Mechanisms of Ageing and Development 150 (2015) 46–54

Contents lists available at ScienceDirect

Mechanisms of Ageing and Development

journal homepage: www.elsevier.com/locate/mechagedev

Primary and secondary haemostasis changes related to aging

Cesar Sepúlveda[a], Iván Palomo[a,b,*], Eduardo Fuentes[a,b,*]

[a] Department of Clinical Biochemistry and Immunohaematology, Faculty of Health Sciences, Interdisciplinary Excellence Research Program on Healthy Aging (PIEI-ES), Universidad de Talca, Talca, Chile
[b] Centro de Estudios en Alimentos Procesados (CEAP), CONICYT- Regional, Gore Maule R09I2001, Chile

ARTICLE INFO

Article history:
Received 6 April 2015
Received in revised form 2 August 2015
Accepted 11 August 2015
Available online 18 August 2015

Keywords:
Haemostasis
Coagulation
Platelets
Aging

ABSTRACT

Life expectancy has increased in many countries as a result the world's population is aging. The projections indicate that the proportion of the elderly in a few decades will increase significantly. Aging carries with it a series of physiological changes; one of them is an imbalance in the hemostatic system. Thus the levels or activity of various proteins involved, such as most coagulation factors, natural anticoagulants and the fibrinolytic system are altered so that the hemostatic balance leans toward thrombosis. Also, platelet activity suggests a state of abnormal activation (P-selectin, beta thromboglobulin and platelet factor). In this review we will systematically examine the alterations in the hemostatic components that occur during aging. Therefore, understanding these hemostatic changes could contribute to developing strategies for the proper management of health in old age.

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1. Introduction

Life expectancy has increased in many countries and the proportion of the aging population in a few decades will increase significantly. In numbers, if today the global percentage of people over 60 years is 11%, it is estimated that by 2050 this percentage could be 21% (Bloom et al., 2011). This means an increase in many pathological conditions related to aging. These include immune senescence (Bueno et al., 2014); hormonal changes, in males a progressive decline in testosterone (Vermeulen et al., 1998), while in women estrogen levels have dropped sharply since menopause (Judd and Fournet, 1994); bone and muscle deterioration occurs (Liu-Seifert et al., 2004; Morley, 2012) and a decrease in cognitive abilities (Fjell and Walhovd, 2010) .

Aging is a series of physiological changes; one of them is an imbalance in the hemostatic system (Reymond et al., 1989; Syed and Ng, 2010; Favaloro et al., 2014; Ritzel et al., 2013; Guarner and Rubio-Ruiz, 2015; Duckles and Miller, 2010; Hamada et al., 2010).

* Corresponding authors at: Immunology and Haematology Laboratory, Faculty of Health Sciences, Universidad de Talca, Talca, Chile. Fax: +56 71 20048.
E-mail addresses: ipalomo@utalca.cl (I. Palomo), edfuentes@utalca.cl (E. Fuentes).

http://dx.doi.org/10.1016/j.mad.2015.08.006
0047-6374/

This system is constituted by the interaction between coagulation factors, natural anticoagulants, endothelium and platelets, which maintain a balance between thrombosis and hemorrhage (Gale, 2011; Versteeg et al., 2013). During aging, some of these components are altered, changing the balance of the hemostatic system (Favaloro et al., 2014; Bucciarelli and Mannucci, 2009). This may in part explain the increased incidence of thrombotic and cardiovascular diseases (CVD) in older adults (Raskob et al., 2014; Sarink et al., 2014; Kovacic et al., 2011; Lopes et al., 2012). Therefore, population aging is one of the causes of the increased incidence of CVD, which is the cause of 30% of deaths worldwide (Lavi et al., 2012).

In this review we will systematically examine the alterations in the hemostatic components that occur during aging, which contribute to the development of CVD. Therefore, understanding these hemostatic changes could contribute to developing strategies for the proper management of health in older people.

2. Hemostasis

The hemostatic system corresponds to mechanisms to stop bleeding after injury. In primary hemostasis platelets and endothelium participate, in addition to proteins such as Von Willebrand factor (vWF). Secondary hemostasis corresponds to the activation of coagulation factors and the formation of the fibrin network. Meanwhile fibrinolysis is a mechanism of fibrin breakdown for blood clotting to occur (Mohebali et al., 2014; Schulman and Kearon, 2005). With advancing age many of these components are altered, generating a pro-coagulant state in older people, which is described below. The main alterations occurring in hemostasis during aging are summarized in Table 1.

2.1. Primary hemostasis during aging

a) Platelets

A study conducted in the United States suggests that the platelet count decreases slightly with age, considering that the average count in the sixth decade of life is $7 \times 10^3/\mu$ L platelets lower than population mean, independent of ethnicity or gender (Segal and Moliterno, 2006). However, the bleeding time, a test that evaluates both the number of circulating platelets as its functionality, decreases with age (Reilly and FitzGerald, 1986; Jorgensen et al., 1980). It has also been observed that with age, lower concentrations of agonists such as ADP or collagen are needed to induce platelet aggregation (Kasjanovova and Balaz, 1986; Bastyr, 1990). In addition, plasma indicators of platelet activation, such as β-thromboglobulin (β-TG), thromboxane A (TxA) and platelet factor 4 (PF-4) increase with age, indicating increase of platelet activity (Reilly and FitzGerald, 1986; Bastyr, 1990; Zahavi et al., 1980).

Moreover, during aging there is an increase in the amount of phosphoinositide in the platelet plasma membrane (basal and after thrombin stimulation), such as phosphatidylinositol 4,5- bisphosphate (PIP2) and phosphatidylinositol 4-phosphate (PIP), which are important in the production of second messengers (inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG)) and trigger platelet activation (Bastyr, 1990). Another important change with aging is the intraplatelet increase of p47phox protein levels (involved in the activity of the enzyme NADPH oxidase) and the superoxide dismutase 1 (SOD-1), which are involved in the production of reactive oxygen species (ROS) (Dayal et al., 2013). Due to increased ROS there is a decrease in the protective activity of nitric oxide and cGMP in platelet (Goubareva et al., 2007). Also the endothelial capacity to produce nitric oxide decreases with age has been described, which favors abnormal platelet activation (Cau et al., 2012). Therefore, this suggests that although the platelet count may decrease slightly, platelets have a state of hyperactivity during aging.

Increased platelet activation results in up-regulation of specific binding to leukocytes that promote a pro-inflammatory state and CVD (Marquardt et al., 2009; Htun et al., 2006). Thus, in older people there is an increase of both platelet P- selectin expression, proinflammatory leukocyte phenotype and platelet-leukocyte interaction (Izzi et al., 2007; Seidler et al., 2010). This increase of leukocytes bound to platelets has been attributed to a decrease in the biological activity of nitric oxide and cGMP in platelet (Goubareva et al., 2007).

b) Von Willebrand factor

The vWF levels increase with age and are associated with an increased risk of thrombotic diseases (Konkle, 2014; Wannamethee et al., 2012; Favaloro et al., 2005a; Conlan et al., 1993). ADAMTS-13 is a plasma metalloprotease that cleaves vWF multimers thereby modulating their participation in primary hemostasis. The insufficient enzymatic activity of ADAMTS-13 causes that vWF is keep in uncleaved high molecular weight form with an increased tendency to thrombosis (Rybaltowski et al., 2011; De et al., 2013; Kokame et al., 2011). In addition, the increased vWF levels are associated with a proinflammatory state and a decrease in the ADAMTS-13 activity (Guarner and Rubio-Ruiz, 2015; Claus et al., 2009; Schlaudecker and Becker, 2014; Frentzou et al., 2012). Therefore, it is important to consider this natural increase of vWF levels during aging in the management of vWF disease type 1 (Sanders et al., 2014).

2.2. Secondary hemostasis during aging

Secondary hemostasis is defined as stable fibrin clot, cross-linked fibrin by activated coagulation factors, specifically thrombin. The pathways for coagulation activation are the intrinsic, extrinsic and common (Achneck et al., 2010; Puy et al., 2015).

a) Intrinsic pathway

It has been reported that in the intrinsic pathway factor VIII, an acute phase protein (Bach et al., 2010), increases with age in both sexes (Conlan et al., 1993; Lowe et al., 1997; Balleisen et al., 1985; Favaloro et al., 2005b). Factor IX also increases with age, this enzyme is in conjunction with FVIII that forms the tenase complex that activates the factor X (Favaloro et al., 2005b). An increase in the activation peptide of this protein released after cleavage by factor XI has also been described in people over 100 years old (Mari et al., 1995).

The genetic and molecular mechanisms underlying factor IX's increase with age is associated with a region in the terminal portion of the gene that is responsible for increased levels of the factor with age. This segment called age-related increase element (AIE) has a segment of 102 base pairs rich in dinucleotide repeats that generate forks in that portion of the mRNA produced (Kurachi and Kurachi, 2000). This would be the site of interaction with a protein called nuclear ribonucleoprotein A3 (RNP A3); such interaction protects the mRNA until its translation. RNP A3 expression increases with age in mice and would produce the increase in the factor IX observed with age (Hamada et al., 2010). With respect to factors XI and XII Favaloro et al. reported that the first increases with age and second does not (Favaloro et al., 2005b), however Cappola et al. evaluated the levels of this activated protein in both sexes and observed that the activated form of factor XII increased in women from age 55, whereas in men the increase was found in centenaries (Coppola et al., 1996).