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The multiplicative interactions of leukocyte counts with some other risk factors enhance the prognostic value for coronary artery disease

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Abstract

Background: *The markers of inflammation and (apo)lipoproteins are associated with coronary artery disease (CAD). Simultaneous assessment of the risk factors has been proposed to improve the diagnosis of CAD. The aim of this study was to examine the potential interactions between leukocyte counts and other risk factors.*

Methods: *The markers of inflammation, (apo)(lipo)proteins, (non)electrolytes, hematological parameters and classical risk factors, were determined in 264 clinically stable angiographically documented subjects. The subjects were classified as CAD cases or controls according to the results of coronary angiography.*

Results: *The frequency and severity of CAD, Framingham CAD scores, relative and absolute risk for CAD and the prevalence of diabetes mellitus and smoking were significantly higher in the third relative to the first tertile of leukocyte counts. Subjects with leukocyte counts in the upper tertile had significant higher levels of serum glucose, triglyceride, hsC-reactive protein, potassium, phosphorus and measured osmolality, and lower levels of apoAI, total protein, albumin and the ratio of albumin/globulins. Analyses by bivariate correlation on differential leukocyte counts showed that these associations are carried mostly by neutrophil, except for diabetes, glucose and triglyceride which were due to lymphocyte counts. By constructing dummy combined variables, high leukocyte counts accompanied by smoking, hypertension, diabetes, and high levels of serum glucose, cholesterol, apoB and apoB/apoAI ratio, exhibited amplified high risk for CAD.*

Conclusions: *The results show that leukocyte count does interact multiplicatively with smoking, hypertension, diabetes, glucose, cholesterol, apoB and apoB/AI ratio. The simultaneous assessment of leukocyte counts and interactive risk factors enhances the diagnosis of CAD.* (Cardiol J 2011; 18, 3: 246–253)

Key words: apoB, coronary artery disease, diabetes mellitus, leukocyte count, hypertension, smoking

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Introduction

It has been demonstrated that low grade inflammation can contribute to vascular injury and atherosclerosis [1]. Inflammation also promotes atherosclerotic plaque rupture and thrombosis [2]. The subject has been meta-analyzed recently for high sensitivity C-reactive protein (hsCRP) and total and differential leukocyte counts [3, 4]. Several prospective studies have indicated a consistent association between the total and differential leukocyte counts and an increased risk for future cardiovascular events in healthy individuals [5–10] and in acute coronary syndromes [11–15] at baseline. But elevated leukocyte counts have not been identified as a risk factor for angina pectoris [16, 17]. Most of the associations between leukocyte counts and cardiovascular events is accounted for by neutrophil counts [18–24].

At practical approach, the levels of inflammatory biomarkers are towards the upper limits of the normal range in coronary artery disease (CAD) patients, and the differences between normal and CAD groups are statistically (but not clinically) significant [3, 4]. This problem limits the application of inflammatory markers for clinical diagnosis. On the other hand, the prognostic value may be much higher if it is combined with other risk factors such as lipid parameters. Ridker et al. [25] and Rifai and Ridker [26] have shown multiplicative interaction between four inflammatory markers with total cholesterol [25, 26]. We have previously found that hsCRP interacts with apoB, or the ratio of apoB/apoAI, better than with cholesterol [27]. In this study, as part of our previous work, we examined the relationship between total and differential leukocyte counts and more than 50 risk factors.

Methods

Experimental design, subjects and angiographic assessment

The experimental design, angiographic assessment and anthropometric measurements were as described previously [27]. In brief, the study population consisted of 138 men and 126 women aged 40–70 with suspected CAD who were consecutively referred and underwent their first coronary angiography at Zahra Hospital in the University of Mazandaran. Those with a recent history of acute myocardial infarction, percutaneous transluminal coronary angioplasty, infectious or inflammatory disease, severe liver or renal disease, neoplasm or hematological disorders were excluded from our study. Subjects with one or more lesions that narrowed the lumen of any coronary artery significantly (≥ 70%) were considered to be CAD cases. Those with no narrowing formed the controls. The severity of coronary occlusion was scored on the basis of the number and extent of lesions: 1 (normal), 2 (mild), 3 (moderate) and 4 (severe) [27].

The study was approved by the local bioethical committee and all patients gave their informed consent.

Biochemical and hematological measurements

Blood sample collection, serum preparation and the measurement of lipids, (apo)lipoproteins and hsCRP are described in [28]. All measurements were done on fresh serum except that of Lp(a), apolipoproteins and hsCRP which were stored at –70°C before analysis (for a maximum of three months). All assays were performed blind. Serum Lp(a), apoB100, apoAI and hsCRP were assayed by immunoturbidometric methods (DiaSys Diagnostics, Holzheim, Germany) performed by the Pars-Azmon company of Tehran. Assay performance was monitored every 20 tests using the lipid control serums Tru-Lab Lp(a), Tru-Lab Lipids and Tru-Lab CRP (DiaSys Diagnostics). Lipid standards Tru Cal Lp(a), apoB, apoAI and CRP were used to calibrate Cobas-Mira Plus auto-analyzer (Roche Diagnostic Systems, Basle, Switzerland). All inter- and intra-assay coefficients of variance were less than 3% [27]. Serum total protein and albumin were measured by biuret and bromocresol green (BCG) methods respectively, using bovine serum albumin as protein standard by LKB spectrophotometer (Biochrom Ltd, Cambridge, UK). Serum proteins and lipoproteins were fractionated by electrophoresis on agarose gels (Sebia, Evry, France) [27]. Serum osmolality was measured by freezing-point depression (Osmomat 030, Genotec, Berlin, Germany) [28]. White blood cells (WBC) were counted in whole blood samples using a model T890 Coulter Counter (Coulter, Miami, Florida, USA). Blood smears were made from EDTA-treated samples and leukocyte differential count was done manually. All other biochemical and hematological parameters were measured by routine laboratory methods.

Statistical analyses

The results are presented as the means ± SD and median (range) for normal and skewed distributed variables respectively. Total leukocyte count was categorized into tertiles based on the cut-off points of the entire distribution, and the patients' characteristics were calculated accordingly. Propor-

Table 1. Demographic and clinical parameters in coronary artery disease (CAD) control and patient groups.

Variables	CAD control group	CAD cases group	P
Anthropometrics:			
Age (year)	51.1 ± 10.3	57.0 ± 10.2	0.005
Gender (male/female)	(41/61)	(97/65)	0.005
BMI [kg/m^2]	25.5 ± 3.2	26.3 ± 4.1	0.3
Physical inactivity	54 (52.9%)	105 (64.8%)	0.09
Smoking	6 (5.9%)	32 (20.0%)	0.005
Diabetes mellitus	13 (12.7%)	61 (37.7%)	0.0001
Hypertension	29 (28.4%)	67 (41.4%)	0.05
FH of premature CAD	28 (27.5%)	51 (31.5%)	0.7
PMH of diabetes mellitus	14 (13.7%)	52 (32.1%)	0.001
Drugs:			
Antilipidemic	16 (15.7%)	42 (25.9%)	0.09
Hypoglycemic	5 (4.9%)	45 (27.8%)	0.0001
Nitrates	34 (33.3%)	85 (52.5%)	0.005
Beta-blocker	58 (56.9%)	90 (55.6%)	0.9
Calcium antagonists	7 (6.9.0%)	23 (14.2%)	0.09
ACE-inhibitors	8 (7.8%)	20 (12.3%)	0.3
Diuretics	2 (2.0%)	4 (2.5%)	0.8

The number of subjects in each group is shown in parenthesis. The significant differences between discontinuous variables were accessed by χ^2, and continuous variables by t-student test; ACE — angiotensin-converting enzyme; BMI — body mass index; FH — family history; PMH — past medical history

tions and means (or median) for baseline risk factors were calculated. The significance of any differences in proportions or medians was tested with Kruskal-Wallis test, and in means using analysis of variance (ANOVA). All p-values are two-tailed and differences were considered significant if p-values were ≤ 0.05. The cut-off points were deduced from receiver operating characteristic (ROC) analyses and used to convert continuous variables into categorized binary states [28, 29]. A multivariate logistic regression analysis was carried out to find out the independency of correlation (SPSS version 10). The results of multivariate analysis were expressed as odds ratio with 95% confidence intervals. Bivariate correlation analysis was used to assess the correlation between total and differential leukocyte counts and other variables. In stratification analysis, the study participants were classified into six or nine groups according to leukocyte count tertiles and tertiles of apoB, glucose, cholesterol or binary state of smoking, diabetes mellitus (DM) and hypertension. The relative odds were calculated by cross-tabulation using χ^2-test. The Framingham CAD risk scores (FCRS), and the relative and absolute risks of CAD, were calculated according to an algorithm based on a seven variables equation [30].

Results

Demographic and clinical parameters of the subjects

The prevalence of DM, hypertension, cigarette smoking and physical inactivity was higher in CAD cases than in control subjects (Table 1). There were no significant differences in the consumption of hypolipidemic agents, β-adrenergic antagonists, angiotensin-converting enzyme inhibitors, calcium channel blockers or diuretics between the two groups. A history of DM and medication by hypoglycemic agents and nitrates was commoner among patients than controls.

Characteristics of the study participants according to tertiles of total leukocyte count

The prevalence and severity of CAD, FCRS, relative and absolute risk and odds ratios for CAD were significantly associated with the tertiles of total leukocyte count (Table 2). Cigarette smoking and DM were more prevalent in the top than in the bottom tertile of leukocyte count. Subjects with leukocyte counts in the upper tertile had significantly higher levels of serum hsCRP, glucose, triglycerides, measured osmolality, potassium and phosphorus. The concentrations of serum apoAI, albumin,

Table 2. Basic characteristics of the study population according to tertiles of leukocyte counts.

Variables	Tertiles of leukocytes count [cell/nL]			P
	< 6.00	6.00–7.40	> 7.40	
Anthropometrics:				
CAD frequency	43 (51.2%)	50 (58.1%)	62 (68.9%)	0.03
CAD severity	1.2 ± 1.1	1.5 ± 1.2	1.8 ± 1.1	0.007
Framingham scores	6.7 ± 4.9	8.0 ± 4.8	8.3 ± 4.7	0.007
Relative risk	1.8 ± 1.1	2.2 ± 1.1	2.5 ± 1.4	0.004
Absolute risk	10.7 ± 8.1	11.9 ± 7.6	14.5 ± 9.9	0.001
Age (years)	55.8 ± 11.3	53.4 ± 10.6	55.6 ± 10.0	0.09
Male sex	41 (48.8%)	36 (41.9%)	53 (58.9%)	0.08
Physical inactivity	29 (34.5%)	38 (44.2%)	32 (35.6%)	0.4
Smoking	5 (6%)	15 (17.4%)	18 (20%)	0.02
Diabetes mellitus	18 (21.4%)	22 (25.6%)	33 (36.7%)	0.05
Hypertension	30 (35.7%)	38 (44.2%)	28 (31.1%)	0.3
Aspirin	37 (44.0%)	36 (41.9%)	39 (43.3%)	0.9
Biochemical and hematological parameters:				
Leukocyte count [cell/nL]	5.2 ± 0.6	6.7 ± 0.4	8.9 ± 1.3	–
hsCRP [mg/L]	1.5 (0–18.5)	2.4 (0–20.1)	2.1 (0–115.1)	0.02
ESR [mm/h]	13 (2–50)	12 (4–45)	14 (2–49)	0.9
Glucose [mg/dL]	111.2 ± 39.8	119.9 ± 48.9	132.6 ± 64.3	0.02
Triglyceride [mg/dL]	140.5 (47–719)	170.5 (66–1426)	195 (40–1331)	0.005
Total cholesterol [mg/dL]	197.5 ± 47.5	206.2 ± 63.0	203.6 ± 53.1	0.6
HDL-cholesterol [mg/dL]	42.3 ± 13.2	39.0 ± 12.0	40.2 ± 10.8	0.2
LDL-cholesterol [mg/dL]	123.2 ± 45.5	128.4 ± 60.8	122.1 ± 46.7	0.7
apoB [mg/dL]	123.8 ± 30.5	130.8 ± 31.9	130.6 ± 26.9	0.2
apoAI [mg/dL]	137.9 ± 22.8	130.1 ± 20.5	132.4 ± 18.1	0.04
Lp(a) [mg/dL]	40.0 (7.0–270.0)	48.0 (4.0–290.0)	43.0 (4.0–280.0)	0.5
Albumin [g/dL]	5.02 ± 0.78	4.55 ± 0.66	4.67 ± 0.75	0.001
Total protein [g/dL]	9.25 ± 1.19	8.74 ± 1.08	9.04 ± 1.25	0.02
Albumin/globulin	1.20 ± 0.18	1.15 ± 0.19	1.12 ± 0.20	0.04
Measured osmolality [mOsm/kg H_2O]	296.7 ± 6.2	297.2 ± 7.3	299.4 ± 9.7	0.05
Potassium [mEq/L]	4.3 ± 0.4	4.4 ± 0.4	4.6 ± 0.5	0.0001
Total calcium [mg/dL]	9.4 ± 0.9	8.9 ± 0.9	9.2 ± 1.1	0.4
Phosphorus [mg/dL]	3.9 ± 0.5	4.0 ± 0.6	4.1 ± 0.7	0.04

The subjects were divided into tertiles on the basis of leukocyte count distribution. The significance of any differences in means (or median) and proportions were tested using analyses of variance and Kruskal-Wallis tests respectively; CAD — coronary artery disease; CRP — C-reactive protein; ESR — erythrocyte sedimentation rate

total protein and the ratio of albumin/globulin decreased from the higher to the lower tertile.

Correlation of total and differential leukocyte counts with other risk factors

Bivariate correlation analysis was performed to address the correlations of leukocyte count and the differential with other risk factors (Table 3). Leukocyte count correlated with the prevalence of smoking and DM positively and significantly. Leukocyte counts correlated positively and significantly with serum glucose, triglycerides, hsCRP, potassium, and phosphorus, and negatively correlated with apoAI, albumin, and the ratio of albumin/globulins. Most of the associations of total leukocyte counts were carried by neutrophils except that of the correlations with smoking, DM, glucose, triglycerides and albumin which correlated more with lymphocytes.

Association of single or leukocyts counts-combined variables with coronary artery disease

Multivariate logistic regression analysis was performed to test the possible interactions between

Table 3. The Pearson's correlation coefficients (r) of leukocyte counts relative to other risk factors. Bivariate correlation analysis was performed using SPSS software.

	Correlation coefficients (r)				
	WBC	Neutrophil	Lymphocyte	Monocyte	Eoesinophil
CAD occurrence	0.147[a]	0.132[a]	0.076	0.022	0.117
CAD severity	0.166[b]	0.151[b]	0.082	0.029	0.134
Framingham score	0.097	0.006	0.136	0.006	0.045
Relative risk	0.168	0.128	0.149	0.086	0.018
Absolute risk	0.143	0.154	0.047	0.091	0.041
Smoking	0.162[a]	0.118[a]	0.165	–0.010	0.001
Diabetes mellitus	0.115[a]	0.091	0.116[a]	0.034	–0.025
Glucose	0.129[a]	0.088	0.150[b]	0.018	0.231
Triglycerides	0.150[b]	0.057	0.212[b]	0.062	–0.040
HDL-cholesterol	–0.098	–0.116	–0.030	–0.055	–0.033
ApoAI	–0.138	–0.135	–0.047	–0.040	–0.056
ApoB100	0.071	0.078	0.054	–0.036	–0.051
Lp(a)	0.021	–0.070	–0.040	–0.091	–0.010
hsCRP	0.209[b]	0.350[c]	–0.096	0.059	–0.049
Albumin/globulin	–0.185[b]	–0.137[a]	–0.169[b]	–0.105	0.016
Albumin	–0.192[b]	–0.142[a]	–0.171[b]	–0.091	–0.005
Potassium	0.223[c]	0.240[c]	0.087	0.021	0.060
Total calcium	–0.031	–0.022	–0.066	–0.036	0.063
Phosphate	0.096[a]	0.064	0.092	0.000	0.087

A, b and c indicate that the correlation coefficients are statistically significant at the confidence levels of $p \leq 0.05$, $p \leq 0.005$ and $p \leq 0.0001$ respectively; CAD — coronary artery disease; CRP — C-reactive protein; WBC — white blood cells

Table 4. Odds ratios for stable coronary artery disease according to the presence of single (left) or leukocyte count-combined risk factors (right).

Single variables	OR (95% CI)	P	Combined variables	OR (95% CI)	P
WBC	1.97 (1.15–3.38)	0.01			
Male sex	3.31 (1.90–5.78)	0.001	Male sex/WBC	3.17 (1.59–6.35)	0.001
Hypertension	1.79 (1.01–3.16)	0.05	Hypertension/WBC	3.86 (1.55–9.59)	0.002
Diabetes mellitus	5.14 (2.47–10.70)	0.0001	Diabetes/WBC	5.22 (1.97–13.82)	0.0001
Smoking	3.87 (1.44–10.39)	0.004	Smoking/WBC	5.03 (1.47–17.23)	0.005
Cholesterol	2.10 (1.02–4.53)	0.05	Cholesterol/WBC	4.78 (1.39–16.43)	0.007
ApoB	2.72 (1.36–5.43)	0.005	ApoB/WBC	4.14 (1.98–8.65)	0.0001
Lp(a)	2.19 (1.14–4.23)	0.009	Lp(a)/WBC	3.77 (1.96–7.26)	0.0001

The following cut-off points were used to convert categorical variables into a binary state: leukocyte count: 6.75×10^9 cells/L; cholesterol: 240 mg/dL; triglycerides: 200 mg/dL, apoB: 130 mg/dL, Lp(a): 30 mg/dL; and hsCRP: 3 mg/L; OR — odds ratio; CI — confidence interval; WBC — white blood cells

leukocyte counts and other risk factors with respect to stable CAD (Table 4). Major classical risk factors, as well as apoB and Lp(a), were included in the analysis. The criteria for variables entering into, and removal from, multivariate regression equation were 0.05 and 0.1 respectively. When single variables were entered into the multivariate analysis, age, male sex, DM, hypertension, apoB, Lp(a), and cholesterol remained in the model significantly (Table 4, left column).

Dummy variables were constructed for the combination of leukocyte counts and other risk factors. We tested all possible combinations of risk factors, in particular for ones which apparently correlated with leukocyte counts according to the results of Tables 2 and 3. The data shows that leuko-

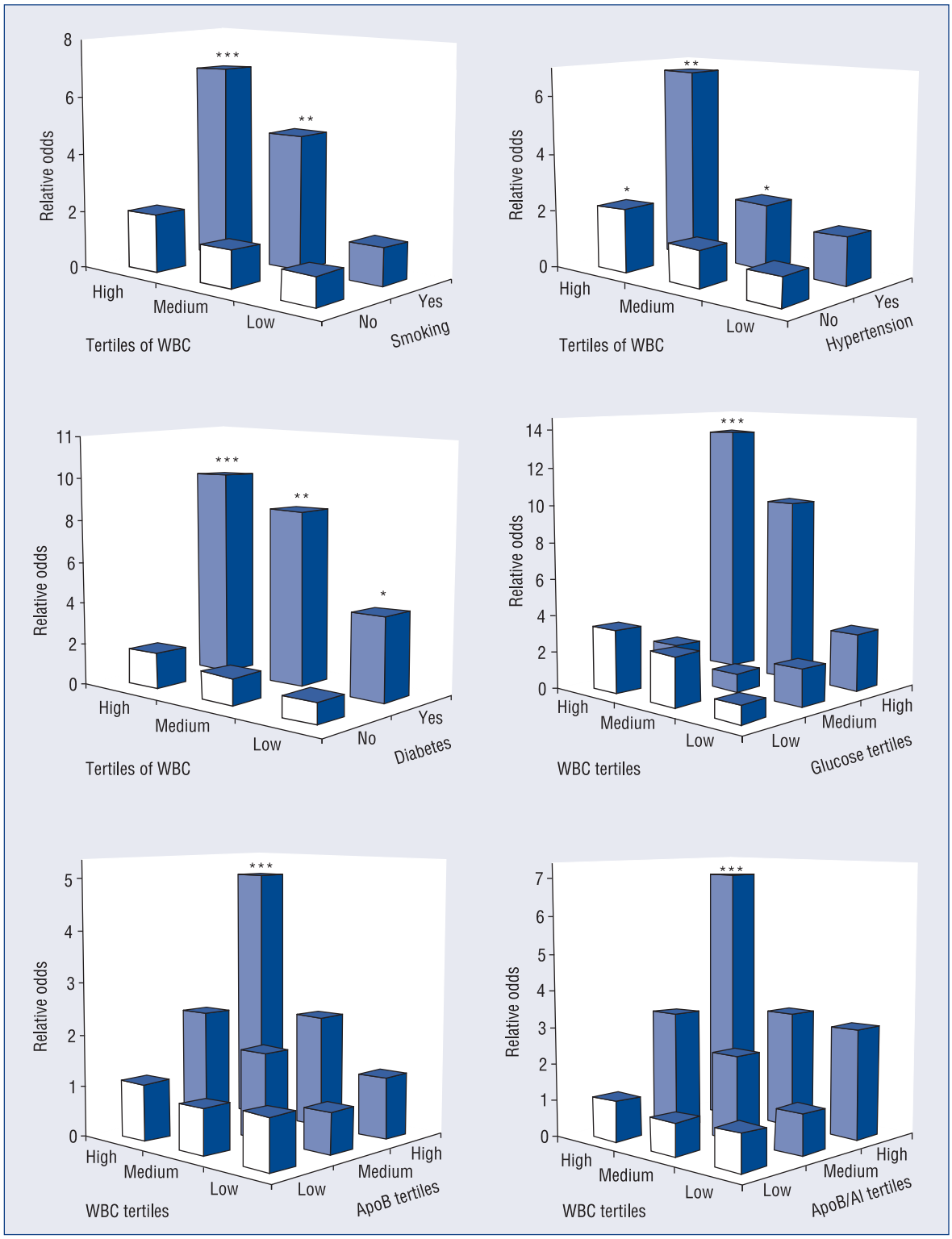

Figure 1. Relative odds for coronary artery disease associated with tertiles of leukocyte count and presence/absence of smoking, hypertension, diabetes and tertiles of glucose, apoB and apoB/AI ratio. The tertiles were < 94, 94–117, > 117 mg/dL for glucose, < 116, 116–139, > 139 mg/dL for apoB and < 0.87, 0.87–1.05, > 1.05 for the ratio of apoB/AI. In any figure, all groups were compared to the group with the lowest odds ratio; *, ** and *** indicate that the corresponding value is significantly different from its respective control at the $p \leq 0.05$, $p \leq 0.01$ and $p \leq 0.001$ confidence levels respectively; WBC — white blood cells.

cyte counts exhibit multiplicative or synergistic elevations in risk (additive in log scale) with hypertension, smoking, apoB and cholesterol (Table 4, right column). No such interactions were observed with any other risk factors (results not shown).

To find out whether leukocyte counts added to the predictive value of the major risk factors, the study participants were stratified into six or nine groups according to leukocyte counts tertiles and binary state of smoking, hypertension, DM or tertiles of glucose, cholesterol, apoB and apoB/apoAI ratio (Fig. 1). The figures show that the relative odds for CAD were lowest among the groups with low leukocyte counts and low glucose, low apoB, and low apoB/apoAI ratio, or in the absence of smoking, hypertension and DM. In contrast, the relative odds tended to be highest among groups with high leukocyte counts and high glucose, apoB, apoB/apoAI ratio or the presence of smoking, hypertension and DM. The figures also show that the interactions between leukocyte counts and apoB are gradual, but with glucose were revealed only in the top tertile, i.e. in diabetic ranges.

Discussion

The results of the present study indicate that the leukocyte counts had significant correlations with the frequency and severity of CAD, FCRS, relative and absolute risk for CAD. Leukocyte counts also were correlates of smoking, DM, hypertension, and the levels of serum glucose, apoB, apoB/apoAI ratio, albumin, albumin/globulin ratio, potassium and phosphate.

Several mechanisms have been postulated whereby leukocyte counts might influence the development of CAD [1, 2]. Leukocytes liberate proteases, inflammatory mediators and radicals which can cause proteolytic and oxidative damage to endothelial cells. Abnormal leukocyte aggregation, and adhesion and hypercoagulability and thrombosis also might be involved [1, 2]. Leukocytes are stiffer and larger than other blood cells and may plug the microvasculature. The associations of leukocytes with other risk factors also may be important.

The correlation between leukocyte counts and FCRS has been reported previously by Park et al. [6] in a study of a healthy American population. Since FCRS is calculated by the values of seven classical risk factors [30], the association implies correlation with some of them, especially smoking, hypertension, DM and cholesterol. The current results also showed that the CAD risk accompanied by elevated total leukocyte count is carried mainly by increased circulating neutrophils. This observation agrees with most reports [18–24].

The association between leukocyte count and frequency and severity of CAD has been depicted by all prospective studies [5–15]. Although, all studies confirmed the association, debate continues regarding the independence of the correlation. Diabetes [31, 32], obesity [33, 34] and smoking [35, 36] are the most important confounding risk factors. In multivariate analysis of our data, the association of leukocyte count with CAD weakened only if the analysis was controlled for DM. A high frequency of diabetic cases in our study might have increased the power of DM to confound the correlation.

Several studies have shown the correlation of inflammatory markers including hsCRP with glucose levels or the presence of DM [31, 32]. Hyperglycemia is known to stimulate the release of inflammatory cytokines from various cell types and can lead to the induction and secretion of acute-phase reactants by adipocytes [37]. But there is limited data regarding the correlation of leukocyte counts and glucose levels. The current results indicate that serum glucose interacts with leukocyte counts only in the top tertile, i.e. in the diabetic range.

In the multimarker approach proposed by Ridker et al. [25] and Rifai and Ridker [26], four inflammatory markers in combination with total cholesterol are used to increase risk assessment for CAD. In the previous report, we examined this approach for the interaction between hsCRP and the ratio of apoB/apoAI [38]. The present results show that the leukocyte counts, in the same way as hsCRP, can interact multiplicatively with the other risk factors including apoB/apoAI ratio. Since the ratio of apoB/apoAI is known as the best markers of CAD [29], simultaneous measurement of inflammatory markers in conjunction with apolipoproteins may be more indicative than with cholesterol ratios. The markers of inflammation and metabolic syndrome (including dyslipidemia) may therefore improve cardiovascular stratification in patients with CAD.

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