Anemia in old age

Elzen, W.P.J. den

10

Summary

Chapter 1 is the general introduction to this thesis. For many years, researchers and clinicians have had a long-lasting and continuous interest in the clinical implications and pathophysiology of anemia in older individuals. Anemia is very common, especially in old age, and has been associated with a number of negative outcomes. However, increasingly data become available that question the extrapolation of 'common' medical knowledge into the highest age groups. Since most studies on anemia have been performed in older persons aged 65 years and over and in selected patient groups only, the impact and etiology of anemia in very old individuals in the general population is largely unknown. Therefore, the aim of this thesis was to study the impact and etiology of anemia in the oldest old in the general population, in order to support the development of evidence-based diagnostic and treatment recommendations for anemia in the oldest old. All studies presented in this thesis are embedded in the Leiden 85-plus Study and the Newcastle 85-plus Study. The chapter concludes with a description of both study populations.

In **Chapter 2**, the impact of anemia in old age was studied. We examined the association between prevalent anemia at age 85 years (at baseline) and incident anemia during follow-up (age 85-90 years) with functional status and mortality. The role of comorbidity in these associations was also investigated. Participants who had anemia at baseline had more disability in activities of daily living, worse cognitive function and more depressive symptoms than participants without anemia at baseline, but these differences disappeared after adjustment for comorbidity. Prevalent anemia and incident anemia were both associated with an increased risk of death, even after adjustment for socio-demographic characteristics and comorbidity. The principal finding of this study was that anemia in old age appears to be associated with an increased risk of death, independent of comorbidity, but the associated functional decline appears to be attributed mainly to comorbidity.

The aim of **Chapter 3** was to investigate whether deficiencies in vitamin B12 and folate are associated with the occurrence of anemia in older persons in the general population. Because serum levels of vitamin B12 and folate alone may not accurately reflect vitamin status at the tissue level, we also studied the effect of elevated serum homocysteine on anemia. Folate deficiency and elevated homocysteine levels were associated with anemia at baseline, but vitamin B12 deficiency was not. Furthermore, vitamin B12 deficiency was not associated with the development of anemia during follow-up or with changes in Mean Corpuscular Volume (MCV). Both folate deficiency and elevated homocysteine levels were associated with the development of anemia from age 85 years onward, but not with an increase in MCV over time. Based on these findings, screening and subsequent treatment of low vitamin B12 levels may not have any beneficial effect on the occurrence of anemia in old age, but early detection of folate deficiency by screening may identify older individuals at risk of developing anemia. Further studies are needed to investigate the effectiveness of vitamin B12 treatment in

older patients with anemia and subnormal vitamin B12 levels and to determine if folic acid fortification of grain and cereal products has a positive effect on the incidence of anemia in old age.

In **Chapter 4**, we performed a systematic review to evaluate the association between subnormal vitamin B12 levels and anemia in older people in published literature to date. Apart from 22 observational studies which showed inconsistent results regarding the association between subnormal vitamin B12 levels or vitamin B12 deficiency and anemia in older subjects, three well-designed placebo-controlled randomized trials showed no effect of vitamin B12 supplementation on hemoglobin levels and MCV during follow-up in subjects with subnormal vitamin B12 levels at the start of the study. We concluded that the evidence of a positive association between subnormal vitamin B12 levels and anemia in older people is limited and inconclusive.

The objective of **Chapter 5** was to investigate the association between low ferritin levels and anemia in old age in the presence and absence of inflammation. At age 85 years, low ferritin was associated with the presence of anemia. This association was more pronounced in participants with elevated C-reactive protein (CRP) levels than in participants with normal CRP levels. Lowest hemoglobin levels and MCV were found in participants with low ferritin and elevated CRP. In the prospective analyses, low ferritin was associated with an accelerated decline in hemoglobin and MCV, especially in participants with elevated CRP at baseline. Although the diagnostic value of serum ferritin levels to detect iron deficiency in patients with anemia, infections and inflammation has been questioned by others because of ferritin's 'acute phase' properties, the findings that we presented in this chapter show the significance of measuring ferritin levels in older individuals, especially among those with infections or inflammation. Future studies are needed to gain more insight into the pathophysiologic mechanisms and clinical implications of these findings.

The aim of **Chapter 6** was to unravel the relation between erythropoietin, hemoglobin and renal function in the oldest old. Erythropoietin levels in our study population of older individuals were comparable to erythropoietin levels found in studies with younger subjects. In both anemic and non-anemic subjects, highest erythropoietin levels were found in subjects with the highest creatinine clearance. Only in participants with severe renal failure, relatively low erythropoietin levels were found.

In **Chapter 7**, we investigated whether high levels of erythropoietin predict mortality in the general population of older individuals. We observed a dose-dependent positive association between increasing erythropoietin levels and mortality, independent of gender, creatinine clearance, hemoglobin level, comorbidity, smoking and CRP level. The association between erythropoietin and

mortality was similar for deaths from cardiovascular and non-cardiovascular causes. We concluded that, in old age, elevated erythropoietin levels are associated with increased mortality, independent of hemoglobin. Further studies are needed to identify the clinical relevance and therapeutic implications of a high erythropoietin level in older people.

Telomere length has been correlated with major age-related diseases. Earlier studies have also shown an association between shorter telomeres and myelodysplastic syndromes and other bone marrow failure syndromes. The objective of **Chapter 8** therefore was to investigate the relation between telomere length and the presence of anemia in the Leiden 85-plus Study and the Newcastle 85-plus Study. In both studies, we observed no differences in telomere length between participants with anemia and participants without anemia. Telomere length also did not correlate with any other hematological parameter. In contrast to other age-related diseases, telomere length appeared not to be associated with anemia in older individuals in the general population, despite the plausible biological mechanism underlying this association. To further investigate this intriguing matter, studies incorporating bone marrow biopsies are needed.

Chapter 9 summarizes the main results of this thesis, discusses implications for clinical practice and includes recommendations for further research. Among other things, it is discussed whether anemia itself is causally related to disability and death using the nine criteria presented by Sir Austin Bradford Hill. In addition, the potential value of a screening program for anemia is discussed according to the criteria from Wilson and Jungner. Next, some of the classical causes of anemia are evaluated using the findings presented in this thesis and recommendations for further research are made, with a clear emphasis on the need to further explore the lack of association between vitamin B12 deficiency and anemia in old age. Because current diagnostic and therapeutic guidelines are based on the classic notions of the etiology of anemia, guidelines on anemia may have to be revisited for the highest age groups in the years to follow. This is necessary because anemia in old age is a highly common clinical condition with a potentially high impact.