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Research article

The association between total leukocyte count and longevity: Evidence from longitudinal and cross-sectional data

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ABSTRACT

The aim of the study was to evaluate the relationship between age-dependent changes in total leukocyte count (TLC) and certain selected differential counts expressed as frequencies (granulocytes, band cells, eosinophils, lymphocytes, and monocytes) and longevity in physically healthy men and women aged 45+. Longitudinal data on cell counts from 142 subjects (68 men and 74 women; all aged 45–70 and examined for 25 years) were compared with cross-sectional data from 225 subjects (113 men and 112 women; this group was divided into four categories of average lifespan; i.e.: 53, 63, 68, and 76+ years of age). ANOVA, *t*-test, and regression analysis were employed. Secular changes in leukocyte count were controlled. Men had continuously higher TLC compared with women. Moreover, sex differences in patterns of changes with age were found. The longitudinal assessment revealed a U-shaped pattern of changes in TLC in men ($y = 0.0026x^2 - 0.2866x + 14.4374$; $R^2 = 0.852$) and women ($y = 0.0048x^2 - 0.5386x + 20.922$; $R^2 = 0.938$), whereas the cross-sectional comparison showed an inverted U-shaped pattern in men ($y = -0.0021x^2 + 0.2421x$; $R^2 = 0.417$) and women ($y = -0.0017x^2 + 0.2061x$; $R^2 = 0.888$). In general, the comparison of longitudinal and cross-sectional data on changes with age in TLC indicates that longevity favors individuals with lower yet normal TLC and this correlation is more pronounced in men. In conclusion, our findings are in line with previous longitudinal studies of aging and suggest that lower TLC within the normal range ($4.0–10.0 \times 10^3\ \mu L^{-1}$) can be a useful predictor of longevity in physically healthy individuals.

1. Introduction

Like erythrocytes and platelets, leukocytes are derived from hematopoietic stem cells (HSCs) in the red bone marrow, which is a mesenchymal-derived complex structure consisting of hematopoietic precursors and a complex microenvironment that facilitates the maintenance of HSCs and supports the differentiation and maturation of the progenitors (Naeim et al., 2013). Unlike erythrocytes and platelets, leukocytes are large, nucleated, translucent, and morphologically heterogeneous cells which fulfill different defensive functions. There are two major categories of leukocytes: granulocytes (neutrophils, eosinophils, and basophils) and agranulocytes (monocytes and lymphocytes). Most of them have a short lifespan, ranging from a few hours or several days (granulocytes) to a few months (monocytes) or even several years (lymphocytes).

Leukocytes are constitutively produced throughout ontogeny and removed from the blood by the liver and spleen. Normally, they constitute less than 1% of whole blood (in adults, range, $4.0–10.0 \times 10^3\ \mu L^{-1}$), but their number can double or can even increase tenfold within hours since there are reserve pools of these cells in bone marrow, spleen, and lymph nodes. Leukocytes can leave the blood by squeezing and migrating between the endothelial cells through pores in the capillary walls. The process of diapedesis is accelerated during inflammation. The functions of leukocytes are not confined to producing and distributing antibodies during the immune response but include removing toxins or wastes and destroying damaged or abnormal cells through phagocytosis. Phagocytic cells located in the reticular connective tissue are part of the mononuclear phagocyte system (MPS).

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Total leukocyte count (TLC) increases in response to infection, trauma, inflammation, and certain diseases. For example, sepsis is accompanied by a surge in the number of leukocytes (Aminzadeh and Parsa, 2011). There are, however, many factors that can affect leukocyte count in healthy subjects such as sex, genetic factors, stress level, diet, nutrition, and lifestyle, e.g. tobacco-induced inflammatory changes. First of all, leukocyte count changes with age: in newborns it is two to three times higher than in adults and in elderly people it diminishes gradually. Although leukopenia, neutropenia, and lymphocytopenia have long been recognized as indicators of poor health and severely impaired immunity, a growing body of evidence suggests now that higher TLC within the normal range is related to increased cumulative all-cause mortality and lower chances of long-term survival. Moreover, some recent studies have revealed that increased TLC is significantly associated with cardiovascular mortality in both sexes and with noncardiovascular mortality in women. Interestingly, hazard ratios were essentially unchanged by adjustment for risk factors such as smoking, hypertension, myocardial infarction, diabetes mellitus, total cholesterol, high-density lipoprotein cholesterol, and body mass index (Nilsson et al., 2014).

The discovery of an increased risk of mortality in older women with elevated yet normal level of baseline leukocyte counts stimulated the ongoing debate about the relationship between TLC or differential cell counts and survival probability in adults and older people (Horne et al., 2005; Leng et al., 2005a,b, 2009). Higher level and upward changes in TLC can be used as an important clinical marker of chronic systemic inflammation and a negative prognostic in patients with cardiovascular disease (CVD), coronary heart disease (CHD), stroke, and cancer (Danesh et al., 1998; Erlinger et al., 2004; Wheeler et al., 2004; Leng and Fried, 2009). Ruggiero et al. (2007) demonstrated a nonlinear relationship between TLC and all-cause mortality and cancer. There was, however, a linear relationship between leukocyte count and mortality from CVD. Nevertheless, the role of TLC as an independent predictor of the first cardiovascular incident remains uncertain. Likewise, there is no evidence that leukocyte count is related to longevity in physically healthy people who are not at higher risk of CVD, CHD, stroke, and cancer.

Although the results of several studies confirmed the positive relationship between TLC and mortality in older adults and elderly people, little work has been devoted to changes with age in leukocyte count in short and long-lived subjects on the basis of longitudinal studies of aging. The purpose of our study was to determine rates and patterns of such longitudinal as well as cross-sectional age-related changes in TLC, including aging-associated alterations in differential cell counts expressed as frequencies (granulocytes, band cells, eosinophils, lymphocytes, and monocytes) in physically healthy men and women aged 45+, with special reference to the correlation with average lifespan (ALS) in the compared groups of subjects; i.e. short versus long-lived individuals.

2. Material and methods

2.1. Study population

Out of the total number of patients (n = 3500) who lived at the Regional Psychiatric Hospital for People with Mental Disorders in Ciborz, Lubuskie Province, Poland, in the years 1960–2000, we have carefully selected longitudinal data on hematological parameters from 142 physically healthy individuals (including 68 men and 74 women) and cross-sectional data from 225 physically healthy individuals (including 113 men and 112 women). All subjects were Caucasian, born in the years 1911–1933. Their health was evaluated during regular physicals at the hospital on its premises by hospital staff. In the years 1960–1989, the asylum provided custody for helpless and resourceless people from the underclass, thereby confining not only individuals with severe mental disorders but also persons who needed special care due to mild mental problems and poverty. The reason for keeping these people there for many years, was to separate them from the rest of the socialistic society, which was a socially and politically motivated decision (Krzymiński, 2000; Borysławski et al., 2015; Chmielewski et al., 2015). During their lengthy stay at the hospital, the patients would take some powerful psychoactive drugs. Therefore, we selected solely data from patients who hardly ever had been treated with strong medicines or who had been treated so every once in a while. It is noteworthy that the patients lived for many years under very similar and relatively prosperous environmental conditions, maintained virtually the same lifestyle and had practically the same diet prescribed by a dietitian at the hospital. This fact undoubtedly boosts the value of the study sample and makes it quite unique. Nevertheless, detailed written data on diet, calorie intake, physical activity, and so forth were not available and were not controlled in the research.

The patients from the longitudinal sample (n = 142), aged 45 at the beginning and 70 years at the end of the analyzed period, stayed continuously at the hospital and all lived to be at least 70 years of age. No further information on lifespan of these patients was available. In the years 1999–2000, there were sweeping reforms in the functioning of the medical institutions in Poland and those from the longitudinal sample who survived to be older than 70 years of age, were transported to other hospitals or medical institutions in the country.

The patients from the cross-sectional sample (n = 225) were confined at the same hospital but differed in lifespan. Leading causes of death were predominantly aging-associated diseases such as 'cardiorespiratory failure' (CRF), cardiovascular disease (CVD), stroke, and cancer. The cross-sectional sample was divided into four categories of average lifespan (ALS), i.e.: (1) 53 years of age (the limit of individual lifespan for this group was 57.5 years of age; the group consisted of 22 men and 12 women, ALS was 53 and 52 years of age, respectively), (2) 63 years of age (the limit of individual lifespan for this group was 65 years; the group was comprised of 27 men and 30 women, ALS was 63 years for both sexes), (3) 68 years of age (the limit of individual lifespan for this group was 72.5 years; the group was made up of 49 men and 40 women, ALS was 67.6 years for men and 68 years for women), and (4) 76+ (there were no limits since this group comprised living subjects, 15 men and 30 women, their average age was 76 for both sexes).

2.2. Data collection and statistical analysis

Data on hematological parameters were obtained from the hospital archives. All information used in the present study was derived from physical examinations of the inmates who were there in the years 1960–2000. The process of data collection was performed with permission and consent of hospital authorities. The study was carried out in accordance with the Declaration of Helsinki and consisted in observation only. No experiments were conducted. The medical files were anonymized so as not to divulge any personal or confidential information. On the basis of medical records and files that had been stored at the archives, we created a large computerized database in the years 2005–2007. Two types of materials were obtained: longitudinal and cross-sectional (see Section 2.1).

All measurements were taken in accordance with internationally accepted standards and requirements by hospital staff. Blood samples from the median cubital vein were drawn by a nurse at the hospital. During the 25-year study period, complete blood tests were performed from 10 up to 18 times within each five-year period for a very long time, that is for 25 years in the case of the longitudinal sample. On the basis of such frequently repeated measurements for