White blood cell count is related to arterial pressure and cholesterolemia in normal children

Vincenzo Capuano, Antonella Bambacaro*, Teodora D'Arminio*, Gianfranco Mazzotta**

*Division of Cardiology-ICCU, Hospital Mercato S. Severino ASL 2 (SA), *Research Center of Campania, Pellezzano (SA), **Cardiology Unit, E.O. Ospedali Galliera, Genoa, Italy*

Key words:
Platelets; Prevention; White blood cells.

Background. **Epidemiological studies have shown a relation between the white blood cell (WBC) count in peripheral blood samples and other cardiovascular risk factors in adult populations. The aim of this study was to investigate for the first time in children the relation between WBC count and patterns of atherogenic risk.**

Methods. **We studied a southern Italian cohort of 1171 children (568 males, 603 females, mean age 10.8 ± 0.06 years) from the fifth elementary classes in Salerno, Italy. This study is included in the screening of scholastic medicine.**

Results. **The WBC count was significantly associated with cholesterolemia ($p < 0.03$), systolic ($p < 0.03$) and diastolic blood pressure ($p < 0.02$), and platelet count ($p < 0.01$). Multivariate regression analysis demonstrated an independent, positive, and significant association of WBC count with the number of platelets, cholesterol levels and diastolic pressure.**

Conclusions. **Even in children, there is a relation between the WBC count and other factors linked with the atherogenic risk. The meaning and the clinical importance of such an association remains to be cleared and it is thus premature to consider 11-year-old children as being at higher cardiovascular risk. An answer to this question might come from follow-up studies of our as well as of other similar cohorts.**

(Ital Heart J 2001; 2 (9): 685-689)

Received March 21, 2001; revision received June 6, 2001; accepted June 25, 2001.

Address:
Dr. Vincenzo Capuano
Via Fontanelle, 30
84080 Coperchia (SA)
E-mail:
capuanov@tiscalinet.it

Introduction

A relation between the white blood cell (WBC) count in peripheral blood and future cardiovascular events is well demonstrated[1-6]. Such a relation has been shown in a population of diabetics too[7], and some investigations have also provided answers on the physiological mechanisms underlying it[8-10]. Even if most of the attention has been focused on the role of WBC during an acute ischemic attack, other investigations have described a relation between WBC count and cardiovascular risk factors in normal volunteers[11-13].

Hypertension[6,13,14] and hypercholesterolemia[5,6,13,15] are linked with WBC count, and this suggests that WBC might play an important role not only during attacks, but also in the development and evolution of the atheroma itself.

This correlation was emphasized in epidemiological studies on adult American[11,12,14] and European[13] populations, but never verified in children.

In the present study we have evaluated, in a population of children, the relation between the WBC count in peripheral blood and some of the traditional cardiovascular risk factors: blood cholesterol, triglyceride levels, glucose concentration, body mass index, and systolic and diastolic blood pressure.

Methods

Between September 1998 and April 1999, 1171 children from the fifth elementary classes in the city of Salerno (568 males, 603 females, mean age 10.8 ± 0.06 years) were studied. This investigation is included in the screening of scholastic medicine. The drawing of blood samples was authorized by the children's parents. Every child underwent physical examination, measurement of blood pressure, weight, height and evaluation of body mass index (calculated as the ratio between weight in kg and height in m^2). Fasting venous blood samples were obtained to determine blood counts, plasma glucose, total cholesterol, triglyceride and urea levels. Cuff blood pressure was measured with a mercury manometer following World Health Organization criteria[16]. We measured it twice, the first value being obtained after at least 5 min of relaxed waiting, and we considered the mean of the two determinations.

Blood concentrations of cholesterol, triglycerides, urea and plasma glucose were assessed by an enzyme method installed on a Cobas Mira (Roche Diagnostics, Milan, Italy) automatic line. The blood count was measured on a sample of whole venous blood by automated standard procedures (Cell Dyn 3000); the WBC count is expressed in cells/dl.

Statistical analysis. Correlation coefficients between the WBC count and each of the other variables were assessed by the Pearson correlation matrix. Multivariate regression analysis was performed to determine which, if any, of the variables measured were significantly and independently correlated with the WBC count.

Results

Table I shows the mean values of the examined variables and related percentiles. The values of blood pressure are in accordance with those of a large American population of children[17].

Correlation matrix analysis (Table II) shows a significant statistical correlation between WBC count and the number of platelets ($p < 0.01$), cholesterolemia ($p < 0.03$), and systolic ($p < 0.03$) and diastolic blood pressure ($p < 0.02$). No correlation was found between the WBC count and the other examined variables (body mass index, red blood cell count, hematocrit, blood iron, hemoglobin, and ferritin, plasma glucose, triglyceride and uric acid levels).

Multivariate regression analysis demonstrated a positive and independent association between WBC and platelet count, cholesterol levels and diastolic blood pressure (Table III).

Discussion

Recently, several studies have elucidated the interaction between the WBC count and each of the other cardiovascular risk factors, suggesting a key role of WBC in the development of atherosclerosis[18,19]. In normal volunteers who participated in large population studies, a positive association has been reported between the WBC count and each of the following: smoking[5,6,13,20,21], cholesterol level[5,6,13,15], hypertriglyceridemia[12,13,22], hyperglycemia[13,22], insulin levels[22], and systemic blood pressure[6,13,14]. A negative relation has been shown between the WBC count and HDL cholesterol[6,11,12].

The relation between the WBC count and each of the other cardiovascular risk factors has been demonstrated not only for the population at large, but also in patients with hypercholesterolemia[23] and hypertension[24]. All these studies were undertaken in adults, while we are showing, for the first time in children, a significant correlation between the WBC count and some other cardiovascular risk factors: platelet count, arterial blood pressure, and cholesterolemia.

White blood cell count and systemic hypertension. The relation between the WBC count and hypertension has been well demonstrated by previous investigations

Table II. Correlation coefficients between white blood cell count and other variables.

Variable	r	p
Body mass index	0.01	NS
Red blood cells	0.05	NS
Sideremia	0.06	NS
Hemoglobin	0.07	NS
Hematocrit	0.03	NS
Ferritin	0.07	NS
Platelets	0.21	< 0.01
Plasma glucose	0.01	NS
Cholesterol	0.18	< 0.01
Triglycerides	0.07	NS
Uric acid	0.05	NS
Systolic blood pressure	0.16	< 0.03
Diastolic blood pressure	0.17	< 0.02

Table III. Correlation between leukocyte count and the other variables at multiple linear regression analysis.

Variable	β	p
Platelets	0.203387	0.005
Cholesterol	0.124662	0.008
Systolic blood pressure	0.089729	0.32
Diastolic blood pressure	0.150961	0.003

Table I. Mean ± standard deviation (SD) of examined variables and proper percentiles.

Variables	Mean ± SD	Percentiles		
		10°	50°	90°
Cholesterol (mg/dl)	174.5 ± 26.8	137	171.5	213
Triglycerides (mg/dl)	83.3 ± 41.6	45	72.5	137.5
Plasma glucose (mg/dl)	88.4 ± 9.6	76.5	86.5	101.5
Systolic blood pressure (mmHg)	112.9 ± 13.9	92	109.5	124
Diastolic blood pressure (mmHg)	73.4 ± 9.5	59	71	83.9
Body mass index (kg/m^2)	18.7 ± 3.7	15.4	19.6	24.2

which are summarized in table IV[6,11,13,14,22,25,26]. Two important epidemiological investigations, the CARDIA[11] and Framingham[6] studies, have emphasized this association in North American populations. Afterwards, similar data were observed in European[13] and African[25] populations. In patients with ischemic heart disease or diabetes mellitus or hypertension, Jackson et al.[27] demonstrated that the neutrophil count and neutrophil elastase levels were significantly higher compared to controls. Friedman et al.[14] were probably the first authors to demonstrate that a high WBC count may represent a risk factor for the subsequent development of hypertension.

It has been hypothesized that two biological mechanisms, which may coexist, explain the relation between WBC and hypertension: an increase in sympathetic tone that may increase the WBC count, and the occlusion of peripheral arterial districts by leucocytes, with increasing peripheral resistance. A more recent study has demonstrated the presence of preactivated peripheral blood monocytes in hypertensive patients. Angiotensin II may be directly involved in the process of monocyte activation[28]. In children, the relation between the WBC count and hypertension may be explained by similar biological mechanisms.

There is also evidence of a relation between WBC and hypertension in animals. It has been assessed that spontaneously hypertensive rats and Dahl-hypertensives have a significant increase in the number of spontaneously activated neutrophils and monocytes in the pool of circulating WBC[29].

It is worth noting that corticosteroids seem to be able to cause hypertension, increase the WBC count, and augment the level of leukocyte activation in rats. Suzuki et al.[30] have demonstrated that in spontaneously hypertensive rats, following bilateral adrenalectomy, not only was the arterial blood pressure reduced to almost normotensive levels, but there also was a decrease in the number of activated neutrophils in the circulation.

White blood cell count and cholesterol: a key interaction for the development of the atheroma? In the Framingham cohort, an association between the WBC count and cholesterolemia has been found[15]. This observation was then confirmed in more recent studies on adult populations[5,6,13]. This correlation suggests that a high WBC count may predict a metabolic profile at risk for atherogenesis. Given the link between insulin resistance and both hypertension[31] and ischemic heart disease[32], the relations between the WBC count and both hypertension and hypercholesterolemia may depend on insulin resistance[22].

In the absence of any clear sign of an active inflammatory process, an increase in the WBC count may be regarded as a sign of active atherogenesis. Monocyte infiltration inside the vessel wall is a precocious and crucial event in the evolution of inflammation and atherogenesis[33,34]. The interaction between leukocytes and endothelial cells is of fundamental importance in the modulation of the inflammatory process, in particular the reaction of monocytes, macrophages, and WBC recruitment itself[35,36].

Recent studies have attributed other more complex roles and interactions to WBC in the context of endocrine syndromes (insulin resistance, increase in glucocorticoid levels)[22,30-32,37] that, in turn, may be one of the causes of the atherosclerotic process.

The association, shown by Leeson et al.[38], between WBC and both cholesterol levels and hypertension is particularly important. They have demonstrated that LDL cholesterol levels have an impact on the arterial elasticity in the first decade of life. Furthermore, in normal children, functional differences depending on the lipid range were demonstrated in the arterial wall, a finding that raises the possibility that cholesterol levels during childhood might be relevant for the development of vascular disease[38]. The implications of these relations, particularly in children, are still unclear and need to be defined better by future investigations. An answer may derive, in the near future, from careful follow-up of cohorts of children, similar to the one we have studied and that for the first time showed a link between WBC counts and risk factors at 11 years of age.

White blood cell count and platelets. Leukocyte accumulation in a platelet thrombus can contribute to further platelet activation and deposition. These events may play a pathogenic role in inflammatory and thrombotic disease[39]. Several experimental studies indicate that platelets either adherent to a surface or activated in

Table IV. Studies demonstrating the relation between white blood cell count and systemic blood pressure.

Author	Year	Study	Population
Friedman et al.[14]	1990	Case-control	2062 American
Friedman et al.[11]	1990	Cohort	4901 American
Kannel et al.[6]	1992	Cohort, Framingham study	2794 American
Facchini et al.[22]	1992	Cohort females	63 American
Sigola et al.[25]	1992	Case-control males	41 Zimbabwean
Gillum and Mussolino[26]	1994	Epidemiologic Follow-up	6456 American
Capuano et al.[13]	1995	Cohort PMR Project	1091 Italian

suspension have an extraordinary efficacy in capturing flowing leukocytes[39].

The physiological relevance of leukocyte deposition on activated platelets within the circulating blood or of leukocyte adherence at the site of vascular damage is still unknown[40].

Activated platelets at the site of an unstable plaque may be unable to produce a full vascular occlusion, but might be the initial trigger of a localized leukocyte-dependent inflammatory response[39]. Platelet-polymorphonuclear leukocyte interaction contributes to the increased production of vasoactive metabolites, such as thromboxane A_2 and leukotriene C_4[41] and may damage endothelial cells and impair the endothelium-dependent fibrinolytic response[42].

Platelet-polymorphonuclear leukocyte interaction, as well as the consequent polymorphonuclear leukocyte activation, may be an essential part of this inflammatory response, and might represent a new parameter in the prediction of the risk and monitoring of the severity of ischemic disease[40]. Epidemiological data about the correlation between WBC and platelet counts do not exist. The implications of our results, showing such an association in so young a population, cannot be fully understood at present.

Conclusions. Considering the link between the WBC count and cardiovascular events, several open questions on the relations between WBC and atherosclerosis, insulin resistance and hypertension still remain to be answered[1-6,43]. In the present investigation, we are confirming, for the first time in children, the relation between WBC count and patterns of atherogenic risk.

Giving an explanation of this relation in a population of children seems impossible at present, and it is difficult to suggest that the WBC count taken at this age could identify groups at different cardiovascular risk. In the light of our study, it might be hypothesized that: 1) the same mechanisms underlying the correlation between WBC and hypertension in adults are present in children too; 2) the WBC number is not only a sign of inflammation in the atherosclerotic process, but might also be an independent risk factor for cardiovascular diseases. Follow-up data are necessary in order to assess whether the WBC count can identify, since childhood, those subpopulations who are at higher risk.

References

1. Friedman GD, Klatsky AL, Siegelaub AB. The leukocyte count as a predictor of myocardial infarction. N Engl J Med 1974; 290: 1275-8.
2. Zalokar GB, Richard JL, Claude JR. Leukocyte count, smoking and myocardial infarction. N Engl J Med 1981; 304: 465-8.
3. Grimm RH, Neaton JD, Ludwig W. Prognostic importance of the white blood cell count for coronary, cancer, and all cause mortality. JAMA 1985; 254: 1932-7.
4. De Labry LO, Campion EW, Glynn RJ, Vokonas PS. White blood cell count as a predictor of mortality: results over 18 years from the Normative Aging Study. J Clin Epidemiol 1990; 43: 153-7.
5. Yarnell JWG, Baker IA, Sweetnam PM, et al. Fibrinogen, viscosity, and white blood cell count are major risk factors for ischemic heart disease: the Caerphilly and Speedwell Collaborative Heart Disease Studies. Circulation 1991; 83: 836-44.
6. Kannel WB, Anderson K, Wilson PWF. White blood cell count and cardiovascular disease. JAMA 1992; 267: 1253-6.
7. Saito I, Folsom AR, Brancati FL, Duncan BB, Chambless LE, McGovern PG. Nontraditional risk factors for coronary heart disease incidence among persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. Ann Intern Med 2000; 133: 81-91.
8. Ernst E, Hammerschmidt DE, Bagge U, Matrai A, Dormandy JA. Leukocytes and the risk of ischemic diseases. JAMA 1987; 257: 2318-24.
9. Metha JL, Nichols WW, Metha P. Neutrophils as potential participants in acute myocardial ischemia: relevance to reperfusion. J Am Coll Cardiol 1988; 11: 1309-16.
10. Shandelya SML, Kuppusamy P, Weisfeldt ML, Zweier JL. Evaluation of the role of polymorphonuclear leukocytes on contractile function in myocardial reperfusion injury. Circulation 1993; 87: 536-46.
11. Friedman GD, Tekawa I, Grimm RH, Manolio T, Shannon SG, Sidney S. The leukocyte count: correlates and relationship to coronary risk factors: the CARDIA study. Int J Epidemiol 1990; 19: 889-93.
12. Hansen LK, Grimm RH Jr, Neaton JD. The relationship of white blood cell count to other cardiovascular risk factors. Int J Epidemiol 1990; 19: 881-8.
13. Capuano V, Lamaida N, De Martino M, Mazzotta G. Association between white blood cell count and risk factors of coronary artery disease. G Ital Cardiol 1995; 25: 1145-52.
14. Friedman GD, Selby JV, Quesenberry CP Jr. The leukocyte count: a predictor of hypertension. J Clin Epidemiol 1990; 43: 907-11.
15. Wilson PWP, Garrison RJ, Abbott RD, Castelli WP. Factors associated with lipoprotein cholesterol levels: the Framingham study. Atherosclerosis 1983; 3: 273-81.
16. Rose GA, Blackburn H. Cardiovascular survey methods. Geneva: WHO, 1968.
17. National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents. Update on the 1987 Task Force report on high blood pressure in children and adolescents: a Working Group report from National High Blood Pressure Education Program. Pediatrics 1996; 98: 649-58.
18. Ross R. Atherosclerosis - an inflammatory disease. N Engl J Med 1999; 340: 115-26.
19. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA 1998; 279: 1477-82.
20. Howell RW. Smoking habits and laboratory tests. Lancet 1970; 2: 152.
21. Corre F, Lellouch J, Schwartz D. Smoking and leukocyte-counts: results of an epidemiological survey. Lancet 1971; 2: 632-4.
22. Facchini F, Hollenbeck CB, Chen YD, Reaven GM. Demonstration of a relationship between white blood cell count, insulin resistance, and several risk factors for coronary heart disease in women. J Intern Med 1992; 232: 267-72.

23. Manttari M, Manninen V, Koskinen P, et al. Leukocytes as a coronary risk factor in a dyslipidemic male population. Am Heart J 1992; 123: 873-7.
24. Capuano V, Lamaida N, Mazzotta G, Scotto di Quacquaro G. Relation between white blood cell count and several risk factors for coronary heart disease in patients with systemic hypertension. G Ital Cardiol 1998; 5: 530-5.
25. Sigola LB, Adewuyi JO, Mufunda J. Plasma fibrinogen levels, leukocyte and platelet counts in male Zimbabwean hypertensives. Centr Afr J Med 1992; 38: 447-50.
26. Gillum RF, Mussolino ME. White blood cell count and hypertension incidence. The NHANES I Epidemiologic Follow-up Study. J Clin Epidemiol 1994; 47: 911-9.
27. Jackson MH, Collier A, Nicoll JJ, et al. Neutrophil count and activation in vascular disease. Scott Med J 1992; 37: 41-3.
28. Dorffel Y, Latsch C, Stuhlmuller B, et al. Preactivated peripheral blood monocytes in patients with essential hypertension. Hypertension 1999; 34: 113-7.
29. Schmid-Schonbein GW, Seiffge D, DeLano FA, Shen K, Zweifach BW. Leukocyte counts and activation in spontaneously hypertensive and normotensive rats. Hypertension 1991; 17: 323-30.
30. Suzuki H, Zweifach BW, Forrest MJ, Schmid-Schonbein GW. Modification of leukocyte adhesion in spontaneously hypertensive rats by adrenal corticosteroids. J Leukoc Biol 1995; 57: 20-6.
31. Reaven GM. Insulin resistance and compensatory hyperinsulinemia: role in hypertension, dyslipidemia, and coronary heart disease. Am Heart J 1991; 121: 1283-8.
32. Stout RW, Vallance-Owen J. Insulin and atheroma. Lancet 1979; i: 1078-80.
33. Faruqi RM, DiCorleto PE. Mechanisms of monocyte recruitment and accumulation. Br Heart J 1993; 69 (Suppl): S19-S29.
34. Beekhuizen H, van Furth R. Monocyte adherence to human vascular endothelium. J Leukoc Biol 1993; 54: 363-78.
35. Takahashi M, Kitagawa S, Masuyama JI, et al. Human monocyte-endothelial cell interaction induces synthesis of granulocyte-macrophage colony-stimulating factor. Circulation 1996; 93: 1185-93.
36. Gaboury JP, Niu XF, Kubes P. Nitric oxide inhibits numerous features of mast cell-induced inflammation. Circulation 1996; 93: 318-24.
37. Reed JP, Hendley ED. Blood cell changes in spontaneously hypertensive rats are not all associated with the hypertensive phenotype. J Hypertens 1994; 12: 391-9.
38. Leeson CM, Whincup PH, Cook DG, et al. Cholesterol and arterial distensibility in the first decade of life. Circulation 2000; 101: 1533-8.
39. Cerletti C, Evangelista V, de Gaetano G. P-selection-β_2-integrin cross-talk: a molecular mechanism for polymorphonuclear leukocyte recruitment at the site of vascular damage. Thromb Haemost 1999; 82: 787-93.
40. de Gaetano G, Evangelista V, Cerletti C. Should cardiologists forget about platelets and take an interest in blood leukocytes? Ital Heart J 2000; 1: 453-6.
41. Maugeri N, Evangelista V, Celardo A, et al. Polymorphonuclear leukocyte-platelet interaction: role of P-selectin in thromboxane B_2 and leukotriene C_4 cooperative synthesis. Thromb Haemost 1994; 72: 450-6.
42. Pintucci P, Iacoviello L, Castelli MP, et al. Cathepsin G-induced release of PAI-1 in the culture medium of endothelial cells: a new thrombogenic role for polymorphonuclear leukocytes? J Lab Clin Med 1993; 122: 69-79.
43. Prentice RL, Szatrowsky TP, Fujikura T, Kato H, Mason MW, Hamilton HH. Leukocyte count and coronary heart disease in a Japanese cohort. Am J Epidemiol 1982; 116: 496-506.