield SB. Metabolic syndrome in normal-weight Americans: new definition of the metabolically obese, normal-weight individual. *Diabetes Care* 2004; 27:2222.
9. Ferrannini E, Haffner SM, Mitchell BD, Stern MP. Hyperinsulinaemia: the key feature of a cardiovascular and metabolic syndrome. *Diabetologia* 1991; 34:416.
10. Haffner SM, Valdez RA, Hazuda HP, et al. Prospective analysis of the insulin-resistance syndrome (syndrome X). *Diabetes* 1992; 41:715.
11. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005; 365:1415.
12. Grundy SM, Brewer HB Jr, Cleeman JI, et al. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004; 109:433.

13. Kahn R, Buse J, Ferrannini E, et al. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2005; 28:2289.
14. Ferrannini E. Metabolic syndrome: a solution in search of a problem. *J Clin Endocrinol Metab* 2007; 92:396.
15. Eckel RH, Kahn R, Robertson RM, Rizza RA. Preventing cardiovascular disease and diabetes: a call to action from the American Diabetes Association and the American Heart Association. *Circulation* 2006; 113:2943.
16. Grundy SM. Metabolic syndrome: a multiplex cardiovascular risk factor. *J Clin Endocrinol Metab* 2007; 92:399.
17. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabetic medicine : a journal of the British Diabetic Association*. 1998 Jul; 15(7):539-53. PubMed PMID: 9686693. Epub 1998/08/01. eng.
18. 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 : the journal of the American Medical Association*. 2001 May 16; 285(19):2486-97. PubMed PMID: 11368702. Epub 2001/05/23. eng.
19. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome - a new worldwide definition. *Lancet*. 2005 Sep 24-30;366(9491):1059-62. PubMed PMID: 16182882. Epub 2005/09/27. eng.
20. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005 Oct 25;112(17):2735-52. PubMed PMID: 16157765. Epub 2005/09/15. eng.
21. Meigs JB. Invited commentary: insulin resistance syndrome? Syndrome X? Multiple metabolic syndrome? A syndrome at all? Factor analysis reveals patterns in the fabric of correlated metabolic risk factors. *Am J Epidemiol* 2000; 152:908.

22. Ford ES. Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. *Diabetes Care* 2005; 28:2745.
23. Adams RJ, Appleton S, Wilson DH, et al. Population comparison of two clinical approaches to the metabolic syndrome: implications of the new International Diabetes Federation consensus definition. *Diabetes Care* 2005; 28:2777.
24. Lawlor DA, Smith GD, Ebrahim S. Does the new International Diabetes Federation definition of the metabolic syndrome predict CHD any more strongly than older definitions? Findings from the British Women's Heart and Health Study. *Diabetologia* 2006; 49:41.
25. Meigs JB, Rutter MK, Sullivan LM, et al. Impact of insulin resistance on risk of type 2 diabetes and cardiovascular disease in people with metabolic syndrome. *Diabetes Care* 2007; 30:1219.
26. Lorenzo C, Williams K, Hunt KJ, Haffner SM. The National Cholesterol Education Program - Adult Treatment Panel III, International Diabetes Federation, and World Health Organization definitions of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. *Diabetes Care* 2007; 30:8.
27. Cull CA, Jensen CC, Retnakaran R, Holman RR. Impact of the metabolic syndrome on macrovascular and microvascular outcomes in type 2 diabetes mellitus: United Kingdom Prospective Diabetes Study 78. *Circulation* 2007; 116:2119.
28. Azizi F, Salehi P, Etemadi A, Zahedi-Asl S. Prevalence of metabolic syndrome in an urban population: Tehran Lipid and Glucose Study. *Diabetes research and clinical practice*. 2003 Jul;61(1):29-37. PubMed PMID: 12849921. Epub 2003/07/10. eng.
29. Zabetian A, Hadaegh F, Sarbakhsh P, Azizi F. Weight change and incident metabolic syndrome in Iranian men and women; a 3 year follow-up study. *BMC public health*. 2009;9:138. PubMed PMID: 19435528. PubMed Central PMCID: PMC2696430. Epub 2009/05/14. eng.
30. Sharifi F, Mousavinasab SN, Saeini M, Dinmohammadi M. Prevalence of metabolic syndrome in an adult urban population of the west of Iran. *Experimental diabetes research*. 2009;2009:136501. PubMed PMID: 19893638. PubMed Central PMCID: PMC2773406. Epub 2009/11/07. eng.

31. Delavari A, Forouzanfar MH, Alikhani S, Sharifian A, Kelishadi R. First Nationwide Study of the Prevalence of the Metabolic Syndrome and Optimal Cutoff Points of Waist Circumference in the Middle East The National Survey of Risk Factors for Noncommunicable Diseases of Iran. *Diabetes care*. 2009;32(6):1092-7.
32. Zabetian A, Hadaegh F, Azizi F. Prevalence of metabolic syndrome in Iranian adult population, concordance between the IDF with the ATPIII and the WHO definitions. *Diabetes research and clinical practice*. 2007;77(2):251-7.
33. Mirmiran P, Esmailzadeh A, Azizi F. Detection of cardiovascular risk factors by anthropometric measures in Tehranian adults: receiver operating characteristic (ROC) curve analysis. *European journal of clinical nutrition*. 2004 Aug;58(8):1110-8. PubMed PMID: 15280905. Epub 2004/07/29. eng.
34. Esteghamati A, Abbasi M, Rashidi A, Meysamie A, Khalilzadeh O, Haghazali M, et al. Optimal waist circumference cut-offs for the diagnosis of metabolic syndrome in Iranian adults: results of the third national survey of risk factors of non-communicable diseases (SuRFNCD-2007). *Diabetic medicine : a journal of the British Diabetic Association*. 2009 Jul;26(7):745-6. PubMed PMID: 19573127. Epub 2009/07/04. eng.
35. Hadaegh F, Zabetian A, Sarbakhsh P, Khalili D, James WP, Azizi F. Appropriate cutoff values of anthropometric variables to predict cardiovascular outcomes: 7.6 years follow-up in an Iranian population. *International journal of obesity (2005)*. 2009 Dec;33(12):1437-45. PubMed PMID: 19752876. Epub 2009/09/16. eng.
36. Azizi F, Khalili D, Aghajani H, Esteghamati A, Hosseinpour F, Delavari A, et al. Appropriate waist circumference cut-off points among Iranian adults: the first report of the Iranian National Committee of Obesity. *Arch Iran Med*. 2010 May;13(3):243-4. PubMed PMID: 20433230.
37. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009

- Oct 20;120(16):1640-5. PubMed PMID: 19805654. Epub 2009/10/07. eng.
38. Rutter MK, Meigs JB, Sullivan LM, et al. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. *Circulation* 2004; 110:380.
 39. Timpson NJ, Lawlor DA, Harbord RM, et al. C-reactive protein and its role in metabolic syndrome: mendelian randomisation study. *Lancet* 2005; 366:1954.
 40. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *J Clin Invest* 2003; 111:1805.
 41. 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.
 42. Ford ES, Giles WH, Mokdad AH. Increasing prevalence of the metabolic syndrome among u.s. Adults. *Diabetes Care* 2004; 27:2444.
 43. Wilson PW, D'Agostino RB, Parise H, et al. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation* 2005; 112:3066.
 44. Park YW, Zhu S, Palaniappan L, et al. 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.
 45. Wilson PW, Kannel WB, Silbershatz H, D'Agostino RB. Clustering of metabolic factors and coronary heart disease. *Arch Intern Med* 1999; 159:1104.
 46. Palaniappan L, Carnethon MR, Wang Y, et al. Predictors of the incident metabolic syndrome in adults: the Insulin Resistance Atherosclerosis Study. *Diabetes Care* 2004; 27:788.
 47. Ferreira I, Twisk JW, van Mechelen W, et al. Development of fatness, fitness, and lifestyle from adolescence to the age of 36 years: determinants of the metabolic syndrome in young adults: the amsterdam growth and health longitudinal study. *Arch Intern Med* 2005; 165:42.
 48. Panhuysen CI, Cupples LA, Wilson PW, et al. A genome scan for loci linked to quantitative insulin traits in persons without diabetes: the Framingham Offspring Study. *Diabetologia* 2003; 46:579.
 49. Luis JR, Rowold DJ, Regueiro M, Caeiro B, Cinnioglu C, Roseman C, et al. The Levant versus the Horn of Africa: evidence for bidirectional corridors of human migrations.

- American journal of human genetics. 2004 Mar;74(3):532-44. PubMed PMID: 14973781. Pubmed Central PMCID: PMC1182266. Epub 2004/02/20. eng.
50. Quintana-Murci L, Semino O, Bandelt HJ, Passarino G, McElreavey K, Santachiara-Benerecetti AS. Genetic evidence of an early exit of Homo sapiens sapiens from Africa through eastern Africa. *Nature genetics*. 1999 Dec;23(4):437-41. PubMed PMID: 10581031. Epub 1999/12/02. eng.
 51. Kivisild T, Bamshad MJ, Kaldma K, Metspalu M, Metspalu E, Reidla M, et al. Deep common ancestry of indian and western-Eurasian mitochondrial DNA lineages. *Current biology : CB*. 1999 Nov 18;9(22):1331-4. PubMed PMID: 10574762. Epub 1999/11/27. eng.
 52. Macaulay V, Hill C, Achilli A, Rengo C, Clarke D, Meehan W, et al. Single, rapid coastal settlement of Asia revealed by analysis of complete mitochondrial genomes. *Science (New York, NY)*. 2005 May 13; 308(5724):1034-6. PubMed PMID: 15890885. Epub 2005/05/14. eng.
 53. Trinkaus E, Biglari F, Mashkour M, Monchot H, Reyss JL, Rougier H, et al. Late Pleistocene human remains from Wezmeh Cave, western Iran. *American journal of physical anthropology*. 2008 Apr;135(4):371-8. PubMed PMID: 18000894. Epub 2007/11/15. eng.
 54. Berillon G, Asgari Khaneghah A, Antoine P, Bahain JJ, Chevrier B, Zeitoun V, et al. Discovery of new open-air Paleolithic localities in Central Alborz, Northern Iran. *Journal of human evolution*. 2007 Apr; 52(4):380-7. PubMed PMID: 17188739. Epub 2006/12/26. eng.
 55. Voigt Mary M, Dyson RH: The chronology of Iran ca. 8000 –2000 B.C.; in Ehrich RW (ed): *Chronologies in Old World History*, 3rd ed. Chicago, London, 1992. 2: 122–178.
 56. Mortensen P: Seasonal camps and early villages in the Zagros; in Dimbleby G, Ucko P, Tringham R (eds): *Man, Settlement and Urbanism*. London, Shenkman Pub. Co., 1972, 293–297.
 57. Cavalli-Sforza LL: The spread of agriculture and nomadic pastoralism: Insights from genetics, linguistics and archaeology; in Harris DR (ed): *The Origins and Spread of Agriculture and Pastoralism in Eurasia*. Washington DC, Smithsonian Institution Press, 1996, 51–69.

58. Gumilyov LN: Ancient Turks. Moscow, 1967, Institute of Ethnology and Anthropology of the Academy of Sciences of USSR.
59. Quintana-Murci L, Chaix R, Wells RS, Behar DM, Sayar H, Scozzari R, et al. Where west meets east: the complex mtDNA landscape of the southwest and Central Asian corridor. *The American Journal of Human Genetics*. 2004;74(5):827-45.
60. Shepard EM, Herrera RJ. Iranian STR variation at the fringes of biogeographical demarcation. *Forensic science international*. 2006 May 10;158(2-3):140-8. PubMed PMID: 15998573. Epub 2005/07/07. eng.
61. Regueiro M, Cadenas AM, Gayden T, Underhill PA, Herrera RJ. Iran: tricontinental nexus for Y-chromosome driven migration. *Human heredity*. 2006;61(3):132-43. PubMed PMID: 16770078. Epub 2006/06/14. eng.
62. Farjadian S, Ghaderi A. HLA class II genetic diversity in Arabs and Jews of Iran. *Iranian journal of immunology : IJI*. 2007 Jun;4(2):85-93. PubMed PMID: 17652848. Epub 2007/07/27. eng.
63. Farjadian S, Ghaderi A. HLA class II similarities in Iranian Kurds and Azeris. *International journal of immunogenetics*. 2007 Dec; 34(6):457-63. PubMed PMID: 18001303. Epub 2007/11/16. eng.
64. Farjadian S, Ota M, Inoko H, Ghaderi A. The genetic relationship among Iranian ethnic groups: an anthropological view based on HLA class II gene polymorphism. *Molecular biology reports*. 2009 Sep;36(7):1943-50. PubMed PMID: 18979226. Epub 2008/11/04. eng.
65. Metspalu M, Kivisild T, Metspalu E, Parik J, Hudjashov G, Kaldma K, et al. Most of the extant mtDNA boundaries in south and southwest Asia were likely shaped during the initial settlement of Eurasia by anatomically modern humans. *BMC genetics*. 2004 Aug 31; 5:26. PubMed PMID: 15339343. Pubmed Central PMCID: PMC516768. Epub 2004/09/02. eng.
66. Nasidze I, Quinque D, Rahmani M, Alemohamad SA, Stoneking M. Concomitant replacement of language and mtDNA in South Caspian populations of Iran. *Current biology: CB*. 2006 Apr 4; 16(7):668-73. PubMed PMID: 16581511. Epub 2006/04/04. eng.
67. Nasidze I, Quinque D, Rahmani M, Alemohamad SA, Stoneking M. Close genetic relationship between Semitic-speaking and Indo-European-speaking groups in Iran. *Annals of human genetics*. 2008 Mar;72(Pt

- 2):241-52. PubMed PMID: 18205892. Epub 2008/01/22. eng.
68. Nasidze I, Quinque D, Rahmani M, Alemohamad SA, Asadova P, Zhukova O, et al. mtDNA and Y-chromosome variation in the Talysh of Iran and Azerbaijan. *American journal of physical anthropology*. 2009 Jan; 138(1):82-9. PubMed PMID: 18711736. Epub 2008/08/20. eng.
69. Organization WH. *World health statistics 2008*: World Health Organization; 2008.
70. Ajlouni K, Khader YS, Batieha A, Ajlouni H, El-Khateeb M. An increase in prevalence of diabetes mellitus in Jordan over 10 years. *Journal of diabetes and its complications*. 2008 Sep-Oct; 22(5):317-24. PubMed PMID: 18413210. Epub 2008/04/17. eng.
71. Hidvegi T, Hetyesi K, Biro L, Nadas J, Jermendy G. Screening for metabolic syndrome within a minority ethnic group (adult Gypsy people) in Hungary. *Bratislavske lekarske listy*. 2012;113(12):721-4. PubMed PMID: 23173631.
72. Dajani R, Khader YS, Hakooz N, Fatahalla R, Quadan F. Metabolic syndrome between two ethnic minority groups (Circassians and Chechens) and the original inhabitants of Jordan. *Endocrine*. 2013 Feb; 43(1):112-9. PubMed PMID: 22740093.
73. Yala SM, Fleck EM, Sciacca R, Castro D, Joseph Z, Giardina EG. Metabolic syndrome and the burden of cardiovascular disease in Caribbean Hispanic women living in northern Manhattan: a red flag for education. *Metabolic syndrome and related disorders*. 2009 Aug;7(4):315-22. PubMed PMID: 19558272. Pubmed Central PMCID: PMC3141735. Epub 2009/06/30. eng.
74. Jalali R, Vasheghani M, Dabbaghmanesh M, Omrani G: Prevalence of metabolic syndrome among adults in a rural area. *Iranian Journal of Endocrinology and Metabolism* 2009, 11:Pe405-Pe414, En477.
75. Ford ES, Giles WH, Dietz WH: Prevalence of the metabolic syndrome among US adults. *JAMA: the journal of the American Medical Association* 2002, 287:356-359.
76. Cankurtaran M, Halil M, Yavuz BB, Dagli N, Oyan B, Ariogul S: Prevalence and correlates of metabolic syndrome (MS) in older adults. *Archives of gerontology and geriatrics* 2006, 42:35-45.
77. Scuteri A, Najjar SS, Morrell CH, Lakatta EG: The metabolic syndrome in older individuals: Prevalence and

- prediction of cardiovascular events The cardiovascular health study. *Diabetes care* 2005, 28:882-887.
78. He Y, Jiang B, Wang J, Feng K, Chang Q, Fan L, Li X, Hu FB: Prevalence of the metabolic syndrome and its relation to cardiovascular disease in an elderly Chinese population. *Journal of the American College of Cardiology* 2006, 47:1588-1594.
 79. Kelishadi R, Ardalan G, Gheiratmand R, Adeli K, Delavari A, Majdzadeh R: Paediatric metabolic syndrome and associated anthropometric indices: the CASPIAN Study. *Acta Paediatrica* 2006, 95:1625-1634.
 80. Azizi F, Raiszadeh F, Salehi P, Rahmani M, Emami H, Ghanbarian A, Hajipour R: Determinants of serum HDL-C level in a Tehran urban population: the Tehran Lipid and Glucose Study. *Nutrition, metabolism, and cardiovascular diseases: NMCD* 2002, 12:80-89.
 81. Heller DA, de Faire U, Pedersen NL, Dahlen G, McClearn GE: Genetic and environmental influences on serum lipid levels in twins. *New England Journal of Medicine* 1993, 328:1150-1156.
 82. Peacock JM, Arnett DK, Atwood LD, Myers RH, Coon H, Rich SS, Province MA, Heiss G: Genome Scan for Quantitative Trait Loci Linked to High-Density Lipoprotein Cholesterol The NHLBI Family Heart Study. *Arteriosclerosis, thrombosis, and vascular biology* 2001, 21:1823-1828.
 83. Mirmiran P, Mohammadi F, Allahverdi S, Azizi F: Estimation of energy requirements for adults: Tehran lipid and glucose study. *International journal for vitamin and nutrition research* 2003, 73:193-200.
 84. Björntorp P, Holm G, Rosmond R: Hypothalamic arousal, insulin resistance and type 2 diabetes mellitus. *Diabetic Medicine* 1999, 16:373-383.
 85. Björntorp P: Neuroendocrine perturbations as a cause of insulin resistance. *Diabetes/metabolism research and reviews* 1999, 15:427-441.
 86. Wakabayashi I: Cross-sectional relationship between alcohol consumption and prevalence of metabolic syndrome in Japanese men and women. *Journal of atherosclerosis and thrombosis* 2010, 17:695-704.
 87. De Luis DA, Lopez Mongil R, Gonzalez Sagrado M, Lopez Trigo JA, Mora PF, Castrodeza Sanz J, Group N: Prevalence of metabolic syndrome with International Diabetes Federation Criteria and ATP III Program in patients 65 years of age or older. *The journal of nutrition, health & aging* 2010, 14:400-404.

88. Chiti H, Hoseinpanah F, Mehrabi Y, Azizi F: The prevalence of metabolic syndrome in adolescents with varying degrees of body weight: Tehran lipid and glucose study (TLGS). *Iranian Journal of Endocrinology and Metabolism* 2009; 11:625-637.
89. Xiang Y, Huang G, Zhou W, Che Z, Zhou P, Zhou Z: Prevalence of metabolic syndrome (MetS) in Chinese subjects gradually increased with impaired glucose homeostasis: a multicenter, clinical based, cross-sectional study. *BMC public health* 2012; 12:675.
90. Rosenzweig JL, Ferrannini E, Grundy SM, et al. Primary prevention of cardiovascular disease and type 2 diabetes in patients at metabolic risk: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2008; 93:3671.
91. Hanson RL, Imperatore G, Bennett PH, Knowler WC. Components of the "metabolic syndrome" and incidence of type 2 diabetes. *Diabetes* 2002; 51:3120.
92. Klein BE, Klein R, Lee KE. Components of the metabolic syndrome and risk of cardiovascular disease and diabetes in Beaver Dam. *Diabetes Care* 2002; 25:1790.
93. Cameron AJ, Magliano DJ, Zimmet PZ, et al. The metabolic syndrome as a tool for predicting future diabetes: the AusDiab study. *J Intern Med* 2008; 264:177.
94. Ford ES. Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. *Diabetes Care* 2005; 28:1769.
95. Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. *Am J Med* 2006; 119:812.
96. Gami AS, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. *J Am Coll Cardiol* 2007; 49:403.
97. Meigs JB, Wilson PW, Fox CS, et al. Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease. *J Clin Endocrinol Metab* 2006; 91:2906.
98. McLaughlin T, Abbasi F, Lamendola C, Reaven G. Heterogeneity in the prevalence of risk factors for cardiovascular disease and type 2 diabetes mellitus in obese individuals: effect of differences in insulin sensitivity. *Arch Intern Med* 2007; 167:642.

99. Ingelsson E, Sullivan LM, Murabito JM, et al. Prevalence and prognostic impact of subclinical cardiovascular disease in individuals with the metabolic syndrome and diabetes. *Diabetes* 2007; 56:1718.
100. Saely CH, Koch L, Schmid F, et al. Adult Treatment Panel III 2001 but not International Diabetes Federation 2005 criteria of the metabolic syndrome predict clinical cardiovascular events in subjects who underwent coronary angiography. *Diabetes Care* 2006; 29:901.
101. Wannamethee SG, Shaper AG, Lennon L, Morris RW. Metabolic syndrome vs Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. *Arch Intern Med* 2005; 165:2644.
102. Sattar N, McConnachie A, Shaper AG, et al. Can metabolic syndrome usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies. *Lancet* 2008; 371:1927.
103. Hanley AJ, Williams K, Festa A, et al. Liver markers and development of the metabolic syndrome: the insulin resistance atherosclerosis study. *Diabetes* 2005; 54:3140.
104. Zhang L, Zuo L, Wang F, et al. Metabolic syndrome and chronic kidney disease in a Chinese population aged 40 years and older. *Mayo Clin Proc* 2007; 82:822.
105. Kurella M, Lo JC, Chertow GM. Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. *J Am Soc Nephrol* 2005; 16:2134.
106. Pasquali R, Gambineri A, Anconetani B, et al. The natural history of the metabolic syndrome in young women with the polycystic ovary syndrome and the effect of long-term oestrogen-progestagen treatment. *Clin Endocrinol (Oxf)* 1999; 50:517.
107. Vgontzas AN, Papanicolaou DA, Bixler EO, et al. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. *J Clin Endocrinol Metab* 2000; 85:1151.
108. Ip MS, Lam B, Ng MM, et al. Obstructive sleep apnea is independently associated with insulin resistance. *Am J Respir Crit Care Med* 2002; 165:670.
109. Choi HK, Ford ES. Prevalence of the metabolic syndrome in individuals with hyperuricemia. *Am J Med* 2007; 120:442.
110. Choi HK, Ford ES, Li C, Curhan G. Prevalence of the metabolic syndrome in patients with gout: the Third

- National Health and Nutrition Examination Survey. *Arthritis Rheum* 2007; 57:109.
111. Meigs JB. The metabolic syndrome. *BMJ* 2003; 327:61.
112. 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.
113. Manson JE, Skerrett PJ, Greenland P, VanItallie TB. The escalating pandemics of obesity and sedentary lifestyle. A call to action for clinicians. *Arch Intern Med* 2004; 164:249.
114. Lloyd-Jones DM, Liu K, Colangelo LA, et al. Consistently stable or decreased body mass index in young adulthood and longitudinal changes in metabolic syndrome components: the Coronary Artery Risk Development in Young Adults Study. *Circulation* 2007; 115:1004.
115. Reaven G, Segal K, Hauptman J, et al. Effect of orlistat-assisted weight loss in decreasing coronary heart disease risk in patients with syndrome X. *Am J Cardiol* 2001; 87:827.
116. Heymsfield SB, Segal KR, Hauptman J, et al. Effects of weight loss with orlistat on glucose tolerance and progression to type 2 diabetes in obese adults. *Arch Intern Med* 2000; 160:1321.
117. Esposito K, Marfella R, Ciotola M, et al. Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *JAMA* 2004; 292:1440.
118. Tortosa A, Bes-Rastrollo M, Sanchez-Villegas A, et al. Mediterranean diet inversely associated with the incidence of metabolic syndrome: the SUN prospective cohort. *Diabetes Care* 2007; 30:2957.
119. Salas-Salvadó J, Fernández-Ballart J, Ros E, et al. Effect of a Mediterranean diet supplemented with nuts on metabolic syndrome status: one-year results of the PREDIMED randomized trial. *Arch Intern Med* 2008; 168:2449.
120. Kastorini CM, Milionis HJ, Esposito K, et al. The effect of Mediterranean diet on metabolic syndrome and its components: a meta-analysis of 50 studies and 534,906 individuals. *J Am Coll Cardiol* 2011; 57:1299.
121. Azadbakht L, Mirmiran P, Esmailzadeh A, et al. Beneficial effects of a Dietary Approaches to Stop Hypertension eating plan on features of the metabolic syndrome. *Diabetes Care* 2005; 28:2823.

122. Brand-Miller J, Hayne S, Petocz P, Colagiuri S. Low-glycemic index diets in the management of diabetes: a meta-analysis of randomized controlled trials. *Diabetes Care* 2003; 26:2261.
123. McKeown NM, Meigs JB, Liu S, et al. Carbohydrate nutrition, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham Offspring Cohort. *Diabetes Care* 2004; 27:538.
124. Després JP, Pouliot MC, Moorjani S, et al. Loss of abdominal fat and metabolic response to exercise training in obese women. *Am J Physiol* 1991; 261:E159.
125. Thompson PD, Buchner D, Pina IL, et al. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). *Circulation* 2003; 107:3109.
126. Klein S, Fontana L, Young VL, et al. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. *N Engl J Med* 2004; 350:2549.
127. Orchard TJ, Tempresa M, Goldberg R, et al. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med* 2005; 142:611.
128. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; 352:854.
129. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2006; 29:1963.
130. Pearson TA, Blair SN, Daniels SR, et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. *Circulation* 2002; 106:388.
131. Eberly LE, Prineas R, Cohen JD, et al. Metabolic syndrome: risk factor distribution and 18-year mortality

- in the multiple risk factor intervention trial. *Diabetes Care* 2006; 29:123.
132. Marroquin OC, Kip KE, Kelley DE, et al. Metabolic syndrome modifies the cardiovascular risk associated with angiographic coronary artery disease in women: a report from the Women's Ischemia Syndrome Evaluation. *Circulation* 2004; 109:714.
133. Ballantyne CM, Olsson AG, Cook TJ, et al. Influence of low high-density lipoprotein cholesterol and elevated triglyceride on coronary heart disease events and response to simvastatin therapy in 4S. *Circulation* 2001; 104:3046.
134. Pyörälä K, Ballantyne CM, Gumbiner B, et al. Reduction of cardiovascular events by simvastatin in nondiabetic coronary heart disease patients with and without the metabolic syndrome: subgroup analyses of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care* 2004; 27:1735.
135. Deedwania P, Barter P, Carmena R, et al. Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: analysis of the Treating to New Targets study. *Lancet* 2006; 368:919.

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