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Total white blood cell count is associated with the presence, severity and extent of coronary atherosclerosis detected by dual-source multislice computed tomographic coronary angiography

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Abstract

Background: Total white blood cell (WBC) count has been consistently shown to be an independent risk factor and predictor for future cardiovascular outcomes, regardless of disease status in coronary artery disease (CAD). The purpose of this study is to evaluate the relationship between total WBC count and the presence, severity and extent of coronary atherosclerosis detected in subjects undergoing multislice computed tomographic (MSCT) coronary angiography for suspected CAD.

Methods: A total of 817 patients were enrolled in this cross-sectional study. Non-significant coronary plaque was defined as lesions causing $\leq 50\%$ luminal narrowing, and significant coronary plaque was defined as lesions causing $> 50\%$ luminal narrowing. For each segment, coronary atherosclerotic lesions were categorized as none, calcified, non-calcified and mixed. All images were interpreted immediately after scanning by an experienced radiologist.

Results: An association between hypertension, diabetes mellitus, age, gender, hyperlipidemia, smoking, total WBC counts and coronary atherosclerosis was found when patients were grouped into two categories according to the presence of coronary atherosclerosis ($p < 0.05$). Although plaque morphology was not associated with total WBC counts, the extent of coronary atherosclerosis was increased with higher total WBC quartiles ($p = 0.006$). Patients with critical luminal stenosis had higher levels of total WBC counts when compared to patients with non-critical luminal narrowing ($7,982 \pm 2,287$ vs $7,184 \pm 1,944$, $p < 0.05$).

Conclusions: Our study demonstrated that total WBC counts play an important role in inflammation and are associated with the presence, severity and extent of coronary atherosclerosis detected by MSCT. Further studies are needed to assess the true impact of WBC counts on coronary atherosclerosis, and to promote its use in predicting CAD. (Cardiol J 2011; 18, x: xx–xx)

Key words: coronary atherosclerosis, computed tomography, leukocytosis

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Introduction

Cardiovascular diseases are the leading cause of death world-wide [1]. Inflammation plays a pivotal role in the progression of atherosclerosis, and white blood cell (WBC) count is a marker of inflammation that is widely available in clinical practice [2, 3]. Leukocytosis affects coronary artery disease (CAD) through multiple pathological mechanisms relevant to inflammation, oxidative damage to the endothelial cells, microvasculature and hypercoagulability.

In recent years, numerous epidemiological prospective and retrospective cohort and case-control studies have demonstrated that leukocytosis is an independent predictor of future cardiovascular events, both in healthy individuals free of CAD and in subjects with CAD [3, 4]. Kostis et al. [5] stated that patients with angiographically documented CAD had higher leukocyte counts than patients lacking CAD and that WBC count was an independent marker of CAD severity after adjusting for cardiovascular risk factors such as age, gender, total cholesterol, triglyceride level and smoking. Correlation of the leukocyte count with CAD and investigations into the utility of the leukocyte count as a risk factor and prognostic indicator in patients with CAD are consistent with the current concept that atherosclerosis is an inflammatory disease.

To the best of our knowledge, there is no published data on the relationship between the total leukocyte count and coronary atherosclerosis detected by dual-source multislice computed tomography (MSCT) coronary angiography, which has the advantage of showing atherosclerotic plaques in the vessel wall in addition to luminal stenosis. In this study, we assess the relationship between total WBC count and the presence, severity and extent of atherosclerotic lesions in patients undergoing MSCT coronary angiography with suspected CAD.

Methods

Study sample and risk factor assessment

This cross-sectional study was performed in a subset of patients admitted to our Cardiology Department for cardiovascular evaluation between January 2007 and June 2008 and in whom MSCT coronary angiography was performed for suspected CAD.

Subjects with documented CAD, history of myocardial infarction, presence of renal dysfunction (creatinine ≥ 1.5 mg/dL), hepatic disorders, concomitant inflammatory diseases, neoplastic diseases or

any systemic disorders, acute or chronic infectious disease, or on medications which can affect leukocyte counts were excluded from the study.

All subjects provided details of their background, medical history, and any medication they were using at the time of clinical consultation. We carried out a complete physical examination for each patient. Diabetes was defined as a fasting plasma glucose level ≥ 126 mg/dL or current diabetes treatment with dietary modification, oral glucose-lowering agents, or insulin [6]. Hypertension was defined as use of blood pressure medication or systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg. Hyperlipidemia was defined as total cholesterol ≥ 200 mg/dL or treatment with a lipid-lowering agent. Global CAD risk was estimated by Framingham risk equation [7]. Complete blood count, blood biochemistry and lipid profile were taken from each patient. This study was approved by the local ethics committee and informed consent was received from each participant.

Blood sample collection, measurement of biochemical markers and leukocyte counts

Venous blood samples were obtained by venipuncture of the large antecubital veins. Blood samples were taken after overnight fasting and the serum was centrifuged at 2,000 rpm for 10 min at 4°C. The serum levels of triglyceride, total, low-density lipoprotein-cholesterol and high-density lipoprotein-cholesterol and fasting glucose were determined enzymatically with a commercially available assay kit (Hitachi P800, Holliston, Massachusetts, USA). A complete blood count analysis including leukocytes was performed within two hours of collection as a laboratory policy of the hospital using a Beckman Coulter (High Wycombe, UK) Gen-S automated analyzer.

Coronary MSCT angiography

All subjects underwent computed tomography coronary angiography imaging using dual-source MSCT scanner (Somatom Definition, Siemens, Erlangen, Germany). Sublingual nitrate (5 mg of isosorbide dinitrate, Fako, Isordil) was given 2–4 min before image acquisition to dilate the coronary arteries. The coronary angiographic scan was obtained with injection of 80 mL nonionic contrast medium (350 mg I/mL iohexol, Amersham Health Omnipaque) at a flow rate of 6 mL/s followed by 50 mL of saline solution with the same injection rate to wash out the contrast material from the right ventricle. Contrast administration was controlled with bolus tracking. Scan parameters were: detec-

tor collimation, 32 × 0.6 mm; slice acquisition, 64 × 0.6 mm; gantry rotation time, 330 ms; temporal resolution, 83 ms; pitch, 0.2–0.47 adapted to the heart rate; tube current, 390 mAs per rotation; tube potential, 120 kV. Scanning time was 5.7–8.4 s, depending on the cardiac dimensions and pitch, in a single breathhold in the craniocaudal direction. Prospective ECG tube-current modulation (ECG pulsing) for radiation dose reduction was used for all patients. Retrospective gating technique was used to synchronize data reconstruction with the ECG signal. Best systolic and diastolic reconstructions were made in all patients at a slice thickness of 0.75 mm and a reconstruction increment of 0.5 mm. The reconstruction with the fewest motion artifacts was chosen and used for further analysis.

MSCT evaluation

All images were interpreted immediately after scanning by an experienced radiologist unaware of the clinical presentation of the patients. Coronary plaque was defined as any clearly discernible structure attributable to the coronary artery wall in at least two independent image planes. Non-significant coronary plaque was defined as lesions causing ≤ 50% luminal narrowing, and significant coronary plaque was defined as lesions causing > 50% luminal narrowing. All the coronary atherosclerotic plaques were included in the analysis. For categorization of the coronary plaques, the coronary system was divided into 16 separate segments based on a modified American Heart Association classification using original axial images, thin slice, maximal intensity projections, and cross-sectional reconstructions orthogonal to the long axis of each coronary segment (0.75 mm thickness) [8]. For each segment, coronary plaques were categorized as (1) none, (2) calcified (defined as a CT density more than the contrast enhanced coronary lumen), (3) non-calcified (defined as a CT density less than the contrast enhanced coronary lumen but greater than the surrounding connective tissue), (4) mixed (having both calcified and non-calcified components) [9]. The extent of coronary atherosclerosis was calculated as the sum of the affected coronary segments. All plaque components and significant stenosis were assessed per segment.

Statistical analysis

Continuous variables were expressed as mean ± SD and categorical variables were expressed as percentages. Comparisons of categorical and continuous variables between the two groups were performed using the χ^2 test and independent sam-

ples *t* test, respectively. Kruskal-Wallis test was used to compare differences in mean values between groups where there were three or more independent groups. To determine independent predictors of presence and severity of coronary atherosclerosis, multiple logistic regression analysis was performed by including the parameters, which were significantly different between the groups. Statistical analyses were performed using SPSS statistical software (version 15.0; SPSS Inc., Chicago, Illinois, USA). A two tailed *p* < 0.05 was considered statistically significant.

Results

Between January 2007 and June 2008, a total of 817 patients who were admitted to our cardiology department and underwent coronary MSCT angiography were enrolled in the study. Of these, 414 were male (50.7%), mean age ± SD 57.4 ± 11.6 years. Basal characteristics of the subjects are shown in Table 1. Among the study population,

Table 1. Basal clinical characteristics of patients enrolled in the study (n = 817).

Variable	Mean ± SD
Age (years)	57.5 ± 11.2
Gender (male)	414
Hypertension	66.2%
Diabetes mellitus	18.2%
Dyslipidemia	63.6%
Smoking	31.1%
History of premature CAD	9.3%
Total cholesterol [mg/dL]	207.6 ± 44.7
Triglyceride [mg/dL]	157.6 ± 82.9
HDL cholesterol [mg/dL]	51.4 ± 15.5
LDL cholesterol [mg/dL]	131.0 ± 38.5
BMI [kg/m ²]	27.9 ± 4.8
Total WBC count	7,438 ± 2,091
Framingham risk score:	
Low risk	41.9%
Intermediate risk	35.5%
High risk	23.3%
Acetylsalicylic acid	63.3%
Beta-blocker	36.4%
Calcium channel blocker	14.6%
ACE inhibitor	20.3%
Angiotensin receptor blocker	33.0%
Statins	47.0%

ACE — angiotensin converting enzyme; BMI — body mass index; CAD — coronary artery disease; HDL — high-density lipoprotein; LDL — low-density lipoprotein; WBC — white blood cells

66.2% had hypertension, 18.2% had diabetes mellitus, 63.6% had hyperlipidemia, 31.1% were smokers, and 9.3% had a history of premature CAD in their family.

An association between several cardiovascular risk factors including hypertension, diabetes mellitus, age, gender, hyperlipidemia, smoking and coronary atherosclerosis was found when patients were grouped into two categories according to the presence or absence of coronary atherosclerosis, as shown in Table 2 ($p < 0.05$).

Patients having coronary atherosclerosis in MSCT angiography had higher levels of serum leukocyte counts when compared to subjects lacking coronary atherosclerosis ($7,657 \pm 2,230$ vs $7,078 \pm 1,785$; $p < 0.001$, respectively). Additionally, patients having critical luminal stenosis detected by MSCT had higher levels of total WBC counts when compared to patients having coronary atherosclerosis but no critical luminal narrowing ($7,982 \pm 2,287$ vs $7,184 \pm 1,944$; $p < 0.05$). Thus severity of coronary atherosclerosis was also related to WBC counts.

In the multiple logistic regression analysis evaluating the relationship between WBC quartiles and the presence of coronary atherosclerosis detected by MSCT, patients were divided into quartiles, with each quartile having a similar number of subjects: 216, 199, 204 and 197. Leukocyte counts were $< 6,000$, $6,000-7,200$, $7,200-8,600$ and $> 8,600$ respectively. Although being in the 1st, 2nd or 3rd quartile caused no significant increase in the risk of the presence of coronary atherosclerosis detected by MSCT, being in the 4th quartile increased the risk of coronary atherosclerosis by 1.8 times (odds ratio [OR], 1.85; 95% confidence interval [CI], 1.15–2.96, $p < 0.005$). Apart from total WBC counts, diabetes mellitus, gender, hyperlipidemia, smoking

Table 3. Multivariate logistic regression analysis demonstrating the association between cardiovascular risk factors including total WBC counts and the presence of coronary plaque.

Variable	OR	95% CI	P
Age	1.09	1.07–1.11	< 0.001
Gender (male)	2.40	1.70–3.50	< 0.001
Hypertension	1.13	0.78–1.62	0.51
Diabetes mellitus	1.59	1.00–2.52	< 0.05
Smoking	1.16	0.80–1.69	< 0.05
Hyperlipidemia	2.14	1.53–3.00	< 0.05
WBC quartile 2	1.14	0.73–1.79	0.55
WBC quartile 3	1.16	0.74–1.82	0.49
WBC quartile 4	1.85	1.15–2.96	< 0.05

OR — odds ratio; CI — confidence interval; WBC — white blood cell

and age were found to be significantly associated with coronary atherosclerosis shown in logistic regression analysis (Table 3). When critical luminal stenosis was assumed, being in the 3rd or 4th quartile increased the risk of detection of critical luminal stenosis by 1.9 and 2.5 times, respectively. For the 3rd quartile: OR 1.9, 95% CI 1.2–3.0, $p < 0.005$; and for the 4th quartile: OR 2.5, 95% CI 1.6–4.0, $p < 0.005$ (Fig. 1). In addition to WBC quartiles, gender, hyperlipidemia, smoking and age were also found to be significantly associated with critical coronary plaque (OR 2.4, 95% CI 1.7–3.5, $p < 0.005$, OR 2.6, 95% CI 0.75–1.6, $p < 0.005$; OR 1.9, 95% CI 1.3–2.7, $p < 0.005$; OR 1.1, 95% CI 1.0–1.18, $p < 0.005$, respectively).

There was no relationship between the morphology of coronary plaques and WBC quartiles when plaque was classified as being exclusively calcified, non-calcified or mixed ($7,255 \pm 2,302$, $7,626 \pm 1,966$, $7,644 \pm 2,158$, $p = 0.42$, respectively) as shown in Figure 2. The extent of coronary atherosclerosis was

Table 2. Comparison of patients with coronary plaque to patients without coronary plaque shown by multislice computed tomography.

Cardiovascular risk factors	Coronary plaque (-) (n = 308)	Coronary plaque (+) (n = 509)	P
Hypertension (%)	56.0	72.3	< 0.001
Diabetes mellitus (%)	11.1	22.6	< 0.001
Hyperlipidemia (%)	50.2	71.7	< 0.001
Smoking (%)	25.4	34.4	< 0.05
Fx CAD (%)	9.4	9.2	0.92
Age	51.2 ± 11.3	61.0 ± 10.2	< 0.001
Gender (male) (%)	43.6	55.0	< 0.05
Total WBC count	$7,078 \pm 1,785$	$7,657 \pm 2,230$	< 0.001

CAD — coronary artery disease; Fx CAD — family history of premature CAD; WBC — white blood cell

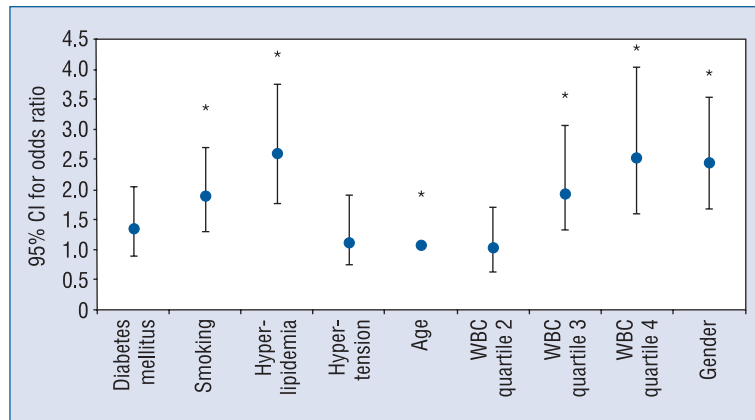


Figure 1. Association between the significant luminal stenosis and white blood cell (WBC) quartiles in multiple logistic regression analysis, showing that being in the 3rd or 4th quartile increases the risk of critical luminal stenosis detected by 1.9 and 2.5 times respectively with smoking, hyperlipidemia and age; *p < 0.05.

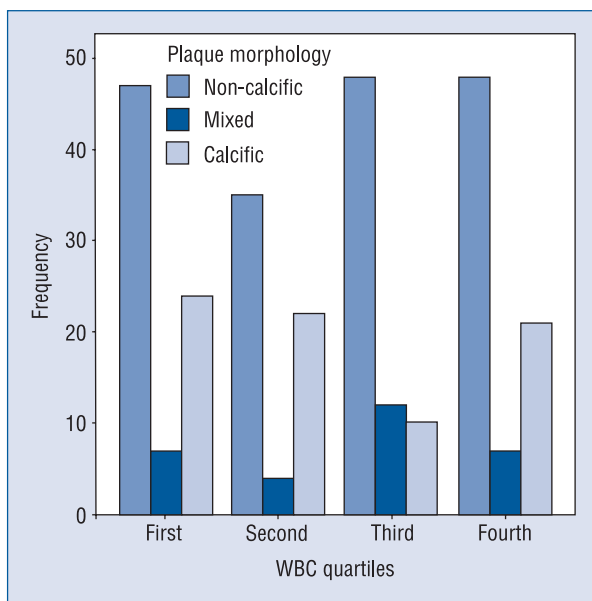


Figure 2. Frequency of plaque morphology according to total white blood cell (WBC) quartiles; p > 0.05.

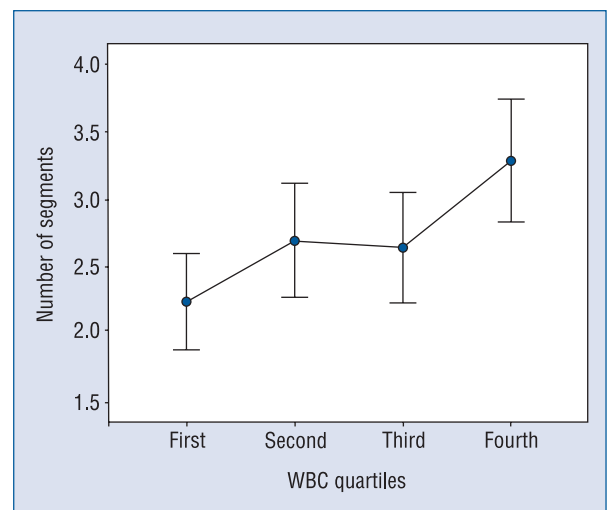


Figure 3. Association between total white blood cell (WBC) quartiles and extent of coronary atherosclerosis due to number of coronary segments involved (p = 0.006, Kruskal-Wallis test).

also investigated according to the number of coronary segments involved. Kruskal-Wallis analysis revealed an association between the number of coronary plaques involved and increasing WBC quartiles, except the 2nd and 3rd quartiles (Fig. 3).

Discussion

Previous studies have shown that a higher total WBC count is a risk factor for CAD [5, 10, 11]. To the best of our knowledge, this is the first study in the literature evaluating the relationship between

total WBC counts and coronary atherosclerosis detected by MSCT, a method evaluating not only luminal narrowing but also atherosclerosis at the coronary artery wall which could not be shown by conventional coronary angiography. Our study found that total WBC counts were independently associated with the presence and severity of coronary atherosclerosis apart from other well-known cardiovascular risk factors, and that this relationship persisted after adjustment for multiple cardiovascular risk factors.

Inflammation is a key feature of atherosclerosis and its clinical manifestations, and total WBC

count is a marker of inflammation that is widely available in clinical practice. Leukocytes affect the development of CAD through multiple mechanisms that mediate inflammation, cause proteolytic and oxidative damage to the endothelial cells, plug the microvasculature, induce hypercoagulability, and promote infarct expansion [3]. Stimulated neutrophils are known to secrete proteolytic neutral proteases, large amounts of chemotactic agents and inflammatory mediators in patients with stable angina [12].

Numerous epidemiological and clinical studies have shown leukocytosis to be an independent predictor of future cardiovascular events, both in healthy individuals free of CAD at baseline and in patients with CAD [13–16]. The role of a higher WBC count as a coronary risk factor was assessed in a case-control study of dyslipidemic middle-aged men participating in the Helsinki Heart Study which was a coronary primary prevention trial. Baseline leukocyte count was significantly higher in subjects with cardiovascular disease than in controls ($p < 0.002$) [17]. In a retrospective study by Takeda et al. [18] including the health-check records of 6,021 Japanese people without any cardiovascular disease, baseline leukocyte counts of patients with acute coronary syndrome were significantly higher than those of subjects without CAD ($9.21 \pm 2.70/\mu\text{L}$ vs $6.20 \pm 1.63/\mu\text{L}$, $p < 0.001$). The leukocyte count was strongly associated with the prognosis of patients who have had an myocardial infarction within the previous three months. Several experimental and pathological studies have suggested that leukocytes play an important role in the destabilization of coronary artery plaques and in causing acute coronary syndrome initiation [19, 20]. Additionally, the blood leukocyte count has important implications regarding the prognosis of CAD. In the TACTICS–TIMI-18 (Treat Angina with Aggrastat Plus Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction-18) trial, among patients with unstable angina or non-ST-segment elevation myocardial infarction, higher baseline WBC counts were associated with poorer reperfusion, more extensive CAD, and higher six-month mortality [21].

Our study found a correlation between coronary atherosclerosis documented by MSCT and total WBC counts, in a population suspected of having, but without a previous history of, CAD. Besides the presence of coronary plaque, total WBC counts were also associated with the severity and extent of coronary atherosclerosis. This may be an important finding when the progression of inflam-

matory process evolving from non-critical plaque to critical stenosis due to atherosclerosis is considered. In a study investigating the relationship between blood leukocyte counts and subclinical atherosclerosis due to carotid intima-media thickness by Loimaala et al. [22], higher blood leukocyte count was associated with carotid artery wall thickening in middle-aged Finnish men, supporting the hypothesis that leukocytes play an independent role in early vascular injury and atherogenesis. Therefore our results are compatible with the role of blood leukocyte counts in the atherosclerotic process.

The relationship between coronary artery calcification and traditional cardiovascular risk factors has been documented in previous reports [23]. Some have also suggested that non-calcified coronary plaques detected by MSCT were associated with acute coronary syndrome compared to calcified plaques [24, 25]. In our study, the relationship between the morphology of atherosclerotic plaque and total WBC counts was also investigated, but coronary plaque morphology was not found to be associated with WBC quartiles. This may be due to the risk profiles and population characteristics of the patients enrolled in the study, as well as to the association of WBC counts with coronary atherosclerosis irrespective of plaque morphology.

The main strength of our paper is that it is the first report about the relationship between an inflammatory marker, total WBC, and coronary atherosclerosis shown by MSCT which can demonstrate early morphologic changes before clinical presentation. However, the usefulness of total WBC count as a surrogate marker for atherosclerosis has some limitations. Firstly, although the study population is free from documented CAD, this cohort has higher risk factors compared to the normal population, as stated previously, because of being a selected group of patients admitted for CAD evaluation. Secondly, this is a cross-sectional study and the aim was to assess the association between leukocyte count and coronary atherosclerosis. Therefore the prognostic role of total WBC counts was not investigated. Thirdly, because of racial differences between the prevalence and extent of coronary atherosclerosis, these findings cannot be extrapolated to all populations [26]. Finally, biochemical analysis did not include more precise markers of inflammation and the analysis of plaque morphology was limited by only one feature of the plaque architecture, i.e. calcification, assessed by MSCT. It is still open to debate whether thin fibrous cap, large lipid core or extent of plaque vascularization correlate with WBC count and other signs of inflammation.

Conclusions

To summarize, because higher blood leukocyte count was shown to be an independent risk factor and prognostic indicator of future cardiovascular outcomes, the association between higher total WBC counts and the presence, severity and extent of coronary atherosclerosis was confirmed in this study. Because aggressive risk modification may be beneficial in this subset of patients, further follow-up studies are needed to clarify the role of inflammatory markers and total WBC counts as a risk factor for atherosclerosis.

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