Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 57 (2008) 1221 – 1226
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Exploring the usefulness of inflammation-sensitive biomarkers to reveal potential sex differences in relation to low-grade inflammation in individuals with the metabolic syndrome

Ori Rogowski, Itzhak Shapira, Shlomo Berliner*

Department of Medicine "D", Tel Aviv Sourasky Medical Center, 64239 Tel Aviv, Israel
Institute for Special Medical Examinations (MALRAM), Tel Aviv Sourasky Medical Center, 64239 Tel Aviv, Israel
Sackler Faculty of Medicine, Tel Aviv University, 69978 Tel Aviv, Israel

Received 15 October 2007; accepted 29 April 2008

Abstract

Sex differences exist in the expression of different inflammation-sensitive biomarkers in relation to the metabolic syndrome (MetS). We have presently explored these differences in relation to commonly used inflammation-sensitive biomarkers including the high-sensitivity C-reactive protein (hs-CRP), quantitative fibrinogen, erythrocyte sedimentation rate (ESR), white blood cell count (WBCC), and absolute number of polymorphonuclear leukocytes. This is a cross-sectional analysis of a group of apparently healthy men (n = 5560) and women (n = 3049) in whom the results of the above-mentioned inflammation-sensitive biomarkers were analyzed in relation to the different components of MetS. The concentration of hs-CRP increased pari passu with the number of components of the MetS, the differences between the sexes being significant for any number of components of the MetS. Regarding fibrinogen, the influence of sex turned significant for waist only, similarly to the results of the ESR. None of these interactions were found to be significant for both the WBCC and the absolute number of polymorphonuclear leukocytes. Quantitative fibrinogen, ESR, WBCC, as well as the absolute number of polymorphonuclear leukocytes are not sensitive enough to reveal the potential sex differences in relation to the various components of the MetS and the expression of the low-grade inflammation. High-sensitivity CRP does have the capability to reveal these differences.

1. Introduction

There is growing evidence to suggest sex differences in the etiopathogenesis of atherothrombosis [1,2]. The presence of multiplicity of atherothrombotic risk factors including the metabolic syndrome (MetS) is a significant contributor to the evolution of this morbid biological process [3]. Most, if not all, atherothrombotic risk factors as well as the MetS are accompanied by a low-grade and subclinical internal inflammation [4]. Inflammation does impose a worse prognosis by being part of this detrimental process [5]. Yet, it is not entirely clear what the role of the sex is, if any, in the existence of this above-mentioned inflammatory process. Exploring this issue became relevant once it was shown that therapeutic manipulation might have an impact on the course of the disease [6-8].

We have presently taken advantage of the possibility to evaluate a relatively large and well-characterized group of apparently healthy individuals and those with atherothrombotic risk factors including the MetS. This exploration that included commonly used inflammation-sensitive biomarkers enables us to define those who seem to be used as appropriate candidates to reveal the above-mentioned sex differences in the complex interrelations that exist between relevant risk factors, low-grade inflammation, and the potential pathogenetic pathways of atherothrombosis.

2. Methods

2.1. Subjects

We have presently analyzed data that have been collected during the last 5 years at the Tel Aviv Medical Center

* Corresponding author. Department of Medicine "D", Tel Aviv Sourasky Medical Center, 64239 Tel Aviv, Israel. Tel.: +972 3 6974254; fax: +972 3 6973635.
E-mail address: shapiraiz@tasmc.health.gov.il (S. Berliner).

0026-0495/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2008.04.015

Table 1
Relevant anthropometric, biochemical, and clinical data in the study population for both women and men

Characteristic	Men (n = 5560)	Women (n = 3049)	*P*
Systolic BP (mm Hg)	125.0 (14.6)	117.4 (15.4)	<.001
Diastolic BP (mm Hg)	78.0 (7.9)	73.8 (7.8)	<.001
BMI (kg/m^2)	26.9 (3.7)	25.4 (4.7)	<.001
Waist (cm)	95.7 (10.5)	82.4 (11.5)	<.001
Total cholesterol (mg/dL)	199.2 (37.9)	205.0 (38.3)	<.001
LDL cholesterol (mg/dL)	122.4 (32.3)	120.1 (33.2)	.003
HDL cholesterol (mg/dL)	50.5 (10.3)	64.5 (14.9)	<.001
Triglycerides (mg/dL)	132.5 (85.7)	103.1 (56.3)	<.001
Glucose (mg/dL)	95.2 (18.5)	90.9 (17.5)	<.001
Alcohol consumption (glass/wk)	1.3 (2.3)	0.6 (1.4)	<.001
Sport intensity (h/wk)	2.4 (3.0)	1.9 (2.9)	<.001
Education (y)	15.4 (2.9)	15.1 (3.0)	<.001
Smoking status, n (%)			<.001
Current	924 (16.6)	592 (19.4)	
Former	1494 (26.9)	603 (19.8)	
Never	3142 (56.5)	1854 (60.8)	
Family Hx of CHD, n (%)	858 (15.4)	578 (19.0)	<.001
Hypertension, n (%)	1384 (24.9)	488 (16.0)	<.001
Dyslipidemia, n (%)	1943 (34.9)	750 (24.6)	<.001
Diabetes mellitus, n (%)	284 (5.1)	112 (3.7)	.002
Atherothrombotic event, n (%)	247 (4.4)	93 (3.1)	.002

Data are arithmetic mean (SD) or n (%). BP indicates blood pressure; LDL, low-density lipoprotein; Hx, history.

Inflammation Survey, a registered data bank of the Israeli Ministry of Justice [9-14]. This is a relatively large cohort of individuals who attended our medical center for a routine annual checkup and gave their written informed consent for participation according to the instruction of the local ethics committee. A total of 10851 subjects gave their informed consent (male, 6821; female, 4030). A systematic examination ruled out enrollment bias due to sociodemographic or biomedical variables. Later, 1986 subjects were excluded from the analysis because of known inflammatory diseases (arthritis, inflammatory bowel disease, psoriasis, etc), pregnancy, steroidal or nonsteroidal treatment (except for aspirin at a dose of ≤325 mg per day), acute infection, or invasive procedures (surgery, catheterization, etc) during the last 6 months. An additional 158 subjects were further excluded for having missing high-sensitivity C-reactive protein (hs-CRP) values; and finally, to avoid individuals with occult infection and/or severe inflammation, we excluded 98 individuals with hs-CRP ≥20 mg/L. After these exclusions, the study group comprised 8609 individuals (male, 5560; female, 3049).

2.2. Definition of atherothrombotic risk factors

Results of the routine health checkup were assessed using certain definitions to recognize atherothrombotic risk factors in individuals. These included *diabetes mellitus*, which was defined as an individual displaying blood glucose of ≥126 mg/dL fasting or the intake of insulin or oral hypoglycemic medications. *Hypertension* was defined as displaying blood pressure of ≥140/90 mm Hg in 2 separate measurements or the intake of antihypertensive medications. *Dyslipidemia* was defined as the low-density lipoprotein or non–high-density lipoprotein (HDL) cholesterol concentrations, for individuals displaying elevated triglyceride concentrations of ≥200 mg/dL, above the recommended levels according to the risk profile defined by the updated Adult Treatment Panel III recommendations [15] or the intake of lipid-lowering medications. The diagnosis of the MetS was based on the National Cholesterol Education Program Adult Treatment Panel III criteria [16] with the modified impaired fasting glucose criteria of the American Diabetes Association [17] as proposed by the updated American Heart Association/National Heart, Lung, and Blood Institute scientific statement [18]. *Smokers* were defined as individuals who smoked at least 5 cigarettes per day, whereas past smokers had quit smoking for at least 30 days before examination.

2.3. Laboratory methods

Analysis of the white blood cell count (WBCC) and its differential was performed using the Coulter STKS (Beckman Coulter, Nyon, Switzerland) electronic cell analyzer;

Table 2
Estimated marginal mean (95% confidence interval [CI]) of hs-CRP according to sex and the presence of each component of the MetS as well as the interaction between the sex and the presence of that component

hs-CRP		Men	Women	*P* for Sex	*P* for parameter	*P* for interaction between sex and parameter
Waist	Low	3.2 (2.9-3.6)	2.7 (2.5-3.0)	.1975	<.0001	<.0001
	High	4.9 (4.4-5.5)	6.1 (5.5-6.9)			
Hypertension	No	3.9 (3.5-4.4)	3.5 (3.2-3.9)	.5977	<.0001	<.0001
	Yes	4.1 (3.7-4.6)	4.5 (4.0-5.0)			
Triglycerides	Low	3.5 (3.1-3.9)	3.2 (2.9-3.5)	.6591	<.0001	.0003
	High	4.4 (4.0-5.0)	5.0 (4.4-5.6)			
HDL cholesterol	High	3.4 (3.1-3.8)	3.2 (2.9-3.5)	.9633	<.0001	.0156
	Low	4.5 (4.0-5.1)	4.9 (4.3-5.5)			
Glucose	Low	3.8 (3.4-4.3)	3.5 (3.2-3.9)	.4643	<.0001	.0001
	High	4.1 (3.7-4.6)	4.7 (4.2-5.4)			
MetS	No	2.6 (2.3-2.9)	2.3 (2.0-2.5)	.0004	<.0001	<.0001
	Yes	4.3 (3.8-4.8)	6.2 (5.4-7.1)			

Means are adjusted for age; smoking status; family history of CHD; personal history of atherothrombotic event; sport intensity; alcohol consumption; and use of aspirin, statins, hormonal replacement therapy, or oral contraceptives for women.

erythrocyte sedimentation rate (ESR), by the Westergren method [19]. Fibrinogen was quantified by the method of Clauss [20] and a Sysmex 6000 (Sysmex, Hyaga, Japan) autoanalyzer, whereas the hs-CRP was measured using a Behring BN II Nephelometer (DADE Behring, Marburg, Germany) [21].

2.4. Statistical analysis

All data were summarized and displayed as mean (SD) for the continuous variables and as number of patients (percentage) in each group for categorical variables.

Because hs-CRP concentrations displayed irregular distribution, we used a logarithmic transformation that converted the distribution to normal one for all statistical procedures. Therefore, all results of hs-CRP concentrations are expressed as back-transformed geometrical mean and SD. The 1-way Kolmogorov-Smirnov test was used to assess the distributions.

For all categorical variables, the χ^2 statistics was used for assessing the statistical significance between the 2 sexes, whereas the independent Student *t* test was used for continuous variables. To evaluate the contribution of sex and each component of the MetS to the variability of each inflammation-sensitive biomarker, we used 2-way analysis of variance with the inflammation-sensitive biomarker as the dependent variable and each component of MetS plus sex as well as the interaction between them as the independent variables, with adjustment to the presence of each of the other 4 components of MetS and, in addition, age; smoking status; family history of coronary heart disease (CHD); personal history of atherothrombotic event; sport intensity; alcohol consumption; and use of aspirin, statins, hormonal replacement therapy, or oral contraceptives for women. The same analysis was done just for hs-CRP and the number of components of the MetS. All above analyses were considered significant at $P < .05$ (2-tailed). The SPSS statistical package was used to perform all statistical evaluations (SSPS, Chicago, IL).

3. Results

We have presently analyzed a total of 5560 men and 3049 women at the respective mean (SD) age of 44.5 (11.2) and 45.3 (10.4) years. Relevant anthropometric information including risk factor, biochemical information, and history of past atherothrombotic events are given in Table 1. It can be seen that men had a worse biological profile in terms of a higher blood pressure and a worse lipid profile and glucose concentration; were more obese; and had more atherothrombotic risk factors including hypertension, dyslipidemia, diabetes mellitus, as well as a history of a past atherothrombotic event. On the contrary, they had an increased consumption of alcohol, were engaged in more sport activities, and had a less prominent familial history of CHD.

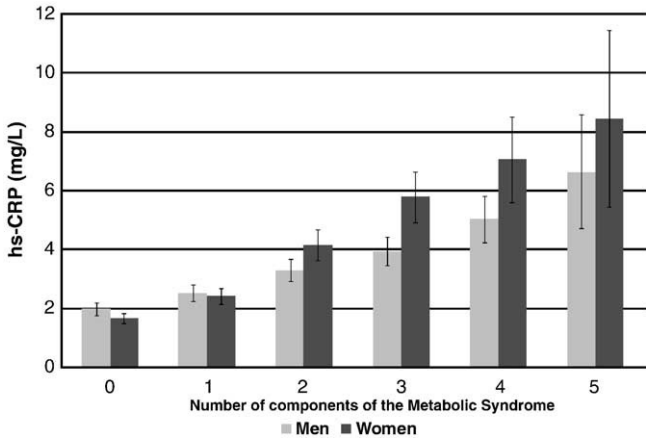

Fig. 1. Estimated marginal mean (and 95% CI) of hs-CRP according to sex and number of components of the MetS.

The individual components of the MetS as well as the concentration of hs-CRP are reported in Table 2. Reported as well is the interaction between the sex and the relevant parameter. This interaction turned to be significant for all of them including the MetS itself. In addition, it is clear that the concentration of hs-CRP is related to the number of the components of the MetS (Table 3 and Fig. 1), the difference between men and women being significant regarding any number of components that was taken into consideration. This situation turned different for fibrinogen, where the influence of sex turned significant only for waist (Table 4 and Fig. 2). As expected, the results of the ESR were similar to those obtained for fibrinogen (Table 5). None of these interactions were found to be significant for both the WBCC (Table 6) and the absolute number of polymorphonuclear leukocytes (data not shown). To further evaluate those

Table 3
Estimated marginal mean (95% CI) of hs-CRP according to sex and number of components of the MetS

hs-CRP		Men	Women	*P* for sex	*P* for no. of components	*P* for interaction between sex and no. of components
No. of components of MetS	0	2.0 (1.8-2.2)	1.7 (1.5-1.8)	<.0001	<.0001	<.0001
	1	2.5 (2.3-2.8)	2.4 (2.2-2.7)			
	2	3.3 (2.9-3.7)	4.2 (3.7-4.7)			
	3	4.0 (3.5-4.5)	5.8 (5.0-6.7)			
	4	5.0 (4.3-5.9)	7.1 (5.8-8.7)			
	5	6.7 (5.0-8.9)	8.5 (6.0-12.0)			

Means are adjusted for age; smoking status; family history of CHD; personal history of atherothrombotic event; sport intensity; alcohol consumption; and use of aspirin, statins, hormonal replacement therapy, or oral contraceptives for women.

Table 4
Estimated marginal mean (95% CI) of fibrinogen according to sex and presence of each component of the MetS

Fibrinogen		Men	Women	*P* for sex	*P* for parameter	*P* for interaction between sex and parameter
Waist	Low	298 (292-305)	317 (311-323)	<.0001	<.0001	.0049
	High	313 (307-320)	340 (333-346)			
Hypertension	No	306 (300-313)	326 (320-332)	<.0001	.2504	.2275
	Yes	306 (300-312)	329 (323-336)			
Triglycerides	Low	306 (300-312)	327 (321-333)	<.0001	.7403	.2660
	High	307 (301-314)	325 (318-332)			
HDL cholesterol	High	303 (297-309)	323 (317-329)	<.0001	<.0001	.6274
	Low	309 (302-316)	331 (324-339)			
Glucose	Low	306 (300-312)	327 (321-332)	<.0001	.9992	.7768
	High	306 (300-313)	326 (319-334)			
MetS	No	296 (290-302)	317 (312-323)	<.0001	<.0001	.1183
	Yes	306 (300-313)	333 (326-341)			

Means are adjusted for age; smoking status; family history of CHD; personal history of atherothrombotic event; sport intensity; alcohol consumption; and use of aspirin, statins, hormonal replacement therapy, or oral contraceptives for women.

findings, we reanalyzed the results for hs-CRP after dividing our cohort into 5 groups of decades of age (20-29, 30-39, 40-49, 50-59, and 60-69) and 3 groups of commonly used body mass indexes (BMIs) (normal weight [BMI $\leq$ 25 kg/m^2], overweight [25 < BMI $\leq$ 30 kg/m^2], and obese [BMI > 30 kg/m^2]) and found similar results for most of those divisions (data not shown).

4. Discussion

This is the first study to explore in detail the potential interactions between sex and commonly used inflammation-sensitive biomarkers in a cohort of well-defined apparently healthy individuals and those with atherothrombotic risk factors. The inflammation-sensitive biomarkers were chosen because of both their usefulness in daily practice as well as the established relevance to atherothrombosis; and this is true for hs-CRP [22], quantitative fibrinogen [23], ESR [24], as well as the WBCC [25]. The main finding of the study is that, from all the above-mentioned relevant inflammation-sensitive biomarkers, only the hs-CRP could reveal clear and significant interactions between sex and each of the individual components of the MetS as well as the MetS itself.

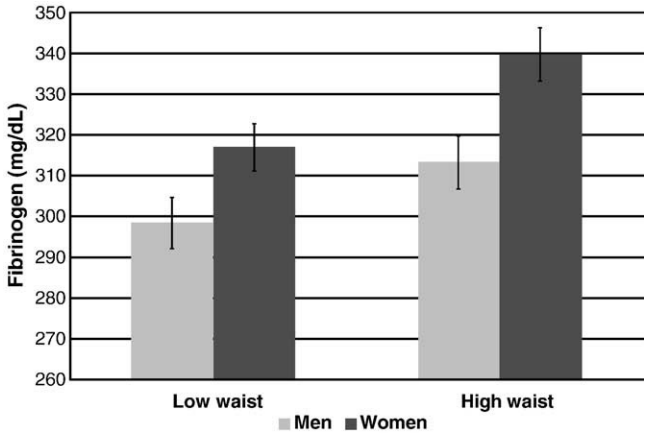

Fig. 2. Estimated marginal mean (and 95% CI) of fibrinogen according to sex and the waist status by the MetS definition.

The association between the MetS and low-grade inflammation has been repeatedly shown in the past. However, conflicting information exists as to whether there exists a difference between the sexes in relation to this accompanying acute phase response. In fact, the prevalence of the MetS was reported to be higher among women compared with men in one sectional survey in China [26]. In addition, CRP levels have also been reported to differ by sex [27-31]. Moreover, existing evidence also suggests that CRP might be more strongly correlated with MetS in women than in men [28,32-34].

The main contribution of the present study is that it shows that, although relevant in terms of the etiopathogenesis of atherothrombosis, quantitative fibrinogen, ESR, WBCC, as well as the absolute number of polymorphonuclear leukocytes are not sensitive enough to reveal the potential sex differences in relation to the various components of the MetS and the expression of the low-grade inflammation. This inflammation has been repeatedly shown to be deleterious in these conditions; and this is true for waist [35], hypertension [36], hyperlipidemia [37], as well as insulin resistance and prediabetic glucose concentrations [38]. Thus, we could show that only hs-CRP was sensitive enough to reveal these sex-related effects.

Sex differences in atherothrombosis became relevant once it was shown that they might influence both the course of the clinical events as well as their management. These differences that were presently shown, as well as those reported in the literature [6-8,39,40], suggest that women might react in a different way to the presence of the relevant factor. In fact, it is possible that women are more prone to respond with a low-grade inflammatory process and thus might be candidates for a potentially more aggressive therapeutic approach.

Finally, the potential mechanisms that could explain, at least in part, the differences between the sexes are only

Table 5
Estimated marginal mean (95% CI) of ESR according to sex and presence of each component of the MetS

ESR		Men	Women	*P* for sex	*P* for parameter	*P* for interaction between sex and parameter
Waist	Low	11 (10-12)	19 (18-20)	<.0001	<.0001	.0011
	High	12 (11-13)	21 (20-22)			
Hypertension	No	11 (10-12)	20 (19-21)	<.0001	.8947	.2612
	Yes	11 (10-12)	20 (19-21)			
Triglycerides	Low	11 (10-12)	19 (18-20)	<.0001	<.0001	.2492
	High	12 (11-13)	21 (20-22)			
HDL cholesterol	High	11 (10-12)	19 (18-20)	<.0001	<.0001	.0239
	Low	12 (10-13)	21 (20-22)			
Glucose	Low	11 (10-12)	20 (19-20)	<.0001	.3732	.9162
	High	11 (10-12)	20 (19-21)			
MetS	No	10 (9-11)	18 (17-19)	<.0001	<.0001	.0533
	Yes	11 (10-12)	21 (20-22)			

Means are adjusted for age; smoking status; family history of CHD; personal history of atherothrombotic event; sport intensity; alcohol consumption; and use of aspirin, statins, hormonal replacement therapy, or oral contraceptives for women.

Table 6
Estimated marginal mean (95% CI) of WBC according to sex and presence of each component of the MetS

WBC		Men	Women	*P* for sex	*P* for parameter	*P* for interaction between sex and parameter
Waist	Low	7.7 (7.6-7.9)	7.7 (7.5-7.9)	.0898	<.0001	.2232
	High	8.1 (7.9-8.3)	8.0 (7.8-8.2)			
Hypertension	No	7.8 (7.6-8.0)	7.7 (7.6-7.9)	.1633	<.0001	.6231
	Yes	8.1 (7.9-8.2)	8.0 (7.8-8.2)			
Triglycerides	Low	7.7 (7.5-7.9)	7.6 (7.5-7.8)	.3044	<.0001	.9503
	High	8.2 (8.0-8.4)	8.1 (7.9-8.3)			
HDL cholesterol	High	7.8 (7.6-8.0)	7.7 (7.6-7.9)	.4668	<.0001	.6901
	Low	8.0 (7.8-8.3)	8.0 (7.8-8.2)			
Glucose	Low	7.9 (7.7-8.1)	7.9 (7.7-8.0)	.2164	.5584	.7575
	High	7.9 (7.8-8.1)	7.9 (7.7-8.1)			
MetS	No	7.5 (7.4-7.7)	7.4 (7.2-7.6)	.2006	<.0001	.1919
	Yes	8.2 (8.0-8.4)	8.2 (7.9-8.4)			

Means are adjusted for age; smoking status; family history of CHD; personal history of atherothrombotic event; sport intensity; alcohol consumption; and use of aspirin, statins, hormonal replacement therapy, or oral contraceptives for women.

partially understood [41]. Relevant for the higher concentration of CRP in women might be the higher concentration of estrogen in women [42]. The present study does therefore contribute to those studies that explore sex-related inflammatory changes. In fact, it clearly reveals that changes may exist in the possibility of certain inflammation-sensitive biomarkers to detect the presence of microinflammatory changes between the sexes in the context of the MetS.

Based on the results of the present study, we conclude that quantitative fibrinogen, ESR, WBCC, as well as the absolute number of polymorphonuclear leukocytes are not sensitive enough to reveal the potential sex differences in relation to the various components of MetS and the expression of low-grade inflammation. High-sensitivity CRP does have the capability to reveal these differences.

References

[1] Mikhail GW. Coronary heart disease in women. BMJ 2005;331:467-8.
[2] Bairey MN, Bonow RO, Sopko G, Balaban RS, Cannon III RO, Gordon D, et al. Women's ischemic syndrome evaluation: current status and future research directions: report of the National Heart, Lung and Blood Institute workshop: October 2-4, 2002: executive summary. Circulation 2004;109:805-7.
[3] Dandona P, Aljada A, Chaudhuri A, Mohanty P, Garg R. Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes, and inflammation. Circulation 2005;111:1448-54.
[4] Ridker PM. High-sensitivity C-reactive protein, inflammation, and cardiovascular risk: from concept to clinical practice to clinical benefit. Am Heart J 2004;148:S19-26.
[5] Torres JL, Ridker PM. Clinical use of high sensitivity C-reactive protein for the prediction of adverse cardiovascular events. Curr Opin Cardiol 2003;18:471-8.
[6] Natarajan S, Liao Y, Sinha D, Cao G, McGee DL, Lipsitz SR. Sex differences in the effect of diabetes duration on coronary heart disease mortality. Arch Intern Med 2005;165:430-5.
[7] Harrington RA. Women, acute ischemic heart disease, and antithrombotic therapy: challenges and opportunities. Circulation 2007;115:2796-8.
[8] Norman PE, Powell JT. Abdominal aortic aneurysm: the prognosis in women is worse than in men. Circulation 2007;115:2865-9.
[9] Rogowski O, Shapira I, Shirom A, Melamed S, Toker S, Berliner S. Heart rate and microinflammation in men: a relevant atherothrombotic link. Heart 2007;92:940-7.
[10] Berliner S, Rogowski O, Aharonov S, Mardi T, Tolshinsky T, Rozenblat M, et al. Erythrocyte adhesiveness/aggregation. A novel biomarker for the detection of low grade internal inflammation in individuals with atherothrombotic risk factors and proven vascular disease. Am Heart J 2005;149:260-7.

[11] Rogowski O, Toker S, Shapira I, Melamed S, Shirom A, Zeltser D, et al. Values of high sensitivity C-reactive protein in each month of the year in apparently healthy individuals. Am J Cardiol 2005;95:152-5.
[12] Zeltser D, Rogowski O, Berliner S, Mardi T, Justo D, Serov J, et al. Sex differences in the expression of haemorheological determinants in individuals with atherothrombotic risk factors and apparently health people. Heart 2004;90:277-81.
[13] Zeltser D, Rogowski O, Mardi T, Justo D, Tolshinsky T, Goldin E, et al. Clinical and laboratory characteristics of patients with atherothrombotic risk factors presenting with low concentrations of highly sensitive C-reactive protein. Atherosclerosis 2004;176:297-301.
[14] Steinvil A, Shapira I, Arbel Y, Justo D, Berliner S, Rogowski O. Determinants of the erythrocyte sedimentation rate at the era of micro-inflammation, excluding individuals with elevated C-reactive protein. Am J Clin Pathol 2008;129:486-91.
[15] 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) final report. Circulation 2002;106:3143-421.
[16] Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
[17] Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, et al. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003;26:3160-7.
[18] 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;112:2735-52.
[19] International committee for standardization in hematology. Recommendation of measurement of erythrocyte sedimentation rate of human blood. Immunochemistry 1965;2:235-54.
[20] Clauss A. Gerinnungsphysiologische Schnellmethode zur Bestimmung des Fibrinogens. Acta Haematol Basel 1957;17:237-46.
[21] Rifai N, Tracy RP, Ridker PM. Clinical efficacy of an automated high-sensitivity C-reactive protein assay. Clin Chem 1999;45:2136-41.
[22] Lowe GD, Pepys MB. C-reactive protein and cardiovascular disease: weighing the evidence. Curr Atheroscler Rep 2006;8:421-8.
[23] Kannel WB, Wolf PA, Castelli WP, D'Agostino RB. Fibrinogen and risk of cardiovascular disease. The Framingham Study. JAMA 1987;258:1183-6.
[24] Erikssen G, Liestol K, Bjornholt JV, Stormorken H, Thaulow E, Erikssen J. Erythrocyte sedimentation rate: a possible marker of atherosclerosis and a strong predictor of coronary heart disease and mortality. Eur Heart J 2000;21:1614-20.
[25] Coller BS. Leukocytosis and ischemic vascular disease morbidity and mortality: is it time to intervene? Arterioscler Thromb Vasc Biol 2005; 25:658-70.
[26] Gu D, Reynolds K, Wu X, Chen J, Duan X, Reynolds RF, et al. Prevalence of the metabolic syndrome and overweight among adults in China. Lancet 2005;365:1398-405.
[27] Rogowski O, Zeltser D, Shapira I, Burke M, Zakuth V, Mardi T, et al. Gender difference in C-reactive protein concentrations in individuals with atherothrombotic risk factors and apparently healthy ones. Biomarkers 2004;9:85-92.
[28] Rutter MK, Meigs JB, Sullivan LM, D'Agostino Sr RB, Wilson PWF. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. Circulation 2004;110:380-5.
[29] Khera A, McGuire DK, Murphy SA, Stanek HG, Das SR, Vongpatanasin W, et al. Race and gender differences in C-reactive protein levels. J Am Coll Cardiol 2005;46:464-9.
[30] Yamada S, Gotoh T, Nakashima Y, Kayaba K, Ishikawa S, Nago N, et al. Distribution of serum C-reactive protein and its association with atherosclerotic risk factors in a Japanese population: Jichi Medical School Cohort Study. Am J Epidemiol 2001;153:1183-90.
[31] Ford ES, Giles WH, Mokdad AH, Myers GL. Distribution and correlates of C-reactive protein concentrations among adult US women. Clin Chem 2004;50:574-81.
[32] Han TS, Sattar N, Williams K, Gonzalez-Villalpando C, Lean MEJ, Haffner SM. Prospective study of C-reactive protein in relation to the development of diabetes and metabolic syndrome in the Mexico City Diabetes Study. Diabetes Care 2002;25:2021.
[33] Nakanishi N, Shiraishi T, Wada M. C-reactive protein concentration is more strongly related to metabolic syndrome in women than in men: the Minoh Study. Circ J 2005;69:386-91.
[34] Bo S, Gentile L, Ciccone G, Baldi C, Benini L, Dusio F, et al. The metabolic syndrome and high C-reactive protein: prevalence and differences by sex in a southern-European population-based cohort. Diabetes Metab Res Rev 2005;21:515-24.
[35] Pou KM, Massaro JM, Hoffmann U, Vasan RS, Maurovich-Horvat P, Larson MG, et al. Visceral and subcutaneous adipose tissue volumes are cross-sectionally related to markers of inflammation and oxidative stress: the Framingham Heart Study. Circulation 2007; 116:1234-41.
[36] Virdis A, Ghiadoni L, Plantinga Y, Taddei S, Salvetti A. C-reactive protein and hypertension: is there a causal relationship? Curr Pharm Des 2007;13:1693-8.
[37] Mora S, Ridker PM. Justification for the use of statins in primary prevention: an intervention trial evaluating rosuvastatin (JUPITER)—can C-reactive protein be used to target statin therapy in primary prevention? Am J Cardiol 2006;97:33A-41A.
[38] Ndumele CE, Pradhan AD, Ridker PM. Interrelationships between inflammation, C-reactive protein, and insulin resistance. J Cardiometab Syndr 2006;1:190-6.
[39] Iso H, Sato S, Kitamura A, Imano H, Kiyama M, Yamagishi K, et al. Metabolic syndrome and the risk of ischemic heart disease and stroke among Japanese men and women. Stroke 2007;38: 1744-51.
[40] Mega JL, Morrow DA, Ostor E, Dorobantu M, Qin J, Antman EM, et al. Outcomes and optimal antithrombotic therapy in women undergoing fibrinolysis for ST-elevation myocardial infarction. Circulation 2007;115:2822-8.
[41] Qiu H, Depre C, Ghosh K, Resuello RG, Natividad FF, Rossi F, et al. Mechanism of gender-specific differences in aortic stiffness with aging in nonhuman primates. Circulation 2007;116:669-76.
[42] Lakoski SG, Cushman M, Criqui M, Rundek T, Blumenthal RS, D'Agostino Jr RB, et al. Gender and C-reactive protein: data from the Multiethnic Study of Atherosclerosis (MESA) cohort. Am Heart J 2006;152:593-8.