How different are blood platelets from women or men, and young or elderly people?

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Received: October 18, 2022.
Accepted: November 9, 2022.
Prepublished: November 17, 2022.

https://doi.org/10.3324/haematol.2022.282131

Gender-specific medicine is the study of how (sex-based) biological and (gender-based) socioeconomic and cultural differences influence people's health. Significant differences are currently described in the development, progression and clinical signs of conditions common to men and women, such as the response to treatments and nutrients, and in lifestyles. Several determinants (genetic, epigenetic, hormonal and environmental) reportedly account for differences between cells from women and men and/or from young or elderly people. To be truly effective, prevention, diagnosis and management of a given condition should be considered in relation to the biological sex of the individual/patient, as well as to other parameters, such as gender identity, age, ethnicity, level of education, religious beliefs, sexual orientation, social and economic conditions.

A Letter to the Editor published in this issue of *Haematologica*[1] gives a small but significant contribution to the progress of gender-specific medicine.

It is well known that platelet count variability is dependent upon genetic factors and is highly heritable. Several genes have been identified to concomitantly influence platelet count, mean platelet volume and platelet activation/function. Many of the variants are in non-coding regions of the genome, suggesting that they may play a role in the expression/modulation of these regions, possibly through epigenetic mechanisms.[2]

Studies trying to identify the non-genetic factors associated with platelet count identified sex, age and ethnicity as major variables. Studies in the general population and in different Italian geographical isolates showed no difference in platelet count in men and women until the age of 15, but subsequently women constantly had more platelets than men, with a slow, progressive, parallel decline with aging in both sexes.[3] These Italian data have been confirmed and extended in other geographical settings, as now also reported in the Letter to the Editor by Sabrkhany *et al.*[1]

The results presented in that Letter suggest that some platelet function parameters may also differ between women and men and change with progression of age. Integrin αIIbβ3 activation increased with age, a finding possibly in agreement with previous observations of increased platelet response to ADP with aging, while P-selectin expression decreased with age. Age was found to be an independent predictor of platelet growth factor (PGF) content and was negatively correlated with intra-platelet concentrations of platelet factor 4 (PF4), connective tissue activating peptide III (CTAP-III) and platelet-derived growth factor (PDGF). In contrast, the relationship with thrombospondin-1 (TSP-1) was not significant. In isolated platelets, the concentration of PDGF, but not of other platelet-derived biomarkers, was significantly higher in women than in men. However, taking into account the higher number of platelets in women, the total circulating concentrations of all biomarkers were significantly higher in women, even when adjusted for age. The translational aspects of these data remain to be defined, but the authors underline the importance of age- and sex-matched controls for future platelet-based biomarker studies.

A previous proposal by Bijno *et al.*[3] to use different normal ranges of platelet count that take into account sex and age has not apparently become a diffuse practice, but has occasionally been adopted. The use of personalized reference intervals, instead of the traditional ones, resulted in relevant differences in the number of patients classified as thrombocytopenic or affected by thrombocytosis; the proportion of subjects with unexplained thrombocytopenia was also smaller.[4] A sex-stratified approach also revealed peculiar relationships between platelet distribution width – an index of platelet size variability – and the intensity of depressive symptoms.[5] Within the Moli-sani Study cohort, using personalized (sex- and age-specific) reference intervals of platelet count, the reduction of the number/proportion of subjects with thrombocytopenia was confirmed; interestingly, the group of possibly true thrombocytopenic subjects (identified by personalized range intervals) had a higher risk of total mortality compared with subjects classified as thrombocytopenic by traditional range intervals. In the same Moli-sani cohort, better adherence to a Mediterranean diet, rich in fibers and antioxidants, was associ-

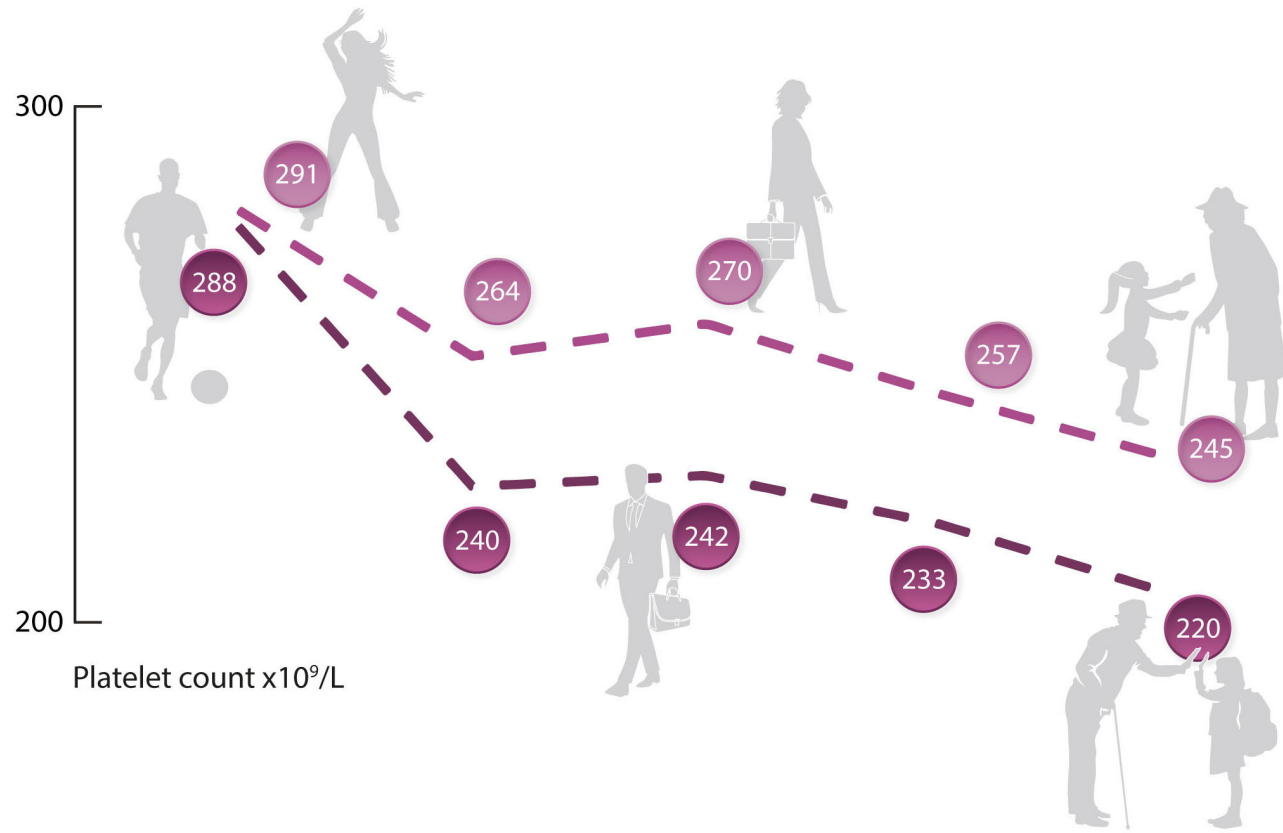

Figure 1. Age, sex and platelets. Some characteristics of human platelets vary according to age and sex. The changes in platelet count are emblematic. The number of platelets decreases with age and after 15 years of age, women have more platelets than men.

ated with reduced platelet (and leukocyte) counts as compared to personalized (sex- and age-specific) reference intervals of platelet count.[6]

The reasons why platelet count and/or some platelet function parameters (and perhaps the response to antiplatelet drugs) vary by age and sex (and possibly by other factors, such as different lifestyles) remain speculative at present.[2] The differences between platelet counts of individuals adhering or not to a Mediterranean diet,[6] as well as those reported in the Letter by Sabrkhany *et al.*,[1] are statistically significant, but quite small in absolute terms. Although it is obvious that statistical significance does not necessarily imply biological or clinical relevance,[7] it has been observed that a difference of only 10,000 platelets/μL corresponds to an average of 50 billion circulating platelets.[2] On the other hand, very small variations in platelet count were reported in men at different 10-year risk of developing cardiovascular disease. Only a few thousand circulating platelets are reportedly able to prevent serious hemorrhage in adults with acute myeloid leukemia. Thus, even minor changes in platelet number and/or function could be associated with different phenotypes and lead to different health outcomes, such as neuropsychiatric and neurodegenerative disorders.[5,8]

The following statement made by Giulio Bizzozero in 1882 "it is hardly permitted to assume that elements represented in blood in a constant fashion and at great number, as is the case for blood platelets, are active only under abnormal or pathological conditions. Their physiological significance therefore remains to be investigated…" is still worth consideration. Adopting personalized, sex- and age-matched controls of platelet number and/or platelet-derived biomarkers will help the studies of platelet (micro)-variability in health and disease. This may open a new interesting window on platelet physiology and will also contribute to better targeted and successful antiplatelet therapy. For example, in a meta-analysis of 53 different studies (and 6,450 individuals) on aspirin-treated normal subjects or cardiovascular patients, the response variability to aspirin, as assessed by the point-of-care platelet function test PFA-100, was similar between men and women, but populations with higher mean age had a significantly higher prevalence of non-responders to aspirin than those with a lower mean age.[9]

Aging is the time-dependent functional decline of an organism at all levels and lies at the intersection of genetics, biology, and the environment; it exhibits marked disparity among individuals. The concept of "biological age" has, therefore, recently attracted interest, as chronological age fails to account for the heterogeneity with which individuals age; indeed, concepts of "biological age" have emerged from the need to account for this variability better and are currently a major focus of research.[10] Whether the data presented by Sabrkhany *et al.*[1] and those discussed in this editorial will contribute to introducing the concepts of biological age into platelet research is not known at the moment, but is a reasonable, exciting perspective.

Disclosures

No conflicts of interest to disclose.

Contributions

GdG wrote the draft; MB and CC contributed information and reviewed the final manuscript.

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