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Health-related quality of life in thyroid and blood disorders

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CHAPTER 1

General introduction and outline of the thesis

According to the European's last Aging Report, published in 2019, the age profile of the European Union is expected to change considerably in the next decades. Decreased fertility rates and increased life expectancy cause aging of the population (1). In 2018, 101.1 million individuals were older than 65 years, which is almost one fifth (19.7%) of the total population. During the next 30 years, the proportion of these older people is expected to gradually increase to 28.5% in 2050 (Figure 1). Therefore, healthy aging will be one of the major challenges in the near future.

As individuals age, the proportion of individuals with one or more chronic diseases rises (2-4). Chronic diseases are often associated with negative health outcomes, including health-related quality of life (HRQoL) (5-7). Thyroid and blood disorders are examples of frequently observed chronic diseases, especially in older individuals.

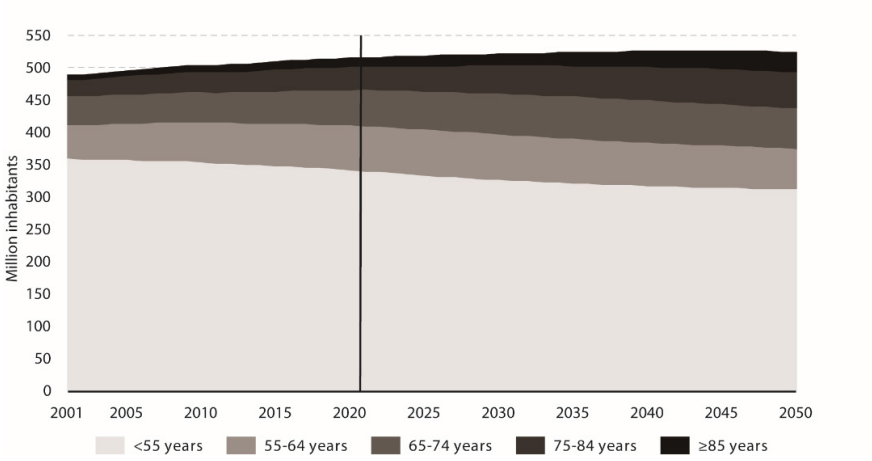

Figure 1. The age profile of the European Union (2001-2050). (Adapted from Eurostat. Ageing Europe — looking at the lives of older people in the EU. 2019) (1)

Part I - Thyroid disorders

Adequate thyroid hormone levels (triiodothyronine (T3) and thyroxine (T4)), are essential for normal growth and differentiation, regulation of energy metabolism, and physiological function of virtually all human organs and tissues. Synthesis and secretion of thyroid hormones in the thyroid gland are regulated by thyroid stimulating hormone (TSH). TSH is produced and secreted in the anterior pituitary. TSH secretion is closely regulated by negative feedback of thyroid hormones and by stimulation of thyrotropin releasing hormone (TRH), which is produced in the hypothalamus.

The thyroid gland produces both T4 and T3. T3 is the active form of thyroid hormone. About 20% of T3 is directly secreted by the thyroid gland. The other 80% of T3 is derived from deiodination of T4 in extra-thyroidal tissue. Two types of deiodinase enzymes catalyse this reaction: deiodinase type 1 (DIO1) and deiodinase type 2 (DIO2). DIO1 is the primary deiodinating enzyme in the liver and kidneys, whereas DIO2 is predominant in the brain and pituitary gland. Conversely, deiodinase type 3 is the main inactivating enzyme, which inactivates both T4 (by conversing it to reverse T3) and T3 (by conversing it to T2). Together, these three enzymes regulate the euthyroid state in blood and tissues. T4 and T3 cross the membranes of target cells via specific transporters. Intracellular, T3 binds to the nuclear thyroid hormone receptor to regulate transcription of target genes (8-10) (Figure 2).

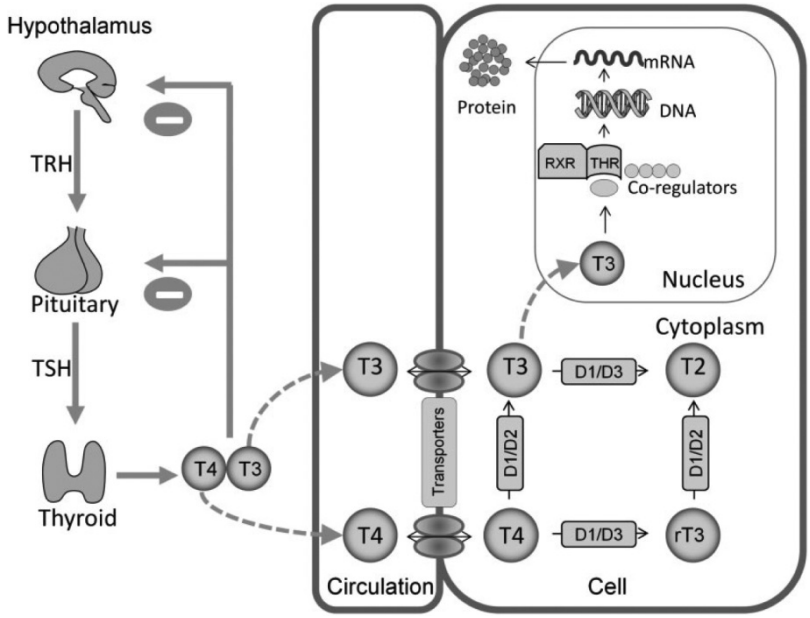

Figure 2. Thyroid hormone regulation and action. (Adapted from Eligar V. Ann Clin Biochem. 2016;53:421-433) (11). D1, deiodinase type 1; D2, deiodinase type 2; D3, deiodinase type 3; rT3, reverse triiodothyronine; RXR retinoic X receptor; T2, diiodothyronine; T3, triiodothyronine; T4, thyroxine; THR, thyroid hormone receptor; TRH, thyrotropin releasing hormone; TSH, thyroid stimulating hormone.

Disorders of thyroid function are prevalent and their prevalences increase with age (12-14). Thyroid dysfunction and the treatment thereof may have great impact on long-term health (15, 16). Hypothyroidism can be classified as primary (due to thyroid hormone deficiency), secondary (due to TSH deficiency), tertiary (due to TRH deficiency), and peripheral (extra-thyroidal). Peripheral hypothyroidism

can be caused by decreased sensitivity to thyroid hormone due to rare genetic syndromes or by consumptive hypothyroidism. Secondary, tertiary and peripheral hypothyroidism are rare. In iodine-sufficient areas, auto-immune thyroiditis (Hashimoto thyroiditis) is the most common cause of primary hypothyroidism. Other causes of primary hypothyroidism are iodine deficiency, drugs, iatrogenic or transient thyroiditis (14).

In primary hypothyroidism, thyroid hormone replacement with synthetic levothyroxine is the standard treatment according to the current guidelines. The goals of this treatment are to reduce or eliminate symptoms and to normalize serum levels of TSH and thyroid hormones (14, 17). Unfortunately, a considerable part of treated patients continues to experience symptoms and disturbed well-being despite the fact that they are biochemically euthyroid (e.g. a TSH level within the normal range) (18, 19). It has been shown that in patients treated with levothyroxine monotherapy, despite having normal TSH levels, FT4 levels were higher and FT3 levels lower, and consequently the FT3 / FT4 ratio was significantly lower than in euthyroid control subjects (20). These observations led to multiple trials of combination therapy in which levothyroxine was combined with liothyronine (LT3), with in general negative results (17). Several potential explanations, other than lower T3 and higher T4 levels, for the decreased well-being have been proposed in a recent comprehensive review. These include ascertainment bias (patients with symptoms may be more likely to be screened for hypothyroidism), levothyroxine may not reverse hypothyroidism in all tissues, TSH may not be the best biomarker for judging adequacy of levothyroxine replacement, genetic susceptibility, detrimental effect of autoimmunity, coexisting chronic diseases and coexisting psychiatric diseases (19). Given the high prevalence of hypothyroidism in the general population and the substantial proportion of treated patients having impaired HRQoL, it is relevant to elucidate underlying factors which might contribute to this phenomenon.

Part II - Blood disorders

Hematopoietic stem cells are expected to maintain adequate blood cell populations of erythrocytes, myeloid cells, lymphocytes, natural killers cells, mast cells, dendritic cells and platelets throughout an individual's lifespan. With aging of the hematopoietic system certain phenotypes can be observed (21 - 23). Red blood cell and platelet counts gradually decrease with advancing age and laboratory results outside the normal reference range are more common in older individuals. Additionally, the aging hematopoietic system is known for skewing towards the myeloid lineage, whereas lymphocyte counts gradually decrease with age (Figure 3) (24-31). Finally, the incidence of myeloid malignancies (like acute myeloid leukaemia and myelodysplastic syndromes) is increased upon ageing (23).

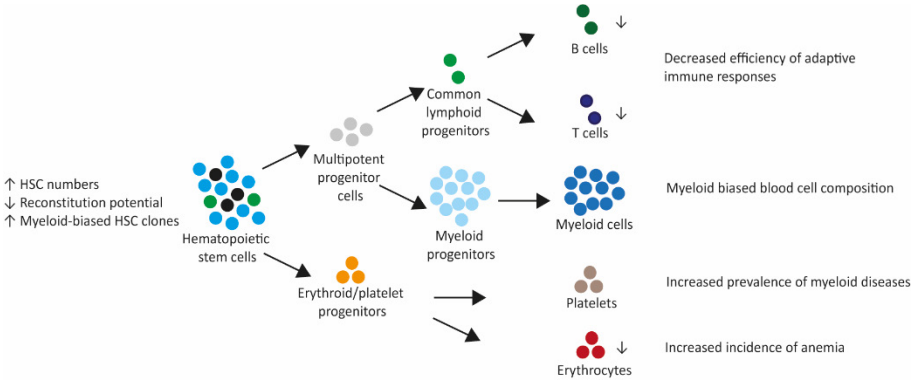

Figure 3. Ageassociated alterations in the hematopoietic system. (Adapted from Wahlestedt M. Stem Cells Transl Med. 2015;4(2):186-94) (23). HSC, hematopoietic stem cell.

Anaemia is frequently present in older individuals and is extensively studied (32). According to the World Health Organization (WHO), anaemia is defined as a haemoglobin concentration <13.0 g/dL (~8.0 mmol/L) in adult males and <12.0 g/dL (~7.5 mmol/L) in adult, non-pregnant females (33). In general, more than half of anaemic older individuals can be diagnosed with nutritional deficiencies or have anaemia of chronic inflammation. The aetiology of anaemia in older individuals remains unknown in about one-third of the cases (34, 35). In older individuals the presence of anaemia, even mild, is associated with numerous adverse health events, including falls, hospitalization and mortality (36-40). In contrast, data about the association between blood cell count abnormalities and HRQoL are scarce.

One of the potential underlying aetiologies of unexplained anaemia in older individuals are myelodysplastic syndromes (MDS). MDS are clonal disorders of the hematopoietic stem cell, characterized by bone marrow failure which results in blood cytopenias including anaemia. MDS is known to be associated with poor survival and decreased HRQoL (41, 42). The only curative treatment option is hematopoietic cell transplantation. Due to advanced age and / or co-existing medical conditions, patients are often ineligible for this procedure. Therefore, treatment often focuses on improving quality of life, especially in lower-risk MDS patients. According to the current guidelines, treatment modalities aiming to increase haemoglobin levels (e.g. red blood cell transfusions or erythropoietin) are first choice (43). However, studies assessing the association between haemoglobin concentration and HRQoL in MDS patients demonstrate conflicting results (44 - 47). Since treatment often focuses on increasing haemoglobin concentration, it is important to have knowledge of the anaemia-independent impact of MDS on HRQoL.

Erythrocytosis, an increase of red blood cell mass, lies at the other end of the spectrum of red blood cell count abnormalities and can be primary or secondary

in origin. Primary erythrocytosis results from increased autonomous production of red blood cells, for example caused by a myeloproliferative neoplasm or a rare inherited condition. Secondary erythrocytosis is used to categorize cases in whom erythropoietin drives the bone marrow to produce more red cells, e.g. in case of chronic hypoxia or in case of an erythropoietin producing tumour. The most common cause of acquired primary erythrocytosis is polycythaemia vera (PV), which is characterized by the presence of the JAK2 V617F mutation or in a minority of cases a JAK2 exon 12 mutation (48). PV is known to be associated with morbidity (especially cardiovascular disease) and mortality. However, in the majority of individuals with erythrocytosis it is secondary in origin. Large scale data of health outcomes in individuals with erythrocytosis from the general population are scarce.

(Health-related) quality of life

Quality of life and health-related quality of life were already discussed in the medical literature in the 1960's respectively 1980's. Since then, quality of life has become increasingly important in health care practice and research. This was caused by the fact that medical treatment became able to extend length of life, sometimes at the expense of quality of life and conversely that treatment modalities became available which improved quality of life without extending life expectancy. Measurement of quality of life gained also importance because of a wish to measure outcomes beyond morbidity and biological functioning (49). In health-related quality of life assessment several instruments can be used. Disease-specific instruments measure symptoms that are specific for the disease being studied, or measure the consequences of a particular disease on a participants' health-related quality of life. On the other hand, disease-generic instruments measure the overall health-related quality of life, independent of the specific disease of an individual. In the studies described in this thesis, the RAND 36-Item Health Survey, which is a disease-generic instrument, is used. The Dutch RAND-36 is comparable with the English Short-Form-36 Health Survey (SF-36). In this thesis the words 'RAND-36' and 'SF-36' are used interchangeable. The RAND-36 measures health perception across eight multi-item health domains. These include domains mainly related to physical health (i.e. physical functioning, role limitations due to physical health problems, bodily pain and general health) and domains mainly related to mental well-being (i.e. social functioning, role limitations due to emotional problems, mental health and vitality) (50).

The Lifelines Cohort Study

All studies described in this thesis are based on data from the Lifelines Cohort Study. In this multi-disciplinary prospective population-based cohort study health and health-related behaviours of 167729 individuals living in the three Northern provinces of The Netherlands are studied in a three generation design. Recruitment of participants was performed between December 2006 and December 2013 using three different strategies. First, a selection of general practitioners invited all of their listed patients between 25 and 50 years of age (index cohort). Individuals were not invited when the participating general practitioner considered the patient not eligible by reason of limited life expectancy, severe psychiatric or physical illness or insufficient knowledge of the Dutch language. Second, when willing to participate, these individuals were asked to invite their family members (such as partners, parents, parents-in-law and children) to participate as well. Third, inhabitants of the northern provinces who were not invited by their general practitioner could register themselves using the Lifelines website. This recruitment strategy resulted in a cohort with low risk of selection bias, a high participation rate and which appeared to be broadly representative for individuals living in the North of the Netherlands (51-53). A comprehensive overview of the data collection can be found in the Lifelines catalogue at www.lifelines.net.

Aims and outline of the thesis

The general aim of this thesis was to provide insight in health outcomes including health-related quality of life in community-dwelling individuals with thyroid and blood disorders. To this end, we used data from the large Dutch Lifelines Cohort Study.

In the first part of this thesis we investigated the epidemiology, comorbid conditions and impact of thyroid disorders on HRQoL. In **Chapter 2** we described the epidemiology of thyroid disorders in the Lifelines cohort and we compared the results with data from another population-based study and the Dutch general practitioner morbidity registry. In **Chapter 3** we assessed in a cross-sectional study the effect of levothyroxine use on HRQoL and cognitive functioning. Furthermore, we investigated whether a polymorphism in deodinase type 2 impacted on thyroid hormone levels, HRQoL and cognitive functioning in both the general population as well as in individuals using levothyroxine. In **Chapter 4** we aimed to provide insight in comorbidities associated with hypothyroidism and their composite impact on HRQoL.

The second part of this thesis focuses on blood count abnormalities and their association with adverse health outcomes including health-related quality of life. First, we studied disorders related to red blood cells. In **Chapter 5**, we assessed the

prevalence of anaemia and the subtypes of anaemia. We studied the association between (subtypes of) anaemia and survival, and HRQoL in both younger and older individuals. We used the association between anaemia and HRQoL to evaluate the currently used WHO definition of anaemia in the perspective of optimal HRQoL, considering the impact of age and gender. In **Chapter 6,** we aimed to provide insight in the anaemia-independent impact of MDS on HRQoL. To achieve this, data from the Lifelines cohort were compared to data from the European MDS Registry, a non-interventional study cohort of newly diagnosed lower-risk MDS patients. In **Chapter 7** we described clinical characteristics, morbidity, mortality and the association with clonal haematopoiesis in individuals with erythrocytosis. We used these associations to evaluate the currently used criteria of erythrocytosis. Second, in **Chapter 8** we assessed the association between other abnormalities in peripheral (differential) blood cell counts and HRQoL. Furthermore, we compared the association between these differential blood cell counts and hs-CRP, as another marker of inflammation, on HRQoL. In **Chapter 9** we evaluated the effect of smoking on mean corpuscular volume of the erythrocytes in participants of two population-based studies; the Lifelines Cohort Study and the Prevention of Renal and Vascular EndStage Disease (PREVEND) study. **Chapter 10** provides a summary and discussion of the main results of the thesis, methodological considerations and perspectives.

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