Lifestyles and Their Association with Hematological Diseases

Abstract

Healthy modulation of lifestyles in many cases has a better therapeutic effect than that obtained by many first-line drugs. These results and the recent slowdown in the development of new drugs have shifted more attention to the preventive and therapeutic role of healthy lifestyles in several chronic diseases. Their role in hematological disorders is also attracting increasing attention. A lifestyle of non-smoking, abstinence or low to moderate alcohol intake, regular physical activity, consumption of a prudent diet, and avoiding weight gain induce a plethora of beneficial effects on the hematological system. Unhealthy lifestyles on the other hand, lead to a host of harmful effects, including anemia, diminished immunity, and clotting abnormalities. Unhealthy lifestyles also play a significant role in the pathogenesis of a wide array of hematological malignancies. The aim of this manuscript is to review this association.

Keywords: Blood disorders, smoking, lifestyles, exercise, alcohol, diet, obesity

Introduction

The hematologic system includes red blood cells, white blood cells, platelets, blood vessels, bone marrow, lymph nodes, spleen, and plasma proteins, and other ingredients. Blood cells make up about 45 percent of the blood volume and include red blood cells (RBC/s), white blood cells (WBC/s), and platelets. Red blood cells or erythrocytes impart the blood its characteristic color. Hemoglobin (Hgb) is the main protein present in the erythrocytes. Its primary function is to transport oxygen from the lung to tissues and carbon dioxide from tissues back to the lungs[1,2]. The World Health Organization (WHO) describes anemia as hemoglobin (Hgb) $\leq$ 7.45 mmol/L (12 g/dL) in women and Hgb $\leq$ 8.07 mmol/L (13 g/dL) in men[4]. Anemia affects almost a quarter of the world's population[5]. Polycythemia is characterized by an elevation in the levels of Hgb or RBCs. The etiology of primary polycythemia is not known. Secondary polycythemia usually occurs from long-term exposure to low oxygen levels, as may occur in smokers, people who spend long hours at high altitudes, or those who are exposed to high levels of carbon monoxide. Patients with heart or lung disease may also develop secondary polycythemia[6]. White blood cells or leukocytes play a major role in the body's defense against disease. They are of different types, each with a specific function. A white blood cell count of less than 4 x 10^9/L indicates leukopenia. Leukopenia is usually due to fewer neutrophils and indicates a neutrophil count of less than 1.5 x 10^9/L[7,8]. Leukopenia occurs due to infections, treatment such as chemotherapy or radiation therapy, a lack of normal growth/maturation within the bone marrow, and malignant disorders such as myelodysplastic syndrome or leukemia. A WBC count of more than 11 x 10^9/L indicates leukocytosis. This may occur due to infection, stress, inflammatory disorders, or

abnormal production as in leukemia[9]. Platelets, the other cells in the blood, help to stop bleeding. Thrombocytopenia refers to a decrease in the platelet count below 150,000/µL. It may be caused by infections, malignancy, liver disease, autoimmune disorders, disseminated intravascular coagulation, pregnancy, medications, and coagulation disorders[10,11]. Patients with platelet counts greater than 50 × 10(3) per µL rarely have symptoms. A platelet count from 30 to 50 × 10(3) per µL may manifest as purpura. A count from 10 to 30 × 10(3) per µL may cause bleeding with minimal trauma. A platelet count less than 5 × 10(3) per µL may cause spontaneous bleeding and is a hematologic emergency[12]. Extremely low platelet counts as seen in immune thrombocytopenia (less than 1000/µL), may cause spontaneous bleeding and even result in death[13]. A high platelet level, with platelets numbering more than 450,000, is called thrombocytosis[14]. Thrombocytosis may be secondary, reflecting an inflammatory state, iron deficiency, or recent surgery. Thrombocytosis sometimes draws attention to an occult solid tumor and hematological condition[15]. Plasma refers to the remaining 55 percent of the blood. Plasma is rich in minerals; nutrients; regulatory substances, such as hormones; gases, such as oxygen and carbon dioxide, and proteins. The latter plays a role in blood clotting as well as defense (i.e., antibodies or immunoglobulins).

Hematological malignancies include leukemias, lymphomas, myelomas, myelodysplastic syndromes, and myeloproliferative disorders. These account for nearly 10% of new cancer diagnoses in the USA[16]. Globally their incidence is 40.3 per 100,000 individuals per year. The distribution is generally as follows: leukemia (12.6), lymphoma (22.4), and multiple myeloma (5.6)[17]**.** Pediatric acute leukemia affects approximately 10–45 children per 106 children per year[18]. Acute lymphoblastic leukemia (ALL) is the most common in this population[19]. In adults, acute myeloid leukemia (AML) is the most common. Hematopoietic cancers have a good prognosis with treatment[20]. The 5-year survival rates are 89% ALL, 61% for AML, 96% for Hodgkin lymphoma (HL), and 89% for non-Hodgkin lymphoma (NHL)[21,22]. Multiple myeloma (MM) is also common and involves the accumulation of plasma cells in bone marrow[23]**.**

This narrative review aims to look at the association between lifestyle behaviors and common benign and malignant hematological disorders. The five major lifestyles that play a major role in human morbidity and mortality are smoking, alcohol consumption, physical activity, body weight, and diet. In general, unhealthy lifestyles inflict deleterious effects on the hematological system. The benefits of practicing healthy behaviors are also discussed.

Literature Review

Hematological disorders are common. A considerable benefit in mitigating these occurs from following five healthy lifestyles namely, not smoking, abstinence or low to moderate alcohol consumption, maintaining a healthy body weight, exercising regularly, and eating a prudent diet24. The result is not only decreased morbidity but longer survival. Li et al. using data from the Nurses' Health Study (1980-2014; n=78,865) and the Health Professionals Follow-up Study (1986-2014, n=44,354), estimated that the life expectancy at age 50 years was 29.0 years for women and 25.5 years for men who practiced unhealthy lifestyles. In contrast, for those who adopted all 5 low-risk factors, they projected a life expectancy at age 50 years of 43.1 years for women (a gain of about 14 years) and 37.6 years for men (a gain of about 12 years)[25].

Smoking

Tobacco smoking is extremely dangerous to most bodily systems[26,27]. The toxins in cigarette smoke also deleteriously affect the hematologic system[28]-. Higher Hgb and hematocrit levels have been noted in individuals smoking more than 10 cigarettes per day[28-50]. Malenica et al. reported that cigarette smoking increases erythrocyte count, Hgb concentration, hematocrit, mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration[29]. Males appear to have a higher hematocrit due to smoking than females. Several other researchers have noted a similar effect on hematologic parameters[30-32]. Carbon monoxide binding to Hgb in smokers has been attributed to causing a higher hemoglobin level to compensate for the reduced oxygen-carrying capacity when compared with non-smokers[33]. Multiple studies have found that smoking induces leukocytosis, especially in males[34-37]. Arterial thrombosis occurs with increased frequency in cigarette smokers[38]. This may be related to the increased quantity of platelets as well as abnormal platelet function (increased platelet aggregation)[39,40]. These effects have also been noted with the use of e-cigarettes**.** and hookah/waterpipe smoking[41]. Antiplatelet agents, such as aspirin, often have a reduced activity in smokers[42]. These actions are important contributory factors in acute coronary events (and related worse outcomes) noted in smokers[43].

Cigarette smoking is associated with an increased risk for leukemia[44]. It is estimated that approximately 14% of all US leukemia cases (including 17% of myeloid and 14% of acute nonlymphocytic leukemias) are related to cigarette smoking[45]. The risk increases as the number of cigarettes smoked goes up. Cigarette smoking also shortens the remission duration and decreases survival in these patienst[46]. Smoking cessation improves the prognosis[47]. Smoking also increases the risk for NHL and HL. Sergentanis et al. reviewed 50 articles (1,53,833 smokers) and found that ever smoking was associated with an increased risk for lymphomas. This included NHL [pooled-effect estimate=1.05) and HL (pooled-effect estimate=1.15). The association was stronger with T-NHL (pooled-effect estimate=1.23) especially with nodular sclerosis and mixed cellularity subtypes[48]. Taborelli et al. found a similar association. In their study, people smoking >15 cigarettes a day had an increased risk of both NHL (Odds Ratio (OR)=1.42) and HL (OR=2.47), especially the risk of follicular NHL (OR=2.43) and mixed cellularity HL (OR=5.60)[49].

A causal relationship between smoking with multiple myeloma has not been established. In a meta-analysis of forty studies, Psaltopouloa et al. reported no association between multiple myeloma and tobacco smoking[50].

Alcohol

Alcohol is widely consumed in different cultures[51]. According to the WHO data from 2016, individuals aged 15 years or older, consumed on an average 6.4 liters of pure alcohol annually or 13.9 grams of pure alcohol per day[52]. Although promoted in low or moderate doses for cardiovascular protection, the World Heart Federation recently issued a recent press release that no amount of alcohol consumption is safe[53]. The International Agency for Research on Cancer has classified alcohol as a type 1 carcinogen in humans[54]. Alcohol directly exerts toxic effects on the bone marrow; the blood cell precursors; and the mature RBCs, WBCs, and platelets. It

indirectly affects the production and function of various blood cells by promoting nutritional deficiencies or its effects stemming from liver damage. Alcohol consumption is associated with higher MCV, and this relationship appears to be dose dependent. Increasing alcohol consumption by 5 units (40 g) per week is associated with a 0.3% increase in MCV[55]. It also reversibly improves erythrocyte deformability and decreases erythrocyte aggregation[56]. There are several causes of anemia in alcoholics. Alcohol, as well as alcohol-induced cirrhosis, leads to decreased RBC production. Hypersplenism, on the other hand, can induce premature RBC destruction[57]. Blood loss (usually gastrointestinal) is increased in patients with reduced platelet numbers. Alcoholism is a well-known cause of macrocytic anemias. Chronic consumption of more than 80 grams of alcohol per day has adverse effects on the hematologic system. Even before anemia develops, approximately 90% of alcoholics have macrocytosis (MCV between 100 and 110 fL)[58]. Macrocytosis is often used to diagnose alcoholism[59]. Abstinence from alcohol rapidly returns elevated MCV to normal levels[60]. The megaloblastic form is due to impaired DNA synthesis from folate and/or vitamin B12 deficiencies. Non-megaloblastic anemia, the absence of hyper segmented neutrophils, may also occur from alcohol consumption. Alcohol intake may also cause sideroblastic anemia[61]. Interestingly, alcohol consumption (2 alcoholic drinks/day) appears to decrease the risk of iron deficiency anemia[62]. Leukopenia is common in heavy alcohol drinkers[63]. Excessive alcohol consumption injures the bone marrow and impairs the granulopoiesis response[64,65]. Alcohol exposure impairs the granulocytes from functioning properly[66]. Alcohol also impairs the function of monocytes and macrophages, and lymphocytes[67]. The associated decrease in immune defense significantly increases the host susceptibility to serious infections, particularly pneumonia and septicemia[68]. Patients with alcoholism, septic infection, and granulocytopenia have an exceedingly high mortality rate. Alcohol also induces thrombocytopenia[69]. It inhibits platelet aggregation, reduces blood coagulation factors (such as fibrinogen, factor VII and von Willebrand factor), and enhances fibrinolysis[70-73]. These actions contribute to its protective effects in certain cardiovascular diseases[74,75].

There is no association found between alcohol intake and leukemia[76,77]. Alcohol consumption appears to decrease the risk of NHL[78-81]. In a recent meta-analysis, Psaltopoulou et al. reviewed 14 studies that included 5 million people in total. They found that NHL risk was reduced by 11% in 10 studies (over 11,000 cases), with alcohol consumption[82]. The risk decreased further with increasing alcohol intake. Light drinkers (<12.5g/day) had a 7% decreased risk, moderate drinkers (12.5-50g/day) had a 15% reduced risk while heavy drinkers (>50g/day) had a 27% reduced risk[82]. An inverse relationship also has been noted between alcohol intake and MM in case-control studies, and in a pooled analysis of six studies[83,84]. In a more recent evaluation, Santo et al. using data of 499,292 participants enrolled in the National Institutes of Health (NIH-AARP Diet and Health Study, 1995-1996), found that increasing frequency of alcohol consumption was inversely associated with the incidence of MM. In men consuming 2 drinks per day, the hazard ratio (HR) was 0.70 and in women consuming less than one drink per day, the HR was 0.73[85].

Obesity

Body mass index (BMI) is computed as the ratio of the measured weight in kilograms to the square of the measured height in meters. It is classified as normal (BMI 18.5-24.9 kg/m2), overweight (BMI 25 to <30 kg/m2), mild obesity (BMI 30 to <35 kg/m2), moderate obesity (BMI 35 to <40 kg/m2), and severe obesity (BMI ≥ 40 kg/m2)[86]. According to the WHO, obesity has nearly tripled since 1975. Obesity increases the risk for many chronic diseases such as type 2 diabetes, hypertension, heart disease, stroke, dyslipidemia, and osteoarthritis[87],

Guiraudou et al. described increased red cell aggregation in obese individuals. Visceral obesity tended to increase the hematocrit. Overall, obese patients had an increased plasma viscosity and red cell rigidity[88]. The causative mechanisms are many. Obese individuals also have a lower serum iron which may be partly contributed by hemodilution[89]. The low-grade inflammation (higher interleukin (IL)-6, IL-1, IL-8, tumor necrosis factor (TNF)-α and a rise in acute phase reactants such as C-reactive protein) seen in obese individuals may also contribute to a higher iron requirement and a poor iron absorption[90]. These factors and insulin resistance may contribute to the increase in RBC count, Hgb, and hematocrit seen with obesity[91]. An increase in WBC count is also seen in overweight/obese people. It is postulated that increased inflammation[92], metabolic dysfunction[93], and other comorbidities like obstructive sleep apnea[90] in obese individuals increases bone marrow granulopoiesis, and accelerates neutrophil release, leading to leukocytosis[93]. Obesity and related inflammation is also associated with increased platelet counts and an increased risk for venous thromboembolism[94,95]. They also have impaired fibrinolysis which further increases the risk of thrombosis[96]**.** Obese individuals are well known to have an increased risk of venous thromboembolism[97].

Obesity increases the risk of many hematological cancers[98]. Obesity is linked with harmful consequences in patients with leukemia. Obesity decreases chemotherapy efficacy[99]. Children with ALL have a higher incidence (50%) of relapse[100]. ALL cells stimulate the release of free fatty acids from adipocytes and use them metabolic fuel[101]. The risk of leukemia in adults is also increased in obese adults[102]. Obesity is associated with an increased risk of non-Hodgkin's lymphoma[103]. Lin et al found that obese individuals with a BMI = or>35, exhibited an increased risk (RR=1.29)[104]. Larsson and Wolk reported a higher risk of diffuse large B-cell lymphoma and higher mortality in patients with NHL[105]. They also found an increased risk (RR=1.41) of HL in obese individuals. There is also a direct enhancing effect of a high BMI on the risk of MM and related mortality in adults[106,107].

Physical Activity

Physical exercise has significant health benefits[108]. Regular exercise can reduce the risk for over 25 chronic diseases. It also reduces premature mortality by 20%–30%. Exercise increases total Hgb and red cell mass[109]. Although there is an increase in intravascular hemolysis of senescent red blood cells, exercise stimulates erythropoiesis by inducing hyperplasia of the hematopoietic bone marrow[110]. The result is an increase in younger red cells providing enhanced oxygen-carrying capacity. Leukocytosis is often seen in men with low fitness. High levels of physical activity reduce total WBC and neutrophil count[111,112]. Leukocytosis is harmful. It is a strong independent risk factor for coronary heart disease morbidity and increases the risk of cardiovascular death by approximately 40%[113,114]. It is also associated with diminished insulin sensitivity and prognosticates an increased risk of type 2 diabetes mellitus in the future[115].

Regular moderate-intensity physical activity also decreases platelet aggregability. The combination of a prudent diet along with moderate physical activity has a more powerful beneficial effect on blood coagulation and fibrinolysis than either of these lifestyle alone[116].

Physical activity also helps prevent several cancers (risk reduction of 20% to 40%)[117]. Overall, exercise helps improve cardiorespiratory fitness, muscle strength, and physical well-being in patients with hematological cancers[118-121]. Exercise results in shorter durations of neutropenia, thrombopenia, and hospitalization and better physical performance at discharge[122]. These patients also note an improvement in fatigue and depression[123,124]. The quality-of-life improves[125]. Cachexia affects 50–80% of cancer patients and up to 80% of those who manifest cachexia end up with a premature death[126,127]**.** It is also seen in hematological cancers such as AML where chemotherapy-induced cachexia is often profound. Exercise in these patients should help mitigate the ominous cachexia[128]. Positive results are also noted in patients suffering from lymphomas. Tailored exercise in MM patients improves the quality of life, fatigue, and muscle strength[129].

Diet

A healthy diet is critical for a healthy hematological system. It is estimated that 25% of people have anemia in the world, with iron deficiency being responsible for 50% of these[130]. Usually, the cause is nutritional. For example, excessive milk or juice intake, prolonged bottle-feeding, and snacking in toddlers may result in iron deficiency anemia[131]. The result is microcytic and hypochromic red cells. Inadequate intake of several other vitamins may also cause anemia[132.133]. For example, folate deficiency results in macrocytic anemia[134]. Vitamin B12 deficiency, sometimes seen in vegans, can also cause profound anemia[134]. Vitamin C deficiency may cause petechiae and excessive bleeding. Vitamin K plays an important role in the clotting process[134].

As mentioned under obesity, excess body weight increases the risk of hematological malignancies**.** Diet plays a major role in the development and sustenance of obesity. Restoration of normal body weight in these patients improves the course of the malignant disease and results in increased survival. Fish intake has also been associated with a decreased risk of leukemia (OR=0.72)[138]**.** Several studies support an inverse association between intakes of vegetables and fish and a lower risk of NHL[139]. On the other hand, high consumption of fats, meat, and dairy products tends to increase lymphoma risk[139]. A high intake of fish has also been associated with a decreased risk of MM[138].

Certain dietary patterns also influence the hematologic system. Plant-based dietary pattern (such as a vegan diet) help decrease platelet counts when compared to a meat-rich eating plan[140]. Vegetarians/vegans are however at an increased risk of developing B12 deficiency **(**and macrocytic anemia**)**[141]**.** The Mediterranean diet keeps both the leukocytes and the platelets within a normal range[142,143]. The WHO has published recommended doses of various macro and micronutrients, and these should be followed for good hematological health[144]. To summarize, a balanced diet not only helps reduce the risk of developing hematological cancers but also helps decrease the ravages of cancer and its treatment on the human body.

Conclusion

Several lifestyle behaviors affect blood parameters. These include smoking, alcohol intake, obesity, physical activity, and diet. The published data is clear on several fronts – healthy lifestyles reduce blood abnormalities and, in most cases, reduce the risk, and improve the prognosis of several hematologic malignancies. Since healthy lifestyles also help mitigate several chronic diseases and increase life expectancy, a serious attempt is needed to partake in these behaviors and adhere to them. It behooves every health care provider to include these in their preventive and therapeutic armamentarium.

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