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Gender differences in the metabolic syndrome and their role for cardiovascular disease

■ **Summary** Women live longer than men and develop cardiovascular disease (CVD) at an older age. The metabolic syndrome represents a major risk factor for the development of CVD, and gender¹

differences in this syndrome may contribute to gender differences in CVD.

In recent years, the metabolic syndrome has been more prevalent in men than in women. Prevalence is increasing and this increase has been steeper in women, particularly in young women, during the last decade. The contributions of the different components of the metabolic syndrome differ between genders and in different countries.

In a recent survey in Germany, 40% of the adult population had been diagnosed with disturbed glucose tolerance or type 2 diabetes. Undiagnosed diabetes was more frequent in men than in women, and risk factors for undiagnosed diabetes differed between the sexes. Worldwide, in individuals with impaired glucose tolerance, impaired fasting glucose was observed more frequently in men, whereas impaired glucose tolerance occurred relatively more often in women. Lipid accumulation patterns differ between women and men. Premenopausal women more frequently develop peripheral obesity with subcutaneous fat accumulation,

whereas men and postmenopausal women are more prone to central or android obesity. In particular, android obesity is associated with increased cardiovascular mortality and the development of type 2 diabetes. Visceral adipocytes differ from peripheral adipocytes in their lipolytic activity and their response to insulin, adrenergic and angiotensin stimulation and sex hormones. Visceral fat is a major source of circulating free fatty acids and cytokines, which are directly delivered via the portal vein to the liver inducing insulin resistance and an atherogenic lipid profile. Inflammation increases cardiovascular risk particularly in women. A relatively greater increase in cardiovascular risk by the appearance of diabetes in women has been reported in many studies.

Thus, the presently available data suggest that the pathophysiology of the metabolic syndrome and its contribution to the relative risk of cardiovascular events and heart failure show gender differences, which might be of potential relevance for prevention, diagnostics, and therapy of the syndrome.

■ Key words

Metabolic syndrome – cardiovascular disease – gender differences

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¹“Gender” is used to include biological sex as well as gender in its strict sense

Current definition of the metabolic syndrome

Clustering of cardiovascular risk factors has been recognized for many years. In 1923 Kylin described the precursor of the metabolic syndrome, characterized by hypertension, hyperglycemia, obesity, and hyperuricemia in the *Zentralblatt für Innere Medizin*. Dyslipidemia has been identified as a part of the syndrome since the early 1960s [1]. Many definitions have been proposed since, all describing a metabolic disorder resulting from the worldwide increasing prevalence of obesity [2]. Nowadays at least four definitions of the metabolic syndrome are in use, slightly differing in their focus, and with differences in practicability regarding measuring the required parameters (Table 1) [3].

The power of the different definitions to predict the development of diabetes and cardiovascular disease varies in different populations. In Mexican Americans, the NCEP (National Cholesterol Education Program) criteria seemed to be more suitable for identifying individuals with metabolic syndrome or with increased risk of diabetes [4, 5]. Using NCEP criteria, the metabolic syndrome is detected in about

40% of the US population over 50 years. The diagnosis is most frequently driven by elevated blood pressure, followed by abdominal obesity and elevated triglycerides. A very consistent finding is a highly agedependent prevalence of the metabolic syndrome worldwide [6]. Diagnosis of the metabolic syndrome with the AACE (American Association of Clinical Endocrinologists) depends on clinical judgement based on risk factors and may therefore be less reproducible.

In Europe, the metabolic syndrome was found to be more frequent in men than in women. Classification according to WHO criteria generally led to a 50% higher estimation of prevalence compared with the EGIR (European Group for the Study of Insulin Resistance) criteria in men [7]. This can mostly be explained by the different cut-off value for central obesity used in the WHO definition. For women, the difference was smaller. Two-hour glucose values are a WHO criterion for metabolic syndrome, and this may indicate that a number of women will be identified only by this criterion. For large scale screening purposes, NCEP/ATP classification is more practicable than the WHO criteria, since determination of fast-

Table 1 Current different definitions of the metabolic syndrome, (adapted from [85–88]). For large scale screening purposes, NCEP/ATP classification is more practicable than the WHO criteria, since determination of insulin resistance is not required. The AACE definition has the potential disadvantage that the diagnosis is left to clinical judgement

EGIR 1999 [85]	WHO 1999 [86]	NCEP ATP III 2001 [87]	AACE Clinical Criteria [88]
Insulin resistance – hyperinsulinemia upper quartile of fasting insulin in non-diabetics	Diabetes or IFG or IGT or Insulin resistance (euglycemic hyperinsulinemic clamp – glucose lowest quartile)		
Plus ≥2 of the criteria below Central obesity waist ≥80 cm female or ≥94 cm male	Plus ≥2 of the criteria below Obesity BMI >30 kg/m ² or WHR >0.85 female or >0.9 male	≥3 of the criteria below Central obesity waist ≥88 cm female or ≥102 cm male	No defined number is specified Overweight/obesity BMI ≥25 kg/m ²
HDL <1.0 mmol/l <40 mg/dl or TG >2.0 mmol/l >180 mg/dl	HDL <1.0 mmol/l <40 mg/dl (women) or <0.9 mmol/l <35 mg/dl (men) male TG ≥1.7 mmol/l ≥194 mg/dl	HDL <1.3 mmol/l <50 mg/dl (women) or <1.0 mmol/l <40 mg/dl (men) TG ≥1.7 mmol/l ≥194 mg/dl	HDL <1.29 mmol/l <50 mg/dl (women) or <1.04 mmol/l <40 mg/dl (men) TG ≥1.69 mmol/l ≥193 mg/dl
Hypertension ≥140/90 mmHg and/or medication	Hypertension ≥140/90 mmHg	Hypertension ≥135/85 mmHg or medication	Hypertension ≥130/85 mmHg
Fasting plasma glucose ≥6.1 mmol/l ≥110 mg/dl		Fasting plasma glucose ≥6.1 mmol/l ≥110 mg/dl	Fasting plasma glucose 6.1–6.99 mmol/l 110–125 mg/dl
	Microalbuminuria >20 µg/min or albumin/creatinine ratio ≥30 mg/g		Family history of type 2 diabetes, CVD, PCOS; Sedentary lifestyle, Advancing age; Ethnic groups with high risk for type 2 diabetes or CVD

ing glucose is sufficient in this scheme and determination of insulin resistance levels is not required. In both definitions, the presence of type 2 diabetes does not exclude a metabolic syndrome. The AACE definition has the potential disadvantage that the diagnosis is left to clinical judgement. In Germany it is general practice to use the NCEP/ATP III definitions for classification of patients, not including a number of women with impaired glucose tolerance, which would be diagnosed with the WHO criteria.

Epidemiology

The prevalence of the metabolic syndrome increases with age, and there is also a trend towards younger subjects being affected [8, 9]. According to census data from 2000, approximately 47 million Americans meet the diagnosis for metabolic syndrome, corresponding to about 40% of the adult population. This correlates with the 61% increase in the incidence of obesity between 1991 and 2000. It is worrisome that the increase in prevalence of the metabolic syndrome is higher in women than in men. In the NHANES III and NHANES 1999–2000 studies there was a statistically significant age-adjusted increase in the prevalence of the metabolic syndrome in women, but not in men. Young women (20–39 ys) had a 76% relative increase of prevalence, compared to a non-significant increase of 5% in men in this age class (Fig. 1) [10]. This is mainly driven by the constant rise in obesity in women, with presently 2 million more women than men being affected in the United States [11].

Several attempts have been undertaken to characterize the major components of the metabolic syndrome in women and men in different populations. In a large community based cross-sectional survey in Mauritius, non-diabetic women had significantly higher body mass indices and 2-h glucose levels

Table 2 Age-adjusted and age-dependent prevalence of the metabolic syndrome (adapted from [10]; see also Fig.1)

	NHANES III	NHANES 1999–2000	Relative change (%)
All	29.2	32.2	10.9
Women	27.0	32.9	24.0
20–39 y	10.8	19.1	76.7
40–59 y	30.5	33.8	10.9
> 60 y	50.3	56.0	11.3
Men	31.4	31.8	1.4
20–39 y	15.7	16.5	4.9
40–59 y	36.3	40.3	10.9
> 60 y	50.5	46.4	–8.2

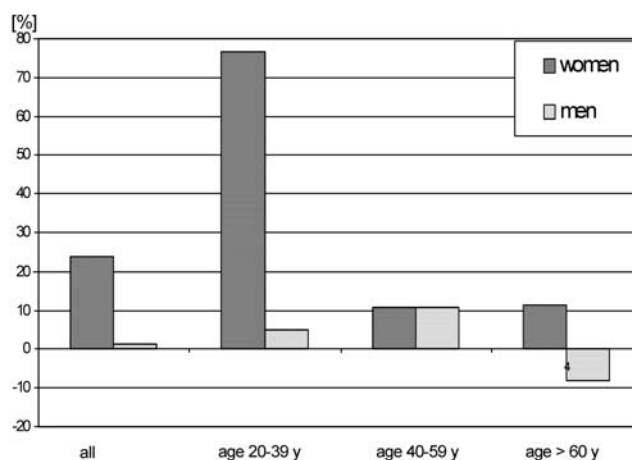


Fig. 1 Relative change (%) in age-adjusted and age-dependent prevalence of the metabolic syndrome in US population in women (black and white) and men (striped), adapted from [10]

than non-diabetic men [12]. Comparable investigations were performed in the French MONICA cohorts to separate the contributions of different factors to the metabolic syndrome. Hierarchical classification of risk factors identified a cluster corresponding to the metabolic syndrome, representing 14 and 15% of women and men, respectively. Elevated body weight, waist girth, and low HDL cholesterol showed a significantly higher effect in women than in men. In contrast, systolic and diastolic blood pressure, and apolipoprotein were more important factors in men [13]. This might be explained by the more favorable fat distribution in women. Abdominal fat tissue is a major source of free fatty acids and cytokines for the liver and is more abundant in men, favoring the early development of insulin resistance, dyslipidemia, and high blood pressure. Thus, women need a higher degree of adiposity to achieve the same metabolic disturbances [14].

In a US study, metabolic syndrome was associated with physical inactivity in overweight men and in normal weight and overweight women, suggesting a high protective value of physical exercise in women [15]. Other protective life styles are also effective, but are unfortunately heavily underused – such as non-smoking or a high cereal fiber intake, which were equally protective in women and men.

Germany

There is only little data about the prevalence of the metabolic syndrome for the German population. Some conclusions can be drawn from the MONICA/KORA cohort in Augsburg, evaluating single compo-

nents of the metabolic syndrome, and from some single studies investigating risk factors for diabetes [16–18].

Rathmann et al. performed a study based on the KORA (Cooperative Health Research in the Region of Augsburg) survey 2000, including 1353 adults aged 55–74 years without known diabetes. About 40% of this population had disturbed glucose tolerance or diabetes, and a clustering of other risk factors for the metabolic syndrome was found in this cohort [16]. Risk factors for undiagnosed diabetes differed in women and men. Hypertriglyceridemia, hypertension, and family history of diabetes were predominant risk factors in women, whereas waist circumference, hypertensive blood pressure, and family history were related to undiagnosed diabetes in men. A total of 8.7% of the study population had known and 8.2% had previously unknown diabetes, 16.4% had impaired glucose tolerance (IGT), and 7.2% had impaired fasting glucose (IFG) [16]. Undiagnosed diabetes was more frequent in men than in women (9.3 vs 6.9%), impaired glucose tolerance reached 17% in men and 15.7% in women, and elevated fasting glucose was more frequent in men (9.9%) than in women (4.4%). In women, half of the subjects with newly diagnosed diabetes and disturbed glucose tolerance were only detected by 2-h glucose (in men: 34%), confirming previously reported sex differences in the WHO and ADA diabetes diagnostic criteria [19]. This is in agreement with investigations from other parts of the world demonstrating that women have higher 2-h glucose levels for the same amount of fasting glucose than men [20, 21].

The RIAD (Risk Factors in Impaired Glucose Tolerance for Atherosclerosis and Diabetes) study evaluated risk factor profiles in patients with increased risk of developing diabetes in Germany [17]. The metabolic syndrome was present in a high percentage of the RIAD population. Again, IGT was more frequent in women (ratio women/men 1.7) and IFG was more characteristic for men (men/women 1.4). There was no difference in age between the IFG and the IGT groups. Since both IGT and IFG are strong risk factors for cardiovascular disease, it may be important to use both criteria for screening risk factor profiles.

Components of the metabolic syndrome in a large German monocenter cohort undergoing bypass surgery

A retrospective single center study in the German Heart Institute Berlin analyzed the distribution of conventional risk factors for coronary artery disease

in 15265 patients (4017 women and 11248 men) for outcome after coronary artery bypass grafting (CABG) [22].

Conventional risk factors contributing to the WHO definition of the metabolic syndrome, such as diabetes, obesity, hypertension and dyslipidemia, were more frequent in women than in men – two risk factors clustered in 45% of women vs 37% of men, and three in 22% of women vs 15% of men ($p < 0.05$). Increased body mass index (BMI) was associated with the number of risk factors without gender differences. Obesity (BMI > 30%) was rare in patients without other risk factors (women 7.5% vs 8% of men), and more frequent in 31% of men and 30% of women with three risk factors. In both sexes, more obese patients were found in younger (<55 years; 28.7% of women, 23% of men) than in older age groups (20.2% of women, 16.6% of men). The percentage of obese patients increased over the years from 14.6% of women and 12.9% of men in 1993 to 25.8% and 23.4%, respectively, in 2004. After logistic regression analysis the prevalence of hyperlipidemia and hypertension, increased in parallel significantly in women and men (Fig. 2, a) women, b) men). The only significant gender difference was found in the increase of diabetes, which over the years was significant in men but not in women. In the general population (Pop), a comparable preva-

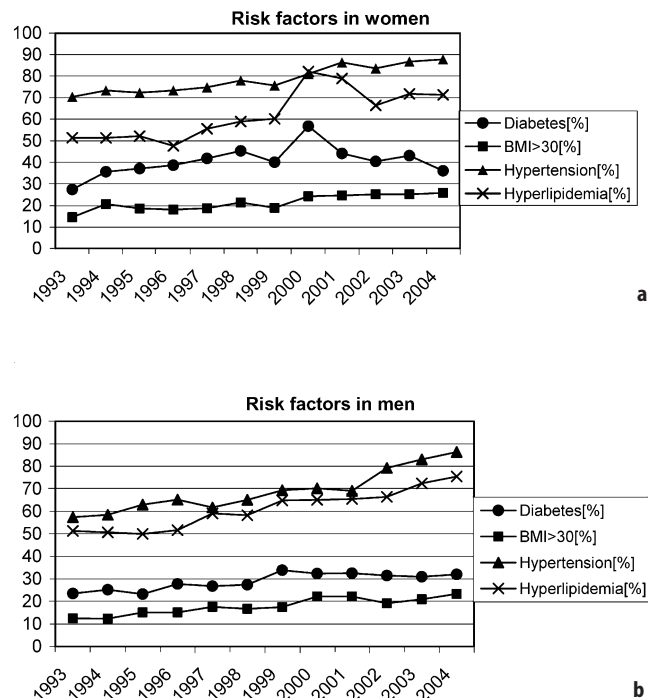


Fig. 2 Increase of patients with diabetes, obesity, hypertension and hyperlipoproteinemia in patients undergoing coronary artery surgery over the years 1993 to 2004 in women (a) and in men (b)

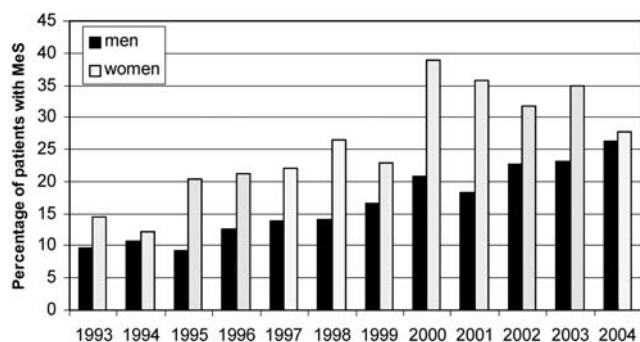


Fig. 3 Percentage of patients with metabolic syndrome over the years 1993 to 2004 in a cohort undergoing coronary artery surgery

lence for obesity was found in 1998 (Pop(men/women): 19/22%; DHZB: 18/20%). However, the prevalence for hypertension and diabetes was much higher in the DHZB cohort (hypertension: Pop (men/women): 25/22%; DHZB 65/78%; diabetes: 4.7/5.6; DHZB 28/45%). The number of patients with diabetes, and two of the risk factors BMI >30, dyslipidemia and hypertension (i.e. which were diagnosed by the definition of the metabolic syndrome by WHO criteria), showed the same increase over the years. There was an increase in women from 14.5% in 1993 to around 26% in 2004, and in men from 12% in 1993 up to 23% in 2004 (Fig. 3). Since only manifest diabetes and BMI, but not waist circumference or 2-h post challenge glucose levels, were available from the databases, these numbers underestimate the population with the metabolic syndrome. Nevertheless, they may indicate the increase of the metabolic syndrome over the last 11 years and they also confirm the more pronounced increase in women compared with men.

Pathophysiology and gender differences in components of the metabolic syndrome

■ Insulin resistance or hyperinsulinemia

Insulin resistance and hyperinsulinemia precede the development of type 2 diabetes by years, and overt diabetes develops when insulin secretion is also affected [23, 24]. Insulin secretion disturbances are mainly reflected by pathological post-challenge glucose levels, whereas primary insulin resistance is more closely related to impaired fasting glucose [17, 23]. Hyperinsulinemia and insulin resistance show different frequencies in women and men, and this seems to depend on the genetic background of the population studied [20]. In Caucasians, girls aged 5 years are intrinsically more insulin resistant than

boys [25]. Several studies have shown that girls are more insulin resistant than boys in puberty and adolescence [21, 26]. Diabetes and impaired glucose homeostasis have been linked to X-chromosomal loci [27], but the relative contribution of these loci to the clinical syndrome is still open.

In the Mauritius study [12] and in the RIAD cohort [17], women had more pronounced impaired glucose tolerance and lower fasting glucose levels than men. In elderly people from the Rancho Bernardo Study, the diagnosis of diabetes solely based on post-challenge hyperglycemia was more frequent in women than in men. Isolated post-challenge hyperglycemia was an independent predictor of CVD in women, but not in men [28], and furthermore was the only predictor of diabetes in 72% in women compared to 48% in men. The diagnosis would have been missed using only the criterion of impaired fasting glucose.

■ Abdominal obesity

In addition to lack of physical activity and overnutrition, genetic variables play a major role in the development of obesity. More than 70 different gene loci have been described that contribute to the adipose phenotype. Some genetic polymorphisms act in a sex specific manner. For example, mutation in the PPAR genes affects obesity differently in women and men. Two polymorphisms in the PPAR gamma-2 gene are associated with severe overweight in women only [29]. This suggests that inherited factors can play a different role in women and men.

The pattern of lipid accumulation differs in women and men. Women more often develop peripheral adiposity, with gluteal fat accumulation, whereas men are more prone to central or android obesity [30]. However, both types can be found in both sexes. After menopause, concentrations of lipoproteins as well as body fat distribution shift to a more male pattern. The capacity for lipogenesis and lipolysis varies according to body region and sex [14]. Higher rates of lipolysis in men are regulated by α - or β -adrenergic receptors [31]. Estrogens decrease noradrenalin-stimulated lipolysis in women by up-regulating the number of alpha-2 adrenergic antilipolytic receptors in adipose tissue [32]. Particularly android obesity is linked to increased cardiovascular mortality and the development of type 2 diabetes [33]. Male obese subjects exhibit altered cortisol secretion, reduced plasma testosterone and growth hormone levels [33]. Visceral fat is an important source of free fatty acids and inflammatory mediators, such as TNF- α , interleukins and adipokines, which are directly delivered to the liver via the portal vein, affecting hepatic glucose and fat metabo-

lism, and likely contributing to the development of hepatic insulin resistance [14]. Lower appearance of visceral fat might explain the reduced tendency to develop a metabolic syndrome in obese women [34].

Sex hormone receptor distribution is different in visceral and subcutaneous fat. Estrogen receptor β is mainly expressed in subcutaneous fat of females, whereas androgen receptors are more prominent in visceral fat in both males and females [35]. A tendency towards an increase in central obesity is observed in both sexes [35] in advanced age and after gonadectomy.

It has been speculated that the reduced tendency to accumulate fat within the intraabdominal sites may be one of the primary metabolic differences underlying the reduced risk of cardiovascular disease, metabolic syndrome, and diabetes [30] in women.

■ Sex differences in adipokine secretion and synthesis

Adipocytes (Fig. 4) produce and secrete various bioactive substances that modulate energy and fat metabolism. The conversion of testosterone to estradiol in women and men is influenced by adipocyte functions. Adipocyte dysfunction in visceral obesity may participate in the development and progression of the metabolic syndrome.

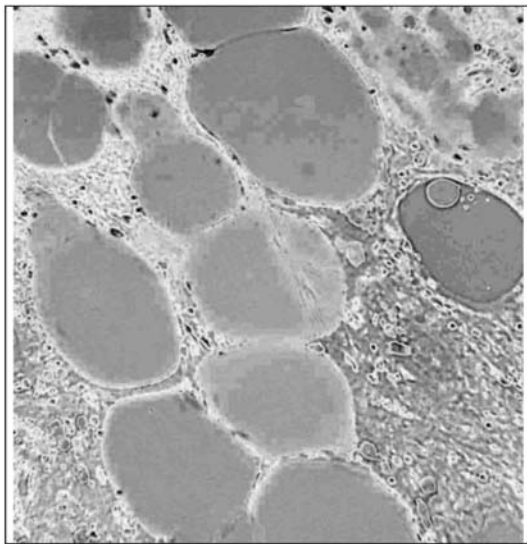


Fig. 4 Mature adipose tissue (adapted from Color Atlas of Basic Histology, Ed. I. Berman, Appleton & Lange, 1993). Premenopausal Women: mainly subcutaneous fat, peripheral adiposity, gluteal fat accumulation, estrogens decrease noradrenalin stimulated lipolysis [32], E2 up-regulates alpha-2 adrenergic antilipolytic receptors, predominant estrogen receptor β . Men: mainly visceral fat, android obesity, higher rates of lipolysis stimulated by α - or β -adrenergic receptors [31], altered testosterone and cortisol levels [33]

Leptin is secreted from adipose tissue and is involved in the central control of food intake. Leptin levels correlate with the amount of body fat and are higher in women than in men [36]. A correlation between leptin and estrogen has been described [35, 37]. However, no differences between pre- and postmenopausal women have been found [38]. In women, leptin is mainly secreted from subcutaneous fat, less from omental fat [38]. Depot and sex specific differences in human leptin mRNA expression have been described, and it has been speculated that low leptin secretion from omental fat contributes to the development of visceral obesity in men [38, 39].

Adiponectin is an adipose-tissue derived plasma protein with anti-atherogenic and insulinsensitizing activities, influencing a number of processes involved in atherosclerotic vascular changes. Hypoadiponectinemia is closely related to the clinical phenotype of the metabolic syndrome [40]. Physiologically, women seem to have higher adiponectin concentrations than men [40, 41]. In the Pittsburgh Diabetes study, adiponectin levels were elevated in women with type 1 diabetes compared to men, and adiponectin levels inversely predicted the incidence of coronary artery disease [41].

Resistin is a recently discovered adipocyte derived cytokine, which creates a link between obesity and diabetes in mice. It also promotes the development of endothelial dysfunction in pigs [42]. However, human resistin only shares about 53% homology with the mouse counterpart [43], and data suggesting a role for resistin in human diabetes and obesity are conflicting. There might be a trend towards elevated resistin levels in females [44]. In women with polycystic ovary syndrome (PCOS), a strong negative correlation was observed between resistin and adiponectin [45].

■ Hyperlipidemia, dyslipidemia

Familial hypercholesterolemia appears as a polygenic syndrome or as an autosomal codominant disorder, caused by a variety of mutations in the LDL receptor gene [46]. Mutation heterogeneity explains, to some extent, the phenotypic variation found in homozygous patients with familial hypercholesterolemia. No gender differences regarding genetic polymorphisms have been described. However, circulating lipids are different, are differently regulated, and have different significance in women and men [30]. Total cholesterol, LDL cholesterol, and triacylglycerols are lower and HDL cholesterol is elevated in premenopausal women compared to men [30]. Visceral fat mass drives increased synthesis of VLDL cholesterol, leading to elevated triacylglycerols in the fasting state,

corresponding to a “male” lipid profile. Indeed, one of the negative effects of hormone replacement therapy may relate to different effects of endogenous estrogens (and those used in the hormone replacement therapy studies (WHI) [47]) on circulating triacylglycerols [30]. The most likely explanation of the effects of orally administered hormone replacement therapy on lipid profiles seems to be a direct effect in the liver. Nevertheless, transdermal application of estrogen also increased the risk for cardiovascular events [48]. Together, the available data indicate that triacylglycerols and elevated triglycerides are a more important risk factor in women than in men. Therefore, the measurement of both parameters might be important for risk assessment in women.

■ Hypertension

Hypertension is an essential factor of the metabolic syndrome. Sex differences have been found for the association of hypertension with polymorphisms in a coactivator of PPAR gamma (PPARGC1) [49, 50], and an angiotensin receptor type 2 (AT2) polymorphism [51]. Premenopausal women have a lower tendency to develop hypertension than age-matched men. However, in advanced age the increase in the rate of hypertension is steeper in women than in men, leading to a prevalence of hypertension at age 65–75 of 69% in men and 72% in women [52]. Obesity induces hypertension by different mechanisms – such as neurohormonal activation, increase in intraabdominal pressure, glomerular and tubular effects [53]. Some of these mechanisms are sex dependent. Visceral fat is associated with hypertension and insulin resistance in men [54]. In centrally obese hypertensive women, accumulation of visceral abdominal fat is accelerated by menopause, and is also associated with higher blood pressure levels and insulin resistance [55]. In addition, women exhibit low salt sensitivity in their blood pressure regulation before menopause and become increasingly salt sensitive after menopause [56]. Pressure natriuresis, renal hemodynamics, and tubular response to salt are influenced by sex hormones and the renin angiotensin system (RAS) [56]. The renin angiotensin system (RAS) may be differently regulated in men and women, with endogenous estrogen suppressing angiotensin receptor type 1 expression and angiotensinogen synthesis [57]. Gender specific activation of the RAS may play a role in the postmenopausal increase in hypertension in women.

■ Inflammation

Inflammation may be a major factor influencing pathophysiological pathways involved in the development of metabolic syndrome [11]. However, to date inflammation is not included in the definition (see Table 1). Inflammation is partially caused by hormones secreted by adipocytes, which have prodiabetic and proinflammatory effects, such as TNF- α , interleukines, resistin and leptin. Increased CRP levels may reflect the degree of inflammation. CRP is released mainly from the liver following cytokine stimulation, but also from vascular endothelial cells. Its pathophysiological role has not yet been completely clarified. It may be proatherogenic by itself, inhibit the production of NO, and stimulate the production of adhesion molecules in endothelial cells [58, 59]. Other studies suggest that CRP is more likely to be a non-specific marker of inflammation and disease.

In the Mexico City diabetes study, the 6 year incidence of the metabolic syndrome adjusted for age, smoking, alcohol and physical activity, was significantly higher in women with high levels of CRP, and reached 7.5, 18.1 and 23.8% in the first, second and third CRP tertiles ($p < 0.001$ for trend), independent of insulin resistance. No significant association was observed in men (14.2, 11.9 and 14.1%, respectively) [60]. Similar findings were obtained in Caucasians [61]. Other authors confirmed the strict relation of CRP to the metabolic syndrome, especially in women [62], and showed that inflammation (elevated CRP) predicted the development of the metabolic syndrome more accurately in women than in men [62, 63].

■ Metabolic syndrome and polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) represents a common endocrine disorder and affects 4–6% of women of reproductive age [64]. Women with PCOS have elevated rates of obesity, central obesity, insulin resistance, impaired glucose tolerance, diabetes mellitus, hypercholesterolemia, and hypertension. Insulin resistance is found in about 50% of young women with PCOS. The relationship of plasma insulin to sex hormones in a small sample of adult African Americans suggested that in females hyperinsulinemia co-segregates with increased androgenicity [20]. In addition, insulin excess directly favors androgen synthesis in the ovary thecal cells, and modifies sex hormone binding globulin in the liver. Thus, obesity-related hyperinsulinemia could play a key

role in the development of the metabolic syndrome [65, 66]. Vice versa, hyperandrogenism per se may favor the development of insulin resistance and android obesity in PCOS women. Thus, the interaction of sex hormones with components of the metabolic syndrome may contribute to the high cardiovascular event rate in women with PCOS [67].

■ Consequences of the metabolic syndrome

The metabolic syndrome is associated with an increased number of cardiovascular events [68, 69]. More specifically, it supports the progression of a number of clinical syndromes, in addition of the development of diabetes, such as coronary artery disease, myocardial infarction, stroke, and heart failure, among others. Some of these exhibit gender specific differences in their pathogenesis, progression, and severity.

■ Increases in cardiovascular events

An early study systematically investigating the cardiovascular risk in people with the metabolic syndrome was published by Isomaa – the Botnia study from Finland and Sweden [68]. The metabolic syndrome increased the risk for coronary artery disease and stroke about threefold, but the outcomes were not specified according to sex [68]. Other studies in predominantly male cohorts confirmed that the metabolic syndrome is associated with increased cardiovascular and total mortality [69].

The metabolic syndrome is associated with an increased prevalence of coronary heart disease [5, 70–72]. In NHANES III the prevalence of coronary heart disease was highest in patients with diabetes and metabolic syndrome (19.2%), was lower in patients with metabolic syndrome without diabetes (13.9%), and again lower in patients without metabolic syndrome independent of the presence of diabetes (7.5 and 8.7%) [5]. Thus, in these studies with mixed or predominantly male populations, metabolic syndrome was a better predictor of future cardiovascular events than diabetes.

In the Framingham offspring study, the metabolic syndrome was also associated with increased risk of cardiovascular events. The increase in risk was comparable with the increase which was attributed to elevated CRP levels. Increased CRP and metabolic syndrome were independent predictors of cardiovascular disease [62], and the relationship of elevated CRP to cardiovascular events was stronger in women than in men [62].

The predictive value of the metabolic syndrome in women was evaluated in the WISE study of

780 women undergoing angiography for suspected coronary heart disease and followed for 3 years [73]. The presence of the metabolic syndrome, but not body mass index, predicted the 3-year cardiovascular risk in the women. Prognosis in all dysmetabolic groups (normal weight, overweight and obese) was worse with hazard ratios for 3-year risk of major coronary events of 2.21, 1.88 and 2.04, respectively, compared to metabolically normal groups (with normal weight, overweight and obese patients; HR 1.0, 0.76 and 0.74). Levels of CRP were more strongly associated with major coronary events than body mass index, but were not independently associated with 3-year risk of death or major coronary events.

The metabolic syndrome worsens the prognosis of cardiovascular disease in women, particularly in those with coronary artery disease [74], with an about 5-fold increase in risk (HR 4.93). In women with cardiovascular disease, the predictive value of the metabolic syndrome was higher than the HOMA Index for insulin resistance alone. In women without coronary artery disease, the development of metabolic syndrome had only a weak impact on the prognosis of cardiovascular events (HR 1.41, ns, mortality or MACE) [74]. It has been speculated that the increased risk due to the metabolic syndrome in women with pre-existing CAD might be caused by associated inflammational processes, promoting destabilization of pre-existing atherosclerotic plaques.

A relatively greater increase in cardiovascular risk by the appearance of diabetes in women than in men has been reported in many studies [28]. Diabetic women have a 3- to 6-fold and diabetic men a 2- to 4-fold increased risk of myocardial infarction [75]. The Framingham study, the Chicago heart study and the Minnesota heart study all obtained evidence that diabetic patients had a greater risk for the development of heart failure after myocardial infarction, and confirmed the higher relative increase in early and late mortality in women compared to men, when diabetes appeared [76]. A relatively greater increase in the diabetes-associated risk of myocardial infarction in women compared to men was also found in the Swedish MONICA project, which attributed 17% of infarctions in women and 11% of infarctions in men to diabetes, and described a higher relative increase in mortality from myocardial infarction in diabetes in women (7-fold) compared to men (4-fold) [75]. This more severe effect of diabetes may, among others, be related to differences in the fibrinolytic system and endothelial function. Diabetes and insulin resistance reduce the physiologically higher fibrinolytic potential in women [77], and also abrogates sex differences in endothelial function, NO availability, and endothelial function [78].

Long-term data have been obtained in the Rancho Bernardo cohort, reporting a 14-year sex specific effect of non-insulin dependent diabetes on cardiovascular outcome. The relative hazard of diabetics versus non-diabetics was 1.8 in men and 3.3 in women, after multivariate adjustment for other risk factors [79]. The role of fasting glucose was found to be different in women and men [80].

■ Heart failure

Impaired glucose tolerance, reduced insulin sensitivity, and diabetes are major features of cardiac hypertrophy, heart failure and post-infarction status. Diabetes by itself increases the risk for heart failure, and this increase in risk is more pronounced in women than in men [81, 82]. Obesity and insulin resistance both affect myocardial metabolism. In young women obesity was a significant predictor of increased myocardial oxygen consumption and decreased myocardial efficiency [83]. The study was limited to women, since the authors felt that obesity was a more severe risk factor for heart failure in women than in men.

Conclusions and clinical implications

The presently available data suggest gender specific pathophysiological differences in the metabolic syndrome. This might contribute to gender specific differences in the relative risk of cardiovascular events and heart failure. Diabetes particularly may have negative effects in women. In addition, obesity and inflammation may play different pathophysiological roles in women and men, and in subpopulations with and without coronary artery disease. This may have practical consequences. Risk factors for diabetes should be considered in a gender-specific manner, with more weight on elevated triglycerides in women and waist circumference in men. Even though there are not yet enough data available to install genderspecific criteria for the diagnosis of diabetes, physicians should recognize that incident diabetes probably carries a stronger cardiovascular risk in women than in men. They should critically evaluate whether other risk factors are present in diabetic women and if so, go on with the diagnostic tests for myocardial ischemia, keeping in mind that pharmacological stress testing and imaging procedures are particularly useful in women [84].

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ERRATUM

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The article contains mistakes regarding the affiliation of the authors. The affiliation should have been as follows:

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The publisher apologises for any inconvenience caused by this mistake.