Journal of Clinical Immunology, Vol. 14, No. 6, 1994

Factors Influencing Serum Neopterin and β2-Microglobulin Levels in a Healthy Diverse Population

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Accepted: July 19, 1994

Sera and questionnaire data from a population-based random sample of healthy adults was used to evaluate factors influencing neopterin and β2-microglobulin (β2m) values. Both neopterin and β2m levels increased with age and were higher among white than blacks (mean values for whites and blacks: neopterin, 5.06 vs 4.49 nmol/L; β2m, 1.36 vs 1.28 mg/L). Gender differences were noted for β2m but not neopterin values (β2m males vs females: 1.37 vs 1.29 mg/L). Neopterin values were lower among current smokers than among nonsmokers (4.32 vs 5.16 nmol/L) and were higher among users of antihistamines (5.46 among users vs 4.65 nmol/L among nonusers). Neopterin and β2m were correlated in this healthy adult population (adjusted $r = 0.53$, $P = 0.001$), yet no other interrelationships with numerous biologic markers except between β2m and serum-soluble interleukin-2 receptor levels (adjusted $r = .41$, $P = 0.05$) were observed. These findings provide important baseline information to consider before planning or evaluating studies utilizing neopterin or β2m levels.

KEY WORDS: Neopterin; β2-microglobulin; immunology; biological markers.

INTRODUCTION

Neopterin and β2-microglobulin (β2m) are among the immunologic biomarkers that have been identified as clinically useful predictors of human immunodeficiency virus (HIV) disease progression, cancer or lymphoproliferative disease progression, and transplant rejection (1–13). As a result, measurement of one or both of these molecules has been strongly advocated in clinical and epidemiological studies of AIDS and HIV infection (14–17). Such investigations are increasingly focused on preclinical disease, creating an urgent need for basic information on neopterin and β2m levels in normal subjects. Unfortunately, information on serum neopterin and β2m values in healthy, heterogeneous populations is very limited. In particular, little is known about ethnic differences and the influence of common, exogenous, or environmental exposures. Age, sex, race, and cigarette smoking, for example, have all been shown to influence other widely used immunological parameters such as T-cell subsets, immunoglobulins, and soluble interleukin-2 receptor (sIL-2r) levels (18, 19). Limited data suggest an age-related increase in neopterin levels (20, 21), but a population-based analysis of normal values by gender and race has not been reported.

The objective of this study was to establish normal ranges of serum neopterin and β2m values in a population-based stratified random sample of healthy adults. The extensive epidemiological and immunological database on this population also allowed us to evaluate the influence of common "environmental" stimuli and the relationship between neopterin and β2m levels and other immune biomarkers.

METHODS

Study Population. Neopterin and β2m levels were measured in serum from a population-based

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0271-9142/94/1100-0368$07.00/0

stratified random sample of healthy adults in the greater Washington, DC, metropolitan area (22). Briefly, random digit dialing and a short screening questionnaire were used to identify a random sample of adults stratified by age, race, gender, and smoking status. Subjects who described themselves as "white" or "black, not of Hispanic origin" were asked to enroll in the study. Individuals from other minority groups were excluded due to the small numbers predicted from U.S. Census records. Potential participants were screened to exclude individuals with lifestyle characteristics (intravenous drug use, homosexual activity) or medical conditions (blood product transfusion since 1975, recent hospitalization, severe allergies, use of steroid medications, history of connective tissue disease, or recent pregnancy) which might affect or be surrogates of effects on immunologic parameters under investigation.

Questionnaire. The questionnaire data used for this analysis included demographic characteristics (age-decade, gender, race, years of education, current employment status, and marital status), current and past smoking habits, medical conditions, and use of medications. Subjects were categorized as "never smokers" (smoked less than one pack of cigarettes during lifetime), "ex-smokers" (previously smoked cigarettes but quit smoking prior to phlebotomy), and "current smokers" (smoked cigarettes at the time of interview and phlebotomy). In analyses where exsmokers and never smokers were similar, they were combined as "nonsmokers." Number of cigarettes smoked per day, duration of smoking, age started and stopped smoking, type of cigarettes smoked (filtered, nonfiltered, or both), and use of other forms of tobacco were also examined. Medical conditions and current medication use were obtained by questionnaire at the time of phlebotomy. Self-reported conditions and current medications used by at least 10% of the sample population were also analyzed, including "hay fever" or "flu" in the last 30 days or 24 hr, arthritis or hypertension diagnosed by a physician, nonprescription antihistamines or sympathomimetics, analgesics other than nonsteroidal antiinflammatory medications (NSAIDs), and NSAIDs.

Immunological Assays. Blood was collected in evacuated tubes and allowed to clot. The serum was separated by centrifugation, divided into 1.0-ml aliquots, frozen, and stored in a liquid nitrogen freezer until withdrawn for analysis. Neopterin was measured by a commercial radioimmunoassay (Neopterin RIAcid; Henning-Berlin, Berlin). Serum β2m was measured using a commercial double-antibody radioimmunoassay (Beta-2-micro RIA; Pharmacia, Uppsala, Sweden). Serum sIL-2R concentrations were measured by a sandwich enzyme-linked immunosorbent assay (ELISA) as described previously (23). Frozen serum samples for immunoglobulins were shipped, on dry ice, to a commercial laboratory (Metpath, Inc., Rockville, MD) for analysis by nephelometry.

For mononuclear cell subset analyses, blood samples were drawn into preservative-free heparin. Peripheral blood mononuclear cells were separated by Ficoll–Hypaque density-gradient centrifugation, washed, counted, and resuspended in modified RPMI 1640 medium. Aliquots of 10 million cells were cryopreserved in dimethylsulfoxide (DMSO) using controlled-rate freezing and stored in liquid nitrogen until needed for flow cytometry analysis. For these assays, directly fluorescein-conjugated monoclonal antibody, OKT4A (CD4+ helper-inducer T-cell subset; Ortho Diagnostics, Raritan, NJ), OKT8 (CD8+ suppressor–cytotoxic T-cell subset; ORTHO), anti-Leu 12 (CD19+ B cells; BD), anti-Leu M3 (CD14+ monocytes; BD), anti-Leu 11A (CD16+ natural killer cells; BD), anti-HLA-DR (nonpolymorphic HLA-DR antigen; BD), and mouse IgG1 (clone 11-63; BD) and IgG2 (a+b) (clones 11-4.1 and MPC-11; BD) as negative control reagents were utilized as previously described (24). Cells were directly stained, then analyzed on a FACS II cell sorter (Becton Dickinson, Mountain View, CA) interfaced to a PDP 11/24 DEC computer (Digital Equipment Corporation, Landover, MD). All samples were analyzed blinded to questionnaire data and in random order.

Statistical Analysis. Relationships between the laboratory markers and the questionnaire data were examined with generalized linear models using a least-squares method. A Gaussian distribution for both neopterin and β2m was approximated with a log-transformation. All effects were considered fixed. The arithmetic (untransformed) means and standard errors of neopterin and β2m were presented for each of the factors examined (25). Significant differences in neopterin and β2m levels by the variables examined were determined by type III sums of squares, with P values computed at the $\alpha = 0.05$ level (26). Spearman rank correlations were used to evaluate associations between selected biomarkers (27). Analyses were performed using Statistical Analysis Software (SAS Institute, Cary, NC).

Table I. Mean Neopterin and β2-Microglobulin Levels: Healthy Adults

		Neopterin (nmol/L)[a]		β2-Microglobulin (mg/L)[a]	
	n	Mean ± SE	*P*	Mean ± SE	*P*
Age			0.01[b]		
0.0001[c]					
20–29	93	4.41 ± 0.14		1.19 ± 0.03	
30–39	118	4.66 ± 0.15		1.21 ± 0.03	
40–49	90	4.80 ± 0.14		1.36 ± 0.03	
50–59	77	5.31 ± 0.22		1.44 ± 0.05	
60–69	60	5.31 ± 0.21		1.60 ± 0.05	
Gender			[d]		0.003[c]
Males	233	4.79 ± 0.10		1.37 ± 0.02	
Females	205	4.88 ± 0.11		1.29 ± 0.02	
Race			0.0004[b]		0.01[c]
Whites	268	5.06 ± 0.09		1.36 ± 0.02	
Blacks	170	4.49 ± 0.12		1.28 ± 0.03	
Smoking status			0.0001[b]		[d]
Never/ex	258	5.16 ± 0.10		1.33 ± 0.02	
Current	180	4.32 ± 0.15		1.33 ± 0.03	
Antihistamines			0.004[b]		[e]
No	335	4.65 ± 0.09		1.31 ± 0.02	
Yes	103	5.46 ± 0.15		1.40 ± 0.04	

[a]Means are marginal arithmetic means. *P* values are derived from the generalized linear model with fixed effects, with log-normal transformation of neopterin and B2-M values.
[b]Adjusted age-decade, race, smoking status, flu, and antihistamines.
[c]Adjusted for age-decade, gender, and race.
[d]Unadjusted *P* value > 0.1
[e]Adjusted *P* value > 0.1.

RESULTS

Demographic Characteristics. The study population consisted of 455 adults aged 20–69 years. Nineteen subjects were excluded from these analyses: 15 (3%) did not have both neopterin and β2m values and 4 subjects had extreme outlier values of either neopterin or β2m.

Women comprised 47% and blacks 39% of the study sample. Both neopterin and β2m values increased significantly with age (Table I). Mean neopterin levels increased by 20% and β2m by 34% among subjects between 20 and 69 years of age. There was no relationship between gender and neopterin values; however, β2m values were significantly higher among men than women (Fig. 1). Both neopterin and β2m values were higher among whites than blacks. These differences were more striking for neopterin, with higher mean neopterin values for each age group (Fig. 2).

Smoking Status. The study sample consisted of 165 (36%) subjects that never used any form of tobacco. Among the subjects that smoked cigarettes, 55 (12%) were ex-smokers and 149 (34%) were current smokers. There were an additional 34 (8%) subjects that were previous and 31 (7%) subjects that were current users of other forms of tobacco (smokers of cigars or pipes or tobacco chewers) and 4 (1%) subjects whose smoking status could not be determined.

No significant differences in neopterin or β2m levels were noted between subjects who *never* and those who *previously* used any form of tobacco; therefore, ex-smokers and never smokers were combined in this analysis. Mean neopterin levels were significantly lower among current smokers than among nonsmokers (4.32 vs 5.16 nmol/L) after adjusting for age and race effects. In contrast, β2m levels were similar in current smokers and nonsmokers. Smoking frequency and duration were not significantly related to neopterin levels.

Common Medications. Only current use of antihistamines, sympathomimetics, nonsteroidal antiinflammatory drugs (NSAIDs), and non-NSAID analgesics were reported by at least 10% of the study sample. Among these medications, current users of antihistamines had significantly higher mean levels of neopterin than did subjects who did not use antihistamines (5.46 vs 4.65), which remained significantly higher after adjustment for age, race, and smoking status ($P = 0.004$). Both neopterin and β2m levels appeared to be higher among users of analgesics, but these effects were not independent of demographic characteristics. Mean levels of the markers also did not differ by NSAID use.

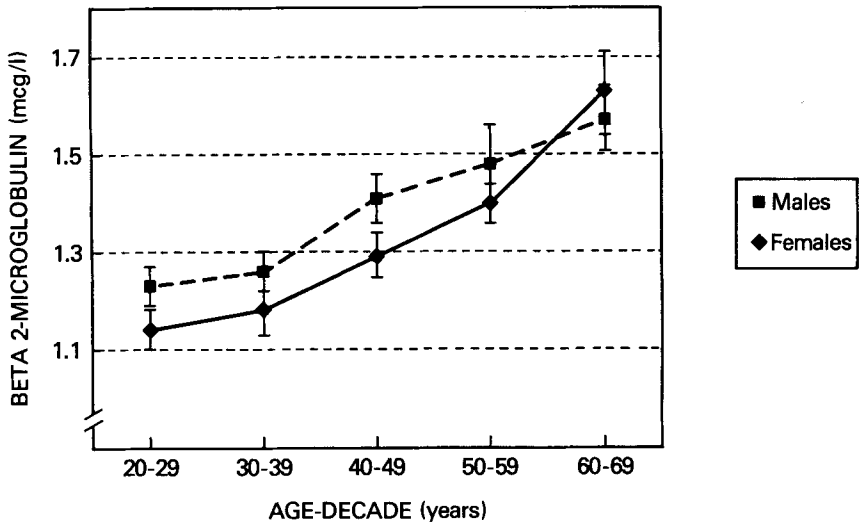

Fig. 1. β2-Microglobulin levels by age-decade and gender: means and SE.

Common Medical Conditions. Medical conditions that were reported by at least 10% of the study sample (arthritis and hypertension) were examined as well as conditions that were reported to have occurred within 1 day or 1 month of phlebotomy (hay fever and flu).

There was an apparent "dose–response" pattern for both neopterin and β2m levels with self-reported recent episodes of flu. However, this relationship became nonsignificant ($P = 0.11$) when considered simultaneously with use of antihistamines. Values did not differ by hay fever status, and apparent differences by arthritis and hypertension were both related to older age rather than the condition itself.

Correlations Among Immunologic Markers. Neopterin and β2m were correlated even after accounting for all other potential influencing factors (adjusted $r = 0.53$, $P = 0.0001$). Neopterin showed no relationships with other immune markers, including sIL-2r, CD4+ or CD8+ lymphocytes, total lymphocytes or monocytes, eosinophils, B cells, natural killer cells, and immunoglobulins. Values of β2m appeared to have a direct relationship with sIL-2r values, independent of demographic variables and smoking status.

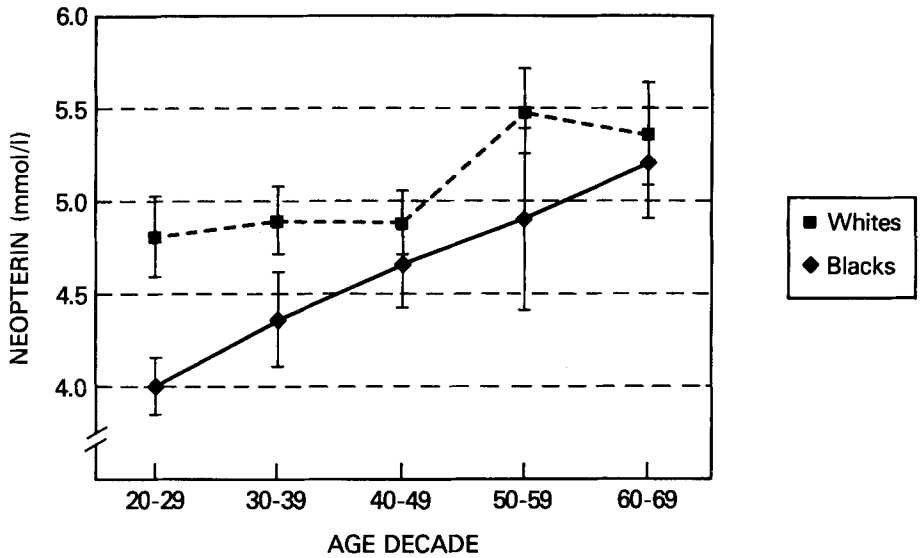

Fig. 2. Neopterin levels by age-decade and race: Means and SE.

DISCUSSION

The purpose of this investigation was to determine the range and variability of serum neopterin and β2m levels in a healthy adult population and to establish the influence of demographic factors and common environmental exposures. Both neopterin and β2m levels increased significantly with age and were higher in whites than in blacks. Although neopterin and β2m serum levels were highly correlated overall, only neopterin levels were significantly associated with cigarette smoking, and only β2m levels were significantly associated with gender. Interestingly, use of antihistamines was associated with significantly increased neopterin, but not β2m, levels.

Neopterin is considered a marker of cell-mediated immunity, produced in and secreted by macrophages. It is derived from a complex cascade of events involving cytokine (interferon-γ) stimulation of a series of enzymatic reactions that eventually convert guanosine triphosphate into the form neopterin (28). Although considered a product of the immunologic response, recent experimental data suggest that neopterin may have an active role as a cofactor of nitric oxide formation (29, 30). Thus, neopterin may have a significant role in the delicate balance between antioxidants and prooxidants required for effective T-cell function. In contrast, β2m is found on the surfaces of MHC class I cells, shares some homology and structure with immunoglobulins, and assists in the assembly of antigen peptides for presentation to T-cell receptors. Both serum neopterin and β2m levels are, in general, elevated in diseases associated with T-cell activation or cell-mediated immune responses (31–34).

The age-related increase in neopterin, but not β2m values, has been reported previously (21, 22). However, the influence of race on these important biomarkers has not been previously reported. Specifically, neopterin and β2m levels were lower among blacks compared to levels among whites. Racial variation in levels of other immune biomarkers have been reported previously, including lower levels of white blood cells and CD3+ cells and higher HLA-DR+ cells among blacks, as well as lower concentrations of IgG subclasses in a pediatric population (35).

Cigarette smoking has been reported to be associated with numerous immunological alterations (18, 19). We observed serum neopterin levels, but not β2m levels, to be significantly lower among current smokers, even after adjusting for all other known influences. Several *in vitro* studies have observed increased intraalveolar cytokine production or macrophage proliferation in response to specific tobacco particulates (36, 37). These observations might reflect a homeostatic relationship between localized pulmonary production of neopterin and systemic serum levels.

Among the medications and medical conditions examined, only antihistamines appeared to exert a significant influence on these markers. Neopterin levels were significantly higher among current users of antihistamines, although after adjusting for medical conditions which might be associated with antihistamine use (hay fever and "flu"), β2m levels were not influenced by use of antihistamines. It was not possible to distinguish "seasonal" versus regular users of antihistamines. Also, the cross-sectional design of the current investigation had limited ability to test hypotheses related to medication use, particularly for common medical conditions such as allergies. A prospective study of serum neopterin (and β2m) before and during antihistamine administration might clarify this point.

Several investigators have reported correlations between neopterin and β2m levels in patients with HIV infection (38); however, it was unclear whether this reflected normal homeostasis or a generalized immunologic dysfunction. In the current investigation, we observed a highly significant correlation between neopterin and β2m in healthy adults, independent of other potentially confounding factors. Among the numerous biomarkers available in these data, only the serum concentration of sIL-2R was observed to have a significant correlation with β2m values. Interestingly, neopterin and sIL-2r, also produced by activated T lymphocytes and a common marker used in HIV-related studies, were not correlated. Among subjects with AIDS, β2m has been reported to be correlated with sIL-2r and serum IgG and inversely related to CD4 cells (39). More specifically, elevations of sIL-2r were observed with HIV seroconversion, followed by increases in levels of neopterin and β2m, correlated with each other but not with sIL-2r levels (15). These observations emphasize the limitations of generalizing data collected in disease populations to normal or preclinical subjects.

In summary, we have investigated serum neopterin and β2m levels in a population-based sample of healthy adults. These important biomarkers are

increasingly employed in clinical and epidemiological studies of HIV infection in preclinical subjects, creating a need for information on normal ranges, natural variability, and the influence of host factors. We observed a significant age-related increase in both markers, and both were higher in whites than in blacks. Neopterin levels were affected by smoking and antihistamine use, while β2m levels were influenced by gender. These data emphasize the importance of carefully considering demographic characteristics and exposures such as cigarette smoking and medications when considering a design or analysis of studies using these markers.

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