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Introduction
General introduction

Our society’s population is ageing rapidly. Nowadays, more than 15% of the Dutch population, 2.5 million persons, is aged 65 years and over and this is expected to increase to 25% in 2040. (1) Unfortunately, not all of these older subjects spent their life in good health. To strive for high quality cure and care for these “complex” older people, knowledge of and research in these aged persons is essential. On the one hand, increasingly data become available that the physiological processes in the oldest old subjects may be distinct from those in young and middle-aged individuals. Therefore, to extrapolate research findings, validated in large studies done with selected younger individuals, into the older populations can be misleading. On the other hand, some organs are less affected than others by the ageing process. For example renal function decreases linearly with increasing age, however there is limited effect of increasing age on bone marrow capacity.

This thesis focuses on the physiological aspects of the interesting triad renal function, erythropoietin production and haemoglobin levels at old age. The decrease in renal function is one of the most relevant functional defects that occurs with increasing age. Erythropoietin (EPO) is produced within the kidney. Furthermore, EPO is the hormone that regulates red blood cell production. Red blood cells develop in the bone marrow and circulate for about 100–120 days in the body. Haemoglobin is the iron-containing oxygen-transport protein within the red blood cells and with increasing age haemoglobin seems to remain stable. Therefore lower haemoglobin levels are not “normal” at old age with increased morbidity and mortality as a result. To develop treatment strategies in the very old, research into the physiology of ageing is needed in population based studies of older subjects. In this thesis we focus on physiological aspects as well as on consequences of decreased renal function and the impact of changes in EPO and haemoglobin levels at old age.

Renal function at old age

A decrease in renal function is one of the most important functional defects that occurs with increasing age. Kidney function is stable until age 30 to 40 and then declines linearly at an average rate of about 8ml/min/1.73m² per decade. (2) Although in clinical practice, the glomerular filtration rate (GFR) is considered to be the best overall reflection of renal function, it cannot be measured easily in daily clinical practice. Therefore GFR is usually estimated from equations (eGFR) such as the classic Cockroft-Gault formula (C-G) (3) and the Modification of Diet and Renal Disease equation (MDRD). (4) More recently
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the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) was suggested as a more accurate estimate of GFR, especially for the relative high ranges of eGFR. (5-7) However, none of these measures are well validated in large samples of older populations. Moreover, impaired renal function has important clinical implications since it has been associated with increased cardiovascular complications and all cause and cardiovascular mortality. (8,9)

**Erythropoietin**

Erythropoietin (EPO) is primarily produced in the kidney and is the principle regulator of red blood cell production. (10) Decreased oxygen availability in the kidney, due to for example anemia or renal hypoperfusion, triggers the production of erythropoietin within the kidney. Conflicting data are available concerning EPO levels at old age. On the one sight it has been suggested that the availability of the kidney to secrete EPO declines with ageing and as a consequence anemia in older subjects is attributed to the decreased levels of erythropoietin. (11) On the other hand, the limited available studies suggest that erythropoietin levels of older subjects are comparable with those of younger individuals. (12,13) Whether endogenous erythropoietin levels are inadequate or nearly normal in elderly is important in clinical practice, because of therapeutic decision making about administrating exogenous erythropoietin for the correction of anemia.

**Haemoglobin**

Anemia, defined as low(er) haemoglobin levels (14), is a common clinical condition in the elderly (15,16) and with advancing age associated with unfavourable events like functional dependency, cardiovascular events, cognitive decline and impaired survival. (17-20) Anemia at old age is not simply a result of diminished hematopoiesis, since there is only little effect of ageing on bone marrow function. (21) Iron deficiency and chronic renal failure are the most common causes of anemia in older subjects. Other well known causes in clinical practice for anemia are folate and vitamin B12 deficiency. Furthermore, several epidemiological studies have found that up to 30% of anemia cases in the older population is unexplained, even when extensive clinical information is available. (22-24) Nowadays, this type of anemia is classified as “unexplained anemia”. The underlying pathophysiological mechanisms of unexplained anemia have yet to be established and it’s clinical relevance for older subjects needs to be determined.
**Aim and outline of this thesis**

In this thesis physiological aspects of the triad haemoglobin, renal function and erythropoietin at very old age are described. Furthermore, the prognostic consequences of changes in haemoglobin, renal function and erythropoietin in a cohort of oldest old subjects is assessed.

Chapter 2 presents the results of calculating renal function in old age by using three different formulae: Cockroft-Gault, MDRD and CKD-EPI equation and to find the best estimate of GFR (eGFR) at old age. The haematopoietic capacity at old age was studied in chapter 3 in two independent, population-based cohorts as well as the relationship between haemoglobin and mortality in oldest old subjects was investigated. The effect of increasing age on renal function and serum levels of haemoglobin and erythropoietin (EPO) in randomly selected individuals in the range of 30-100 years was described in chapter 4. Since high erythropoietin levels have been shown to predict the risk of death among patients with chronic heart failure, in chapter 5 the prognostic value of elevated erythropoietin levels on mortality among very elderly people in the general population was assessed. In chapter 6 the independent predictive value of clinical markers of inflammation in relation to mortality, both vascular and nonvascular, was studied in very old participants, since there predictive value have already been shown in middle-aged populations. Given that in approximately 30% of older persons with anemia, the cause of the anemia is unexplained, in chapter 7 we assessed the clinical differences between older subjects with explained and unexplained anemia and investigated whether these subjects have different mortality patterns compared to subjects without anemia. Finally, in chapter 8 is assessed whether higher haemoglobin levels predict length of hospital stay after hip fracture surgery in elderly subjects. The goal of treating anaemia in older patients who have undergone hip fracture surgery is to enhance functional recovery. In chapter 9 the findings and the possible clinical implications of all presented studies are summarized with brief recommendations for clinicians working with older patients.
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References


