Medizinische Fakultät
der
Universität Duisburg-Essen

Aus der Klinik für Endokrinologie, Diabetologie und Stoffwechsel

Thyroid related quality of life in elderly with borderline hypothyroidism and influence of levothyroxine therapy in comparison to young patients (TSAGE)

I n a u g u r a l – D i s s e r t a t i o n
zur
Erlangung des Doktorgrades der Medizin
durch die Medizinische Fakultät
der Universität Duisburg-Essen

Vorgelegt von
Mag[a]. rer. nat. Stefanie Recker

aus
Rheine
2019

DuEPublico

Duisburg-Essen Publications online

UNIVERSITÄT DUISBURG ESSEN

Offen im Denken

ub | universitäts bibliothek

Diese Dissertation wird über DuEPublico, dem Dokumenten- und Publikationsserver der Universität Duisburg-Essen, zur Verfügung gestellt und liegt auch als Print-Version vor.

DOI: 10.17185/duepublico/72926
URN: urn:nbn:de:hbz:464-20201118-095844-9

Alle Rechte vorbehalten.

Dekan:	Herr Univ.-Prof. Dr. med. J. Buer
1. Gutachter:	Frau Univ.-Prof. Dr. Dr. med. D. Führer-Sakel
2. Gutachter:	Frau Priv.-Doz. Dr. med. S. Hahn
3. Gutachter:	Herr Univ.-Prof. Dr. med. Ch. Rischpler

Tag der mündlichen Prüfung: 23. September 2020

Own publications on thyroid related quality of life in older and younger patients with thyroid dysfunction:

Scientific Article

Recker, S., Voigtländer, R., Viehmann, A., Dunschen, K., Kerp, H., Frank-Raue, K., Leidig-Bruckner, G., Graf, D., Lederbogen, S., Dietrich, J. W., Görges, R., Brabant, G., Völker, U., Watt, T., Zwanziger, D., Moeller, L. C., Führer, D. (2019). Thyroid Related Quality of Life in Elderly with Subclinical Hypothyroidism and Improvement on Levothyroxine is Distinct from that in Young Patients (TSAGE). Horm Metab Res 51, 568-574.

Poster:

Recker, S., Voigtländer, R., Lederbogen, S., Frank-Raue, K., Raue, F., Graf, D., Görges, R., Dunschen, K., Viehmann, A., Strucksberg, K., Friedrich, N., Moeller, L., Führer, D. (2017) Elderly patients with thyroid dysfunction benefit from treatment. Posterbeitrag 60. Deutscher Kongress für Endokrinologie am 16.03.2017 in Würzburg

INDEX

Page

1 INTRODUCTION 1

1.1 The Thyroid Gland 1

1.2 Hypothyroidism 3

1.2.1 Epidemiology of hypothyroidism 5

1.2.2 Aetiology of hypothyroidism 5

1.3 Hyperthyroidism 6

1.3.1 Epidemiology of hyperthyroidism 7

1.3.2 Aetiology of hyperthyroidism 8

1.4 Treatment Recommendations for Thyroid Dysfunction 9

1.5 Quality of Life 10

1.5.1 QoL and HRQL Measures 11

1.5.2 QoL in Thyroid Dysfunction 12

2 RESEARCH QUESTIONS OF THE THESIS: 14

2.1 Impact of Age on QoL in Thyroid Dysfunction 14

3 MATERIAL AND METHODS 17

3.1 Patient Populations 17

3.2 QoL Measures 17

3.2.1 The SF-36 Health Survey 17

3.2.2 The ThyPro Questionnaire 18

3.3 Laboratory parameters 20
3.4 Statistical analyses 20

4 RESULTS 22

4.1 Differences in QoL to the Age and Standard Specific Norm 24
4.2 Disease-Specific QoL Measured by ThyPRO 27
4.3 QoL and HRQL in Younger and Older Hyperthyroid Patients 30
4.3.1 Differences in generic QoL compared by age and standard specific norm 31
4.3.2 Disease-specific QoL measured by ThyPRO in hyperthyroid patients 34
4.4 QoL and HRQL in Younger and Older Overt Hypothyroid Patients 37
4.4.1 Differences in generic QoL compared to age and standard specific norm in overt hypothyroid patients 38
4.4.2 Disease-specific QoL measured by ThyPRO in overt hypothyroid patients 40

5 DISCUSSION 42

6 ABSTRACT 49

7 LITERATUR 50

8 APPENDIX 57

8.1 Abbreviation 57
8.2 Index of Tables 57

8.3 Index of Figures 58

8.4 Questionnaires used 59

8.4.1 ThyPRO 59

8.4.2 SF-36 69

9 ACKNOWLEDGEMENTS 73

10 CURRICULUM VITAE 74

1 INTRODUCTION

1.1 The Thyroid Gland

As an endocrine organ, the thyroid gland produces hormones that are essential for almost all functions of the body. Thyroid hormones (TH) control metabolism, including processes such as protein synthesis, carbohydrate and fat metabolism, as well as neuronal development and function, growth and bone maturation, cardiovascular, and renal functions (Mondal et al., 2016). TH increase tissue thermogenesis and metabolic basal rate and lower serum cholesterol and systemic vascular resistance (Ross et al., 2016).
The classical TH comprise levothyroxine (T4) and 3,5,3'-triiodothyronine (T3). The thyroid gland mainly produces T4 as a prohormone and a smaller fraction of the biologically active hormone T3. A majority of T3 is generated in the periphery by 5'-deiodination of T4 through iodothyronine deiodinases. THs unfold their specific functions at different target organs, mostly but not exclusively through canonical action on nuclear TH receptors (TR) alpha and beta (Mondal et al., 2016).

The biosynthesis of TH takes place in the colloid filled follicles of the thyroid gland. The colloid mainly contains the protein thyroglobulin (Tg). The synthesis of T4 takes place on Tg, which contains many tyrosyl residues to bind the iodine. First, the iodide required for synthesis is transported from the blood into the thyrocytes through the sodium iodide symporter (NIS). Following, iodide is oxidized by the thyroid peroxidase (TPO) to iodine, thus becomes now unable to leave the thyroid follicle again. In the presence of hydrogen peroxide (H_2O_2) and TPO, iodine binds to tyrosyl residues of the thyroglobulin and forms monoiodotyrosine and diiodothyrosine as precursors of T4 and T3. Finally, T4 is generated by phenolic coupling of the iodotyrosyl residues on Tg by TPO. Thyroglobulin is taken up from the follicular cells via endocytosis into the epithelial cell of the thyroid gland. In order to release TH into the blood stream, T4 and a small fraction of T3 are liberated by proteolysis (Mondal et al., 2016) and are exported via the TH transporter MCT8 (Di Cosmo et al., 2010).

The production of TH is regulated and controlled by an endocrine feedback loop, consisting of the hypothalamus and pituitary gland, known as the hypothalamus-pituitary-thyroid axis. Within the hypothalamus neurons in the paraventricular nucleus

secrete thyrotropin-releasing hormone (TRH). TRH passes through the portal vascular system into the pituitary frontal lobe. The secretion of TRH is stimulated by energy-demanding processes such as stress, physical strain or cold. TRH stimulates the secretion of the thyroid-stimulating hormone (TSH). TSH binds to its receptor in the thyroid gland where the biosynthesis of T4 and T3 is initiated. The set value of plasma TSH is adjusted by negative feedback of THs at the levels of the hypothalamus and the pituitary. TH concentrations are adjusted to the physiological need of the body by the function of the hypothalamus-pituitary-thyroid axis (Mondal et al., 2016).

Because THs are poorly water-soluble THs need transport proteins. These include the thyroxine-binding globulin (TBG), transthyretin (TTR), and serum albumin (HAS). The high affinity of the transport proteins to T4 and T3 cause a slow release and long half-life of TH in the blood serum (Mondal et al., 2016).

It was only discovered in 2004 that THs require membrane transporter proteins for translocation across membranes (that is, to enter and leave the cell). The discovery of the need for membrane transport proteins was made when mutations in the TH transmembrane transporter, monocarboxylate transporter 8 (MCT8) were found in patients with severe psychomotor retardation (Allan-Herndon-Dudley Syndrome). THs enter cells via transmembrane transport proteins such as MCT8 and MCT10. After TH have entered the cell, they can be metabolized by cytosolic enzymes, that is iodothyronine deiodinases (DIOs). These selenoenzyms have different selectivity for deiodination and transduce the barely biologically active T4 into the active form T3. For the local TH homeostasis, the selective deiodination of the phenol and tyrosyl ring plays a major role. T4 is converted to T3 by monodeiodination on the phenolic ring. Deiodination of the tyrosyl ring converts T4 into the biologically inactive metabolite of L-3,3',5'-triiodothyronine (rT3). In addition, T3 and T4 are bound by the nuclear thyroid hormone receptors α and *β* with different affinity. Thyroid receptors (TRs) are able to bind as homo- and / or heterodimers and thereby form receptor complexes that bind to thyroid hormone responsive elements (TREs) through the presence of a specific nucleotide sequence in the target genes. The binding of TREs to the receptor complexes induces the activation of co-repressor and co-activators, thereby regulating gene expression. Because of their tissue-specific expression

patterns, the effects of TRs are also very specific. TRα is relevant for heart and bone function, while TR*β* controls metabolism in the liver and mediates TH feedback in the pituitary gland (Mendoza et al., 2017; Mondal et al., 2016).

1.2 Hypothyroidism

Hypothyroidism is a condition where the body lacks TH or proper TH action and several of the organ functions may be impaired. The clinical picture of hypothyroidism is characterized by its aetiology, the duration or the extent of TH deficiency, and existing comorbidities (see Table 1 for a list of possible symptoms). Depending on the severity of TH deficiency, different degrees of hypothyroidism are defined, ranging from subclinical, to overt hypothyroidism, to the rare, to an extremely rare condition of coma (Chaker et al., 2017).

Subclinical hypothyroidism (sHT) is characterized by an increased concentration of TSH with normal T4 levels. Overt hypothyroidism is defined by elevated TSH and decreased fT4 serum concentrations.

Hypothyroidism usually begins insidiously; severe symptoms may only occur with sustained TH deprivation. Each individual patient may have any number of these symptoms. The most common symptoms are cold intolerance, constipation, weight gain, oligomenorrhea/amenorrhea, fatigue, memory deficits, and depression (Chaker et al., 2017).

General symptoms
- Reduction in performance, fatigue, weakness
- Weight gain
- Cold intolerance

Thyroid
- Absent, small or normal size, or goitre

Cardiovascular system
- Sinus bradycardia
- Heart failure, cardiomegaly, pericardial effusion
- Arterial hypotension, paradoxical hypertension

Lungs
- Respiratory insufficiency
- Hypercapnia

Skin and appendages
- Dry, pale skin (palms), hair loss, brittle nails
- Pretibial myxedema (Graves' disease)

Eyes
- Eyelid edema
- Exophthalmos (rare in autoimmune thyroiditis)

Mouth and larynx
- Macroglossia
- Slurred speech, deep, harsh voice

Nervous system
- Lethargy, apathy, drowsiness, difficulty concentrating, weakness of memory
- Depressions, psychosis
- Stupor, coma
- Cerebellar ataxia, inner ear deafness
- Hyporeflexia

Musculoskeletal system
- Muscle weakness, muscle atrophy, muscle pain, increase in creatine kinase
- Delayed skeletal maturity in children

Gastrointestinal tract
- Loss of appetite
- Constipation
- Megacolon, ileus (rare)
- Ascites (rare)

Gonads
- Women: irregular menses, amenorrhea, menorrhagia, infertility
- Men: decrease in libido, impotence and gynecomastia

Metabolism
- Decreased metabolic rate with weight gain, obesity
- High cholesterol
- Low blood sugar

Other laboratory values
- Hyponatremia
- Anemia

Table 1 Symptoms of Hypothyroidism

1.2.1 Epidemiology of hypothyroidism

In the general population, the prevalence of hypothyroidism depends on the defined TSH references ranges; hence, different frequencies have been reported in cohorts worldwide. M. P. Vanderpump (2011) screened large population samples from the USA and Europe and found a prevalence of 1–2% for overt hypothyroidism in iodine-replete communities. The prevalence of sHT in the general population is estimated to be between 3 and 10% according to epidemiological data for the United States, Denmark, and the United Kingdom (Blum et al., 2015; Canaris et al., 2000; Hollowell et al., 2002; Knudsen et al., 2000; Vanderpump et al., 1995). In Germany, there are regional differences in the prevalence of thyroid disorders, among others, depending on the regional iodine supply. This was examined in two population-based surveys: the Study of Health in Pomerania (SHIP) in the northeast of Germany and the Kooperative Gesundheitsforschung in der Region Augsburg (KORA) in the south of Germany. Elevated TSH values or sHT (TSH reference range of 0.3–3.0mIU/l) in 25 to 88-year-olds was found in 1.5% of the population in SHIP and 4.1% in KORA. There was no significant difference in the frequency of positive TPO Antibodies between KORA and SHIP (Meisinger et al., 2012). Hintze et al. (2010) report the prevalence of overt hypothyroidism for 0.1% and, for sHT, 6.1% in the German population-based Nixdorf Recall study that included 4400 persons aged 45–74 years. TSH values increased with age. Studies report prevalence data of sHT of up to 18% in people >65 years of age (J.Diez, 2002; Meisinger et al., 2012; Rodondi et al., 2010)

1.2.2 Aetiology of hypothyroidism

The causes of hypothyroidism include either the thyroid itself (primary), or the pituitary gland or hypothalamus (secondary), that is, diminished pituitary TSH secretion or hypothalamic TRH deficiency.

Primary hypothyroidism is more frequent than secondary hypothyroidism and can be either congenital or acquired (autoimmunity, therapeutic measures). The most common cause of acquired primary hypothyroidism is chronic autoimmune thyroiditis (often called Hashimoto’s thyroiditis). Other possible causes include radioiodine

therapy, thyroid surgery, excessive iodine intake (for example, amiodarone), antithyroid drugs, interferon, and PD1 inhibitor therapy.

1.3 Hyperthyroidism

Hyperthyroidism is associated with weight loss, osteoporosis, atrial fibrillation, embolic events, heart failure, muscle weakness, tremor, neuropsychiatric symptoms and, more rarely, cardiovascular collapse and increased mortality (Table 2) (Kahaly et al., 2018; Ross et al., 2016). There is no direct association between the degree of serum TH excess and the severity of clinical signs and symptoms. The effects of THs on the central nervous system and the sympathetic autonomic nervous system include anxiety, agitation, tachycardia, sweating, and tremor. In younger patients and patients with a larger goitre, these symptoms may be more pronounced (Boelaert et al., 2010). Hyperthyroidism is associated with increased cardiovascular morbidity (arrhythmia, cardiomyopathy, stroke) and mortality, particularly in the elderly (Kahaly et al., 2018; Ross et al., 2016).

Subclinical hyperthyroidism (sHY) is defined by normal thyroxine (T4) and triiodothyronine (T3) concentrations with low or undetectable TSH. Overt hyperthyroidism is defined as a suppressed serum thyrotropin (TSH) with elevated serum levels of T_3 and/or free T_4 (Kahaly et al., 2018).

General symptoms
- Reduction in performance, fatigue, weakness
- Weight loss
- Heat intolerance

Thyroid
- Goitre

Cardiovascular system
- Tachycardia
- Stenocardia
- Arterial hypertension

Lungs
- Respiratory insufficiency
- Hypercapnia

Skin and appendages
- Warm, wet skin (palms), hair loss, brittle nails

Eyes
- Exophthalmos (endocrine orbitopathy) in case of immune hyperthyroidism

Nervous system
- Lethargy, apathy
- Psychomotor restlessness and irritability
- Sleep disorders
- Hyperreflexia, tremor and sweating

Musculoskeletal system
- Myopathy or osteopathy
- Adynamia in combination with pain in the legs (mainly thighs)
- Muscle cramps

Gastrointestinal tract
- Increase of appetite
- Diarrhea

Gonads
- Women: irregular menses, amenorrhea, menorrhagia, infertility
- Men: decrease in libido, impotence and gynecomastia

Metabolism
- Increased metabolic rate with weight loss
- High cholesterol
- Pathological glucose tolerance

Table 2 Symptoms of Hyperthyroidism

1.3.1 Epidemiology of hyperthyroidism

The European Thyroid Association reports a prevalence of 1.2–1.6% hyperthyroidism in the general population with 0.5–0.6% corresponding to overt hyperthyroidism and 0.7–1.0% to sHY (Kahaly et al., 2018). The prevalence of sHY in Germany as detected in the SHIP cohort by Völzke and colleagues in 2003 was 1.8%; the prevalence of overt hyperthyroidism was 0.4%. When applying a TSH reference

range of 0.3–3.0 mIU/l, the prevalence of low TSH/sHY was 5.2% in SHIP and 2.0% in KORA (Meisinger et al., 2012). There is evidence that subclinical and overt hyperthyroidism are age-dependent, with a higher prevalence in the older population (Hollowell et al., 2002; Völzke et al., 2003). In other cohorts, the prevalence of sHY in the elderly varies from 0.8–2% (de Jongh et al., 2011; Hollowell et al., 2002; Wilson et al., 2006). This may be due to different study entry criteria, TSH assays, and reference ranges used in epidemiological studies. Furthermore, the prevalence of endogenous sHY in a population is affected by gender and iodine intake (Garmendia Madariaga et al., 2014; Hollowell et al., 2002; Schouten et al., 2011).

1.3.2 Aetiology of hyperthyroidism

Hyperthyroidism is a condition defined by excess THs or increased TH action. Hyperthyroidism may be endogenous due to the presence of multinodular toxic goitre (an autonomous thyroid nodule), Graves' disease, thyroiditis, or it may be exogenous secondary to TH administration (factitious thyrotoxicosis) (Kahaly et al., 2018; Ross et al., 2016; Schouten et al., 2011). In iodine-rich parts of the world, Graves' disease is the most common cause of hyperthyroidism, whereas, in iodine-deficient regions, toxic nodular hyperthyroidism is the most common cause (Hamburger, 1980). With regard to elderly populations, toxic multinodular goitre is responsible for the majority of cases of hyperthyroidism (Franklyn et al., 2012; Völzke et al., 2003).

Iodine deficiency (often over the course of multiple years) may lead, from diffuse thyroid enlargement, to the development of one or more nodules and eventually the autonomous function of one or more of these nodules, resulting in hyperthyroidism. Furthermore, sudden high iodine exposure (for example, intake of iodine-containing contrast agents or drugs, particularly amiodarone) may trigger thyrotoxicosis. Frequently, a long history of progression from thyroid enlargement leads to the development of thyroid autonomy. Elderly patients presenting with hyperthyroidism often describe the presence of goitre for many years (Hamburger, 1980).

Another major cause of hyperthyroidism is Grave's disease (GD). GD is an autoimmune disease characterized by circulating autoantibodies that activate the thyroid-stimulating hormone receptor (TSH-R), leading to unregulated TH production and release, and thyroid growth (Kahaly et al., 2018).

A familial cluster of GD or autoimmune thyroiditis has been observed. An estimated 30% of GD patients have a family history of autoimmune thyroid disease. Furthermore, the susceptibility to GD is genetic. There is an association between alleles of the major histocompatibility complex with GD (susceptibility being carried with HLA-DR3 and HLA-DR4 haplotypes). Other risk factors for GD include environmental factors such as cigarette smoking, high dietary iodine intake, stress, and pregnancy (Kahaly et al., 2018). TSH-R-Ab can be detected in most cases of GD at initial presentation, and a hypervascular and hypoechogenic thyroid can be found at ultrasonography, occasionally in association with endocrine orbitopathy (Ross et al., 2016; Smith et al., 2016).

Treatment of hyperthyroidism includes antithyroid drugs that block TH synthesis, radioactive iodine treatment, and thyroid surgery. GD hyperthyroidism is usually treated with methimazole (MMI) as the preferred drug for 12 to 18 months. Spontaneous remission occurs in up to 50% of cases (Kahaly et al., 2018). In thyroid autonomy, ablation is carried out either by 131-I therapy or surgery.

1.4 Treatment Recommendations for Thyroid Dysfunction

There is consensus in the literature that overt hyper and hypothyroidism, as well as sHY with TSH levels below 0,1 mU/l, require treatment; the situation is less clear for sHT (Biondi et al., 2015). In this situation, (Pearce et al., 2013), where elevated TSH values are understood as a continuum, additional criteria may be needed for the decision to start a levothyroxine substitution. Furthermore, sHT does not necessarily progress to overt hypothyroidism, and the chance of a spontaneous remission of elevated TSH is comparatively high (Verma et al., 2009). Since latent hypothyroidism is associated with elevated antibody titers, the risk of developing overt hypothyroidism is about 4% per year. If there is either an isolated TSH increase or positive thyroid antibodies, the annual risk falls to 2%(Vanderpump et al., 1995).

The risk of progression from sHY to overt hyperthyroidism is about 5–8% per year. The risk of progression is influenced by disease aetiology. The cumulative percentage of the population requiring therapy for overt disease at 5 years was 9%

for GD, 21% for multinodular goitre, and 61% for autonomous thyroid nodule (Schouten et al., 2011).

1.5 Quality of Life

Outcomes research and health-technology assessment are important fields of interest in order to assess cost effectiveness, efficacy, and benefits of new therapeutic strategies; these assessments can help determine whether associated increased expenses for health care are justified. With regard to changes in the older population as well as potentially chronically ill and long-term treatable individuals (with an increased likelihood of medical intervention), quality of life (QoL) becomes increasingly important (Kovács, 2016; Testa et al., 1996).

In 1947, the mindset of health changed when the WHO defined health as a state of complete physical, mental and social well-being and not only the absence of disease. Following this definition, the understanding of health expanded to encompass the biopsychosocial model, thus moving away from the purely biological concept. Along with progressing medical possibilities, the need for the development of QoL research in medicine became apparent (Bullinger, 1997; Bullinger et al., 2000).

Starting with initial skepticism toward the validity of classical clinical parameters such as mortality and morbidity for the overall assessment of the success of therapy, the demand for better methods to assess treatment success evolved (Bullinger, 1997). There is no linear relationship between the objective health status of a patient and the actual experienced QoL. QoL is affected by the patient's subjective perceptions, experiences, beliefs, expectations, and their ability to cope with limitations (Testa et al., 1996). In order to assess the extent of subjectively experienced limitations that are due to disease, the concept of “health-related quality of life” (HRQL) evolved. HRQL as a more specific component of QoL is a multi-dimensional construct strongly based on the health concept of the WHO. It is designed to assess the extent of subjectively experienced limitations that are due to disease. Through this, areas that may require special therapeutic attention can be identified (Rose et al., 2000). With reference to the WHO definition of health, Rose et al. (2000) define HRQL as a construct composed of physical and mental well-being, everyday functioning and social inclusion (Rose et al., 2000).

Thus, from the perspective of the respondent, the concept of HRQL includes the mental state, the physical condition, the social embedding and the fulfillment of everyday roles, both in terms of feeling and functioning (Bullinger et al., 2000).

1.5.1 QoL and HRQL Measures

In order to assess this complex construct of QoL/HRQL, standardized questionnaires are used. These questionnaires capture different components of QoL (see Chapter 1.4) such as physical, mental and social well-being and functioning (Watt et al., 2006).

There are disease-specific and generic questionnaires. Disease-specific questionnaires are used to display the particular problem areas that are impaired in patients with a specific medical condition, whereas generic instruments measure aspects common to most patients. The advantage of disease-specific questionnaires is their greater sensitivity compared to generic questionnaires. Generic measures have the advantage of enabling comparison across various diseases and treatments. Ideally, studies examining QoL or HRQL combine disease-specific and generic instruments to make use of complementary information that these instruments supply (Watt et al., 2006).

Psychometric quality criteria should apply to the standardized questionnaires used. These criteria are, for example, validity (the instrument measures what it intended to), content validity (evidence that a questionnaire covers all HRQL aspects relevant for the intended purpose), construct validity (the extent to which a scale measures the hypothesized construct), responsiveness (the ability of an instrument to detect relevant changes in HRQL over time, for example, as the result of a clinical intervention), and reliability (the extent to which a measure yields the same score at independent assessments), and so on (Watt et al., 2006).

Concerning generic QoL instruments, there are well-established questionnaires (for example, SF-36 or EQ-5D) that meet all of the mentioned quality criteria. One of the most applied, best-known, and well-accepted instruments is the SF-36 (Watt et al., 2014). The SF-36 has substantial documentation of its measurement properties and allows the comparison of QoL to a German standard sample. Therefore the SF-36 was selected to measure generic QoL in this study.

For the evaluation of the thyroid diseases, HRQL specific questionnaires exist, for example, the Chronic Thyroid Questionnaire, the Thyroid Symptom Questionnaire, the Graves' Ophthalmopathy Quality of Life Questionnaire, and the Hyperthyroidism Complaint Questionnaire. Yet, only one carefully validated questionnaire existed for endocrine orbitopathy (TAO) (Watt et al., 2010). According to Watt et al. (2006, 2010, 2014), the available questionnaires are not well-validated and lack documented coverage of relevant HRQL issues. Furthermore, these questionnaires do not enable a direct comparison of HRQL across different thyroid diseases (Watt et al., 2006; Watt et al., 2010).

This led to the development of a validated, thyroid-specific patient-reported outcome instrument (ThyPRO) by Watt and colleagues in 2007. The ThyPRO is suggested for patient-reported outcome measurements in clinical studies as well as in clinical management (Watt et al., 2014; Wong et al., 2016). The well-documented measurement properties led to the selection of the ThyPRO as an instrument to measure disease-specific QoL in this study (Watt et al., 2010). Currently, the ThyPRO is translated into 19 languages and has been used in recent studies examining HRQL in patients with thyroid disease (Cramon P. et al., 2015; Stott et al., 2017; Watt et al., 2015; Winther et al., 2016).

There is evidence that treatment of thyroid disease alters HRQL (Bianchi et al., 2004; Cramon P. et al., 2015; Elberling et al., 2004; Gulseren et al., 2006; Razvi et al., 2005; Watt et al., 2012; Winther et al., 2016).

1.5.2 QoL in Thyroid Dysfunction

Thyroid dysfunction, in addition to its negative effects on health, may severely impair well-being and QoL. Patients with untreated thyroid disease suffer from a wide variety of symptoms (see Tables 1 and 2). This leads to major impairments in the majority of HRQL fields. Bianchi et al. (2004) found that overall HRQL was poorer in subjects with hypo- and hyperthyroidism, compared to the general Italian population. Interestingly, only hypothyroid patients reported an increased impairment associated with everyday life (for example, jobs around the house, home life, interests, and hobbies). Although hyperthyroid patients reported similarly increased impairments, differences from the general population were not significant. The authors of the study suggest that due to the small sample size of the subgroup, a type II error may have occurred. Bianchi et al. (2004) found no evidence for a lower QoL in patients with

subclinical disease (both hyper- and hypothyroidism); however, Gulseren et al. (2006) reported a deteriorated QoL in all thyroid dysfunction subgroups (patients with overt- and subclinical hyper- and hypothyroidism). The majority of frequent symptoms were identical in patients with subclinical and overt thyroid dysfunction, but anxiety and depressive symptoms were more severe in patients with overt hypo- and hyperthyroidism. After the initiation of treatment, psychological symptoms and QoL improved in two groups: overt and subclinical hypothyroidism and overt hyperthyroidism. An improvement of QoL in the sHY group was not found. The authors claimed that this might have been due to the small sample size in the subgroup (n=10). The results of Razvi et al. (2005) support the view that patients with sHT benefit from an improved QoL due to levothyroxine substitution. Patients with sHT perceive significant impairment of their QoL, as measured by all scales of the SF-36 (Razvi et al., 2005).

QoL is additionally impaired in the thyrotoxic phase of GD in the physical, mental and social dimensions. After treatment, QoL improves (Elberling et al., 2004). This additionally accounts for endogenous sHY in young and middle-aged patients (Biondi et al., 2000)

Razvi et al. (2005) found that older patients (>64 years) with sHT have significantly lower QoL compared with younger people. But this may not be assigned to sHT because the decreased QoL is probably associated with age. The authors did not have the normative data of an older standard sample to compare the QoL of older patients with the sHT of older persons without sHT.

2 RESEARCH QUESTIONS OF THE THESIS:

2.1 Impact of Age on QoL in Thyroid Dysfunction

Large epidemiological cohorts such as NHANES, TEARS or the Busselton Health Study show that TSH concentrations rise with age, which does not appear to be due to an increased incidence of autoimmune thyroid disease, but rather due to a true shift of the TSH range with age (for example, Busselton Health, NHANES: (Atzmon et al., 2009; Hollowell et al., 2002; Surks et al., 2010). Hence, in their current guidelines, the European Thyroid Association and the American Thyroid Association recommend treatment of hypothyroidism in elderly patients (>70 years) only if the TSH concentration has persistently increased (>10 mU/l over a six-month period) and symptoms are present (Gharib et al., 2005; Pearce et al., 2013).

Hypothyroidism is often oligosymptomatic in the elderly (J.Diez, 2002; Verma et al., 2009). Thus, the question arises whether there is a specific decrease in QoL due to hypothyroidism in addition to the expected decrease that comes with aging. One of the main goals of the treatment of chronic disease is improving patient symptoms to enable them to participate in everyday life and keep them living in the community. For elderly patients, higher QoL may even have a greater significance than longevity (Brunner-La Rocca et al., 2012). The importance of QoL has also increasingly been acknowledged for thyroid disorders by recent studies (Bektas Uysal et al., 2016; Watt et al., 2006). QoL is reduced in younger patients with overt hypothyroidism and the condition improves with the administration of levothyroxine (Bianchi et al., 2004; Jaeschke et al., 1996; Watt et al., 2014; Winther et al., 2016). No study has yet investigated QoL in elderly patients with overt hypothyroidism, and few studies have examined QoL in elderly patients with sHT, these studies having inconsistent findings. For example, Jaeschke and colleagues (1996) did not observe a benefit for levothyroxine treatment used in in a randomized placebo-controlled study for a cohort of middle-aged or elderly patients (older than 55 years) that had sHT. Furthermore, a recent prospective randomized placebo-controlled trial showed no apparent benefits of treatment of elderly patients with mild sHT (Stott et al., 2017). However, other data suggest that overt hypothyroidism and sHT may represent a serious risk factor for depression and anxiety in middle-aged and elderly patients (Chueire et al., 2007;

Larisch et al., 2004). Thus, age and QoL are possibly additional parameters for determining if levothyroxine substitution is indicated in sHT.

There is no longitudinal data on QoL in elderly hyperthyroid and sHY patients before and after treatment. Boelaert et al. (2010) reported classical symptoms and signs of hyperthyroidism to be less prevalent in older patients. However, treatment is recommended in older patients even with mild symptoms of thyrotoxicosis because sHY presents an important risk factor for atrial fibrillation, coronary heart disease, heart failure, fractures, and increased mortality (Biondi et al., 2015; Boelaert et al., 2010). In contrast to older patients, young, middle-aged hyperthyroid patients, including patients with sHY, have an increased prevalence of symptoms caused by thyroid hormone excess and impaired QoL (Biondi et al., 2000). With regard to the mild symptoms of sHY in older patients, the question arises of whether older patients experience a decrease in QoL compared to an age-matched healthy control group.

This thesis aims to:

1. analyse if older individuals' (>60 years of age) QoL or HRQL is impacted by the presence of sHT compared to the general German population of the same age
2. examine if there is a significant change in general QoL and disease-specific QoL with the treatment of sHT
3. analyse the dynamics of impairment and change in QoL in older patients (>60 years of age) with sHT before and after treatment, in comparison with younger patients (<40 years of age)
4. analyse if older patients' QoL or HRQL is impacted by the presence of sHY (>60 years of age) compared to the general German population of the same age
5. examine if there is a significant change in general QoL and disease-specific QoL after treatment of sHY
6. analyse the dynamics of impairment and change in the QoL for older patients (>60 years of age) with hyperthyroidism before and after treatment, in comparison with younger patients (<40 years of age)

The prospective, longitudinal Thyroid Study of Age in Germany (TSAGE) is reported in order to answer these questions; the study investigates QoL in older (>60 years) and younger (<40 years) patients with new onsets of sHT, sHY as well as overt hypo- and hyperthyroidism before and after initiation of therapy. A generic (SF-36) and a disease-specific (ThyPRO) questionnaire on QoL were used in order to obtain valid health-related QoL (HRQL), maximize precision, and maximize sensitivity. Additionally, the longitudinal approach allowed the examination of possible age differences in overall and thyroid disease-related QoL between old and young patients after restoration of euthyroidism.

3 MATERIAL AND METHODS

3.1 Patient Populations

TSAGE: The study included male and female patients older than 18 years with newly diagnosed, untreated, overt endogenous hyperthyroidism (TSH < 0.3 mU/l and elevated free T4 or free triiodothyronine (fT3)), endogenous hypothyroidism (TSH > 8 mU/l, free T4 < 11.5 pmol/l and/or fT3 < 3.5 pmol/l), and sHT (TSH > 8 mU/l; free T4 and fT3 within the reference range). Patients were recruited in six endocrine practices throughout Germany**.** The recruitment period lasted four years (1.01.2013–31.12.2016). Patients were evaluated by clinical assessment, blood sampling, and questionnaires to measure health-related QoL (SF-36 Version 2) (Bullinger et al., 1998) and thyroid-related QoL (ThyPRO) (Watt et al., 2015). Evaluations took place at the time of diagnosis (T1) and six months after the initiation of treatment (levothyroxine) (T2).

Only patients with confirmed hypothyroidism (second laboratory analysis from aliquot sample) at baseline and only patients who were confirmed with euthyroid after at least 6 months duration of levothyroxine substitution were entered in the present analysis. Clinical variables including age, cause and symptoms of hypothyroidism, blood pressure, heart rate, body weight, and history of smoking were collected during the survey. Written informed consent of patients who agreed to participate in the study was taken, and ethics permission was granted (Nr. 12-5132-BO).

3.2 QoL Measures

QoL was assessed using the German version 2 of the SF-36 and the ThyPRO (see supplements for detailed information).

3.2.1 The SF-36 Health Survey

The SF-36 Health Survey (SF-36) (Bullinger et al., 1998) is a generic instrument for assessing HRQL. The German version of the SF-36 is the translation of the original US version, SF-36 Health Survey, by Ware, Snow, Kosinski and Gandek (1993). The German version of the SF-36 was used, for example, in the Federal Health Survey in

1998 and was standardized on a sample of 6,964 people aged between 18 to 80 years (Bullinger & Kirchberger, 1998).
The SF-36 Health Survey consists of eight subscales which can be conceptualized into two areas: "physical health" and "mental health":

- Physical Function (PF): measures the extent to which the state of health is affected by physical activity
- Social Functioning (SF): measures the extent to which physical health or emotional issues affect normal social activities
- Role Limitations due to Physical Problems (RP): measures the extent to which pain affects normal home and outside work
- Role Limitations due to Emotional Problems (RE): describes the extent to which emotional issues affect work or everyday activities
- Mental Health (MH): assess general mental health, along with depression, anxiety, emotional and behavioral control, and general positive mood
- Vitality (VT) measures how energetic and full of momentum people feel and how tired and exhausted they are
- Bodily Pain (BP) measures the extent to which pain affects normal home and outside work
- General Health (GH): measures the personal assessment of health, including future expectations

The dimensional scores range from 0 (low) to 100 (high QoL level). Two component summary measures of SF-36, that is, Physical Component Summary (PCS) and Mental Component Summary (MCS), can be calculated. They are standardized to a mean score of 0 and a standard deviation of 100 with higher scores indicates better QoL. In addition to the subscales, one single-item measures the change in health status during the last year.

3.2.2 The ThyPRO Questionnaire

ThyPRO is a disease-specific QoL questionnaire developed by T. Watt (Watt et al., 2014; Watt et al., 2015; Watt et al., 2010) for evaluating the QoL of patients with benign thyroid diseases. It is a robust, standardized questionnaire that has been

translated and validated in several languages, including German. The questionnaire consists of 84 items summarized in 13 scales and one overall QoL item.

Physical components:

- Goitre Symptoms: for example, pressure in throat, pain in front neck, clears throat often
- Hyperthyroid Physical Symptoms: trembling hands, increased sweating, shortness of breath, increased appetite
- Hypothyroid Physical Symptoms: dry skin, sensitive to cold, itching skin
- Eye Symptoms: watery eyes, double vision, pain reduced sight

Mental Components:

- Tiredness: been tired, been exhausted, problems getting motivated, and so on
- Cognitive Impairment: problems remembering, difficulty finding words, state of confusion
- Anxiety: nervous, anxious, tense, uneasy, restless
- Depressivity: sad, unhappy, discouraged
- Emotional susceptibility: easily stressed, mood swings, irritable

Impact of thyroid disease:

- Impaired social life: burden to other people, difficulty being with other people, and so on
- Impaired daily life: difficulty managing daily life, difficulty getting around, all tasks take longer
- Impaired sex life: decreased sexual desire, negative influence on sex life
- Cosmetic complaints: disease affects appearance, unsatisfied with appearance, and so on

Each of the 13 ThyPRO scales is scored as a summary score and linearly transformed to a range of 0–100, with higher scores indicating more symptoms or impairment.

3.3 Laboratory parameters

TSH, fT3 and fT4 serum concentrations of all patients in this study were initially measured in the private practices at T1 and T2. A second independent analysis was performed in the Department of Clinical Chemistry – Division of Laboratory Research at the University Hospital Essen. Prior to analysis in Essen, serum samples were stored at -80°C, and an accurate temperature was controlled by an in-house master display in the West German Biobank at the University Hospital Essen.
Thyroid function parameters (TSH, fT3 and fT4) were determined on thawed serum samples with the Siemens ADVIA Centaur immunoassay-system (Siemens Healthineers, Erlangen, Germany). Reference ranges, according to the manufacturer, were: TSH = 0.3–3.0 mU/l, fT3 = 3.5–6.5 pmol/l and fT4 = 11.5–22.7 pmol/l. The ADVIA Centaur® TSH3-Ultra Assay is a chemiluminescence immunoassay with intra-assay variation < 4.3%, inter-assay variation < 4.7%, functional sensitivity of 0.008 mU/l and detection limit at 0.008 mU/l. The ADVIA Centaur® fT3- and fT4-assays are competitive chemiluminescence immunoassays with intra-assay variations < 4.1% for fT3 and < 4.0% for fT4, inter-assay variations < 3.1% for fT3 and < 3.3% for fT4 and analytical sensitivities of 0.3 pmol/l for fT3 and 1.3 pmol/l for fT4, respectively. The Department of Clinical Chemistry is accredited according to DIN EN ISO 15189:2014.

3.4 Statistical analyses

The change to treatment in HRQL was evaluated as the change in scale scores in the SF-36 and the ThyPRO from baseline (T1) to follow-up (T2).

In order to take age- and sex-dependent differences in generic QoL into account, the final SF-36 scores were corrected for age- and sex-specific values from the German norm-base dataset.

The differences between patients' values and the age- and sex-specific normative values were calculated for T1 and T2 separately. T2 and T1 values were subtracted to evaluate the response to treatment. In order to examine whether the effect of therapy on HRQL differed between older patients (>60years of age) and younger patients (18–40 years of age), an independent sample t-test for these differences was carried out.

For the evaluation of the ThyPRO, changes in mean scale scores were compared between T2 and T1 using the paired Student's t-test. Values of $p < 0.05$ were considered statistically significant.

In addition to statistical significance testing, effect sizes (mean differences divided by standard deviations at baseline) were also calculated to enhance interpretability (Watt et al., 2014). In accordance with Cohen, effect sizes between 0.2 and 0.5 were classified as small, 0.5–0.8 as moderate, and 0.8 as large (Cohen, 1988).

All analyses were performed with SPSS software, version 22.0 (Inc., Chicago, IL).

4 RESULTS

Initial (T1), data was received from 147 patients; 9 patients were not included at T1: 3 patients because they did not show thyroid dysfunction in our control laboratory, 2 patients because they did not meet the age criteria (< 18 years of age), and 4 patients because they did not complete the questionnaires. 138 patients remained, having newly diagnosed, untreated overt hyperthyroidism (TSH < 0.3 mU/l), overt hypothyroidism or sHT (TSH > 8 mU/l, fT4 and fT3 within range; fT4 = 11,5 -22,7 pmol/l; fT3 = 3.5–6.5 pmol/l) who completed the ThyPRO and SF-36 (Version 2) at baseline (T1).

At the six-month follow-up (T2), 95 patients entered the study (see Figure 1). This resulted in a response rate of 69%. 43 patients dropped out at T2 because they reached the treatment goal of euthyroidism (17 patients) or did not complete the second session (10 patients had incomplete questionnaires, 14 were absent for the second examination at the private practice, of which 2 passed away). The TSAGE cohort consisted of four groups with thyroid dysfunction: sHY, overt hyperthyroidism, sHT, and overt hyperthyroidism, each subdivided into three different age categories. See Figure 1 for detailed information.

To answer the specific research questions of this thesis, with a focus on age impact on QoL in hypothyroidism, QoL was evaluated in patients who completed both sessions (T1 and T2). This resulted in two patient groups: patients with sHT > 60 years of age (“old patients”, n=11; male: 5; female: 6) and patients with sHT < 40 years of age (“young patients”, n=17; male: 4, female: 13). Age, mean arterial blood pressure, and thyroid function tests are presented in Table 3. There was no significant difference in either clinical parameters (heart rate, mean arterial blood pressure) or TSH, fT4, and fT3 concentrations between the two patient groups.

Hypothyroidism was caused by autoimmune thyroid disease (AIT) in all patients, confirmed by elevated thyroid peroxidase autoantibodies (above reference range in the laboratory of private practice) and thyroid ultrasound findings suggestive of AIT (documented in private practice).

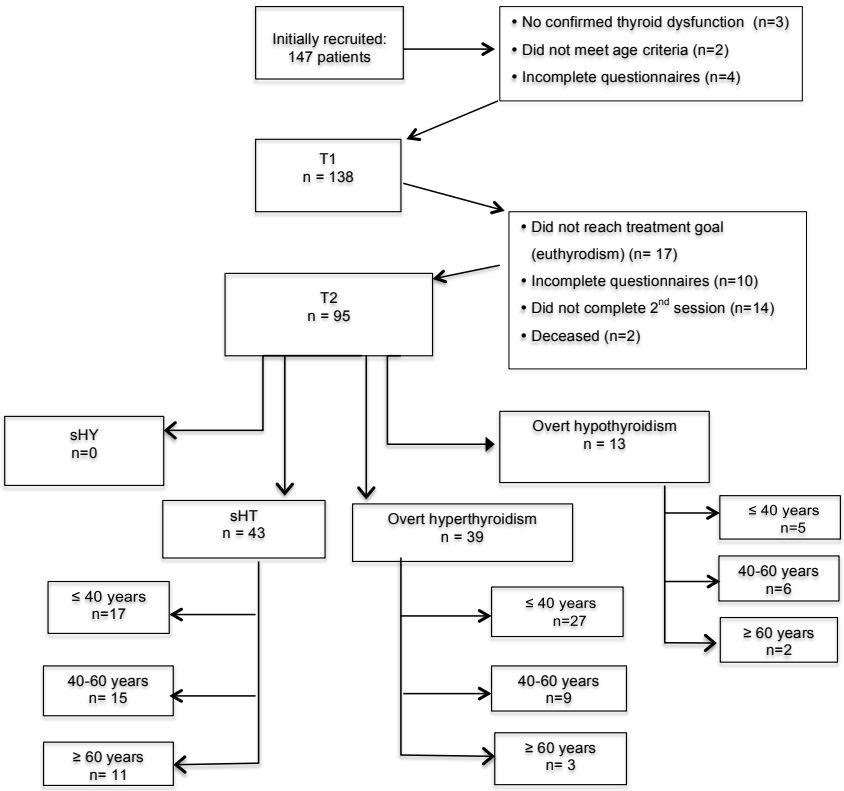


Figure 1 Flow-chart presenting the process of including participants into the study sample. Patients included at baseline (T1) and six months after initiation of treatment with normal TSH and TH values (T2). Displayed is the sample size in the four different subgroups: sHY (subclinical hyperthyroidism), sHT (subclinical hypothyroidism), overt hyperthyroidism, overt hypothyroidism. Patients were further subdivided three age categories: old: >60 years of age, middle-aged 40–60 years of age, and young 18–39 years of age

	Baseline		Follow-up	
	Old Patients (n =11)	Young Patients (n= 17)	Old Patients (n =11)	Young Patients (n= 17)
Age	66 (60-75)	26 (19-35)	67 (61-76)	27 (20-36)
MAD	98 (96-106)	91 (71-106)	96 (88-103)	93 (60-80)
Heart rate	72 (60-96)	73 (64-88)	69 (60-80)	70 (88-113)
TSH	13 (8-32)	16 (8-85)	3 (1-3)	2 (0-3)
fT4	16 (12-21)	14 (12-18)	21 (15-23)	18 (14-23)
fT3	4 (3-5)	5 ± 1 (3-6)	5 (4-6)	5 (4-6)

Table 3 Age, heart rate, mean arterial blood pressure (MAD) and thyroid function parameters in the study population before and six months after initiation of levothyroxine substitution (Mean data; (range))

4.1 Differences in QoL to the Age and Standard Specific Norm

With regard to generic QoL, measured with the SF-36 Health Survey, we found significantly lower QoL in both young and old patients with sHT compared to healthy individuals. Larger differences were found in all QoL subscales for old—compared to young—patients and persisted after correction for age- and gender-matched healthy individuals (Figure 2 and Table 4). Treatment with levothyroxine was associated with significant improvement in SF-36 subscales, Physical Function and Vitality, and the calculated PCS in old patients while young patients reported a significant improvement in SF-36 subscales, Physical Function and Social Functioning and the derived MCS (Table 4). There was no change in Mental Health from baseline to follow-up after treatment in either patient group. For all other SF-36 subscales, all patients showed higher scores on follow-up, irrespective of age, that is, improved QoL with LT4 substitution.

	Old patients (n = 11)				Young patients (n=17)			
	Baseline (T1)	**Follow-up (T2)**	**Change**	**p-value**	**Baseline**	**Follow- up**	**Change**	**p-value**
Physical Function	-15 **± 31**	-11 **± 30**	4	.642	-7 **±** 14	-1 **±** 10	**6**	**.039**
Physical Problems**	-37 **± 42**	-15 **± 43**	**22**	**.029**	-10 **±** 27	1 **± 18**	9	.104
Bodily Pain	-12 **± 40**	-5 **±** 42	7	.284	-5 **±** 26	0 **± 17**	5	.411
General Health	-14 **± 20**	-6 **±** 26	8	.139	-9 **±** 18	-8 **± 26**	1	.686
Vitality	-25 **± 18**	-13 **±** 21	**12**	**.036**	-14 **±** 20	-10 **± 21**	4	.225
Social Functioning	-33 **± 27**	-26 **±** 29	7	.523	-9 **±** 15	1 **± 12**	**8**	**.003**
Emotional Problems **	-41 **± 43**	-34 **±** 50	7	.678	-20 **±** 39	-6 **± 30**	14	.312
Mental Health	-18 **± 17**	-18 **±** 17	0	.146	-4 **±** 15	-4 **± 15**	0	.151
MCS	-5 **± 13**	-1 **±** 15	4	.55	-2 **±** 7	0 **± 5**	**2**	**.045**
PCS	-15 **± 11**	-13 **±** 13	**2**	**.068**	-6 **±** 10	-3 **± 9**	3	.216

Table 4 Impact of age and levothyroxine substitution on SF-36 scales (mean differences ± standard deviation from gender and age-matched norm *). Mean deviations from the age- and gender-matched normal population at baseline (T1) and six months after initiation of levothyroxine substitution (T2). Significant changes ($p < 0.05$) from baseline to follow-up are indicated in bold. *German norm-based dataset of the SF36. ** Role limitations due to physical problems or emotional problems.

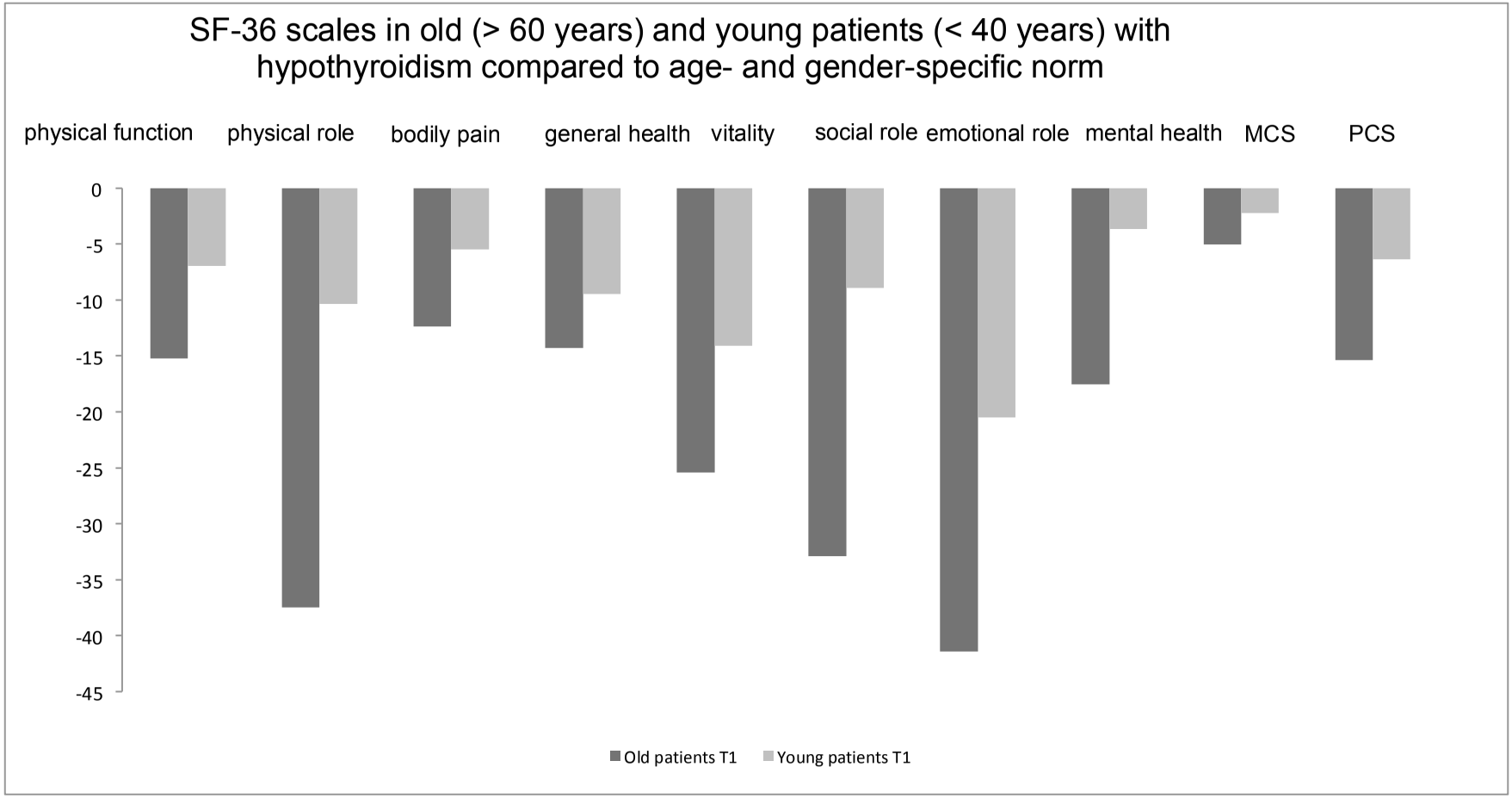


Figure 2: Newly diagnosed untreated hypothyroidism (T1). Shown are differences to the respective age- and gender-specific norm in the SF-36 questionnaire

4.2 Disease-Specific QoL Measured by ThyPRO

In the thyroid-specific QoL (ThyPRO) questionnaire, old patients expressed significantly less Tiredness and Impaired day life in addition to a significant improvement in Emotional susceptibility under LT4 substitution ($p < 0.5$). Young patients reported significantly less Impaired day life, Cognitive complaints and Emotional susceptibility compared to baseline ($p < 0.5$) (Table 5).

	Old patients (n= 11)				Young patients (n= 17)			
	Baseline (T1)	**Follow-up (T2)**	**Change**	**p-value**	**Baseline (T1)**	**Follow- up (T2)**	**Change**	**p- value**
Goitre symptoms	38 **± 22**	36 **± 17**	-2	.657	28 **± 11**	28 **± 9**	0	.87
Hyperthyroid symptoms	44 **± 16**	46 **± 16**	+2	.556	35 **± 11**	34 **± 9**	-1	.607
Hypothyroid symptoms	37 **± 20**	35 **± 18**	-2	.518	29 **± 10**	29 **± 12**	0	.1
Eye symptoms	41 **± 20**	39 **± 23**	-2	.456	31 **± 10**	34 **± 18**	+3	.648
Tiredness	62 **± 8**	54 **± 11**	**-8**	**.038**	57 **± 10**	59 **± 9**	+2	.562
Cognitive problems	55 **± 26**	47 **± 22**	-8	.226	41 **± 20**	34 **± 16**	**-7**	**.032**
Anxiety	61 **± 21**	56 ± 19	**-5**	**.021**	49 **± 33**	37 **± 19**	-12	.137
Depressivity	57 **± 17**	57 ± 18	0	1	50 **± 11**	53 **± 35**	+3	.779
Emotional susceptibility	59 **± 17**	55 **± 13**	**-4**	**.05**	53 **± 13**	50 **± 12**	**-3**	**.022**
Social impairment	45 **± 24**	40 **± 23**	-5	.452	27 **± 10**	24 **± 12**	-3	.492
Impaired day life	55 **± 23**	43 **± 18**	**-12**	**.013**	36 **± 15**	28 **± 8**	**-8**	**.01**
Impaired sex life	54 **± 26**	50 **± 15**	-4	.0191	28 **± 19**	25 **± 9**	-3	.351
Cosmetic complaints	35 **± 18**	33 **± 14**	-2	.33	32 **± 16**	27 **± 12**	-5	.119

Table 5 Impact of age and levothyroxine substitution on ThyPRO scales (mean ± standard deviation). Mean (SD) scale scores in the ThyPRO questionnaire at baseline (T1) and six months after initiation of thyroxine substitution (T2) in old (>60 years) and young (<40 years) patients with hypothyroidism. Significant changes ($p < 0.05$) from baseline to follow-up are indicated in bold. Higher scores indicate more health problems (worse = QoL)

The magnitudes in changes, estimated by the standardized effect sizes, at 6 months after initiation of levothyroxine treatment are shown for each of the ThyPRO scales in Table 6. In old patients, the change under LT4 substitution was large (>0.8) for tiredness and moderate (0.5–0.8) for Impaired day life, small (0.20-0.50) for Eye symptoms, Cognitive problems, Anxiety, Emotional susceptibility, Social impairment, Impaired sex life and Cosmetic complaints. There were no changes (<0.20) for four scales: Goitre symptoms, physical Hyperthyroid symptoms, physical Hypothyroid symptoms and Depressivity.

ThyPRO Scales	**Old patients (n= 11)**	**Young patients (n= 17)**
Goitre symptoms	0.09	-0.04
Hyperthyroid symptoms	-0.17	0.12
Hypothyroid symptoms	0.11	0.00
Eye symptoms	0.24	-0.21
Tiredness	***1.02***	-0.17
Cognitive problems	0.32	0.35
Anxiety	0.40	0.35
Depressivity	0.00	-0.24
Emotional susceptibility	0.26	0.18
Social impairment	0.20	0.26
Impaired daily life	**0.54**	**0.54**
Impaired sex life	0.27	0.16
Cosmetic complaints	0.21	0.27

Table 6 Effect Size (mean change or SD baseline) of levothyroxine substitution in young and old patients with sHT. Magnitude of change. Small effect (0.2–0.5), moderate effect (0.5–0.8) in bold, large effect sizes (>0.8) in ***bold/ italics.***

In young patients, the change in Impaired day life was moderate under LT4 substitution (0.5–0.8), and only small changes (0.20–0.50) were found for Eye symptoms, Tiredness, Cognitive problems, Anxiety, Depressivity, Social impairment, Impaired sex life and cosmetic complaints. Six scales showed no change (<0.20) in young patients under LT4 substitution: Goitre symptoms, physical Hyperthyroid

symptoms, physical Hypothyroid symptoms, Tiredness, Emotional susceptibility, and Impaired sex life.

Thus, compared to young patients, LT4 substitution in old patients with hypothyroidism was associated with more pronounced changes in thyroid disease-specific QoL in addition to larger improvement of Tiredness from T1 to T2.

4.3 QoL and HRQL in Younger and Older Hyperthyroid Patients

Due to the very small sample size for older hyperthyroid patients, only descriptive data is presented.

Age-impact on QoL was described in two thyroid patient groups: patients with overt hyperthyroidism >60 years of age (“old patients”, n=3; male) and <40 years of age (“young patients”, n=27; male: 3, female: 24). Age, mean arterial blood pressure, and thyroid function tests are presented in Table 7.

Hyperthyroidism was due to autoimmune thyroid disease (GD) in all patients, confirmed by elevated TSH-R autoantibodies (above reference range in private practice laboratory) and thyroid ultrasound findings suggestive of Graves´ disease (documented in private practice).

	Baseline		Follow-up	
	Old Patients (n =3)	Young Patients (n= 27)	Old Patients (n =3)	Young Patients (n= 27)
Age	74 (72-75)	28 (21-39)	74 (72-76)	31 (22-40)
MAD	102 (95-110)	92 (75-127)	95 (95-95)	91 (71-106)
Heart rate	92 (64-120)	95 (64-130)	79 (78-80)	77 (60-116)
TSH	0.01(0.01-0,0)	0 (0)	1 (0.4-2.24)	1 (0.2-3,35)
fT4	25 (20-30)	42 (23-102)	16 (12-19)	22 (12-24)
fT3	8 (7-8)	15 (0-30)	4 (4-5)	5 (4-7)

Table 7 Age, heart rate, mean arterial blood pressure (MAD) and thyroid function parameters in the hyperthyroid patients before and six months after initiation of treatment (Mean data; (range))

4.3.1 Differences in generic QoL compared by age and standard specific norm

With regard to the generic QoL, measured with the SF-36 Health Survey, significantly lower QoL was found in young hyperthyroid patients compared to healthy individuals. Treatment was associated with a significant improvement in all SF-36 subscales, excluding for GH and social functioning in young patients (see Table 8).

At baseline, the 3 older hyperthyroid men included in this study reported a lower generic QoL compared to men of the same age in the German standard sample. Patient 1 reported a lower QoL at follow-up. Patient 2 did not experience a change in BP. All other areas of the generic QoL measures by the SF-36 improved at follow-up for the 3 patients (see Table 9).

Young Hyperthyroid Patients (n= 27)						
	Baseline (T1)		**Follow- up (T2)**		**Change**	**p -value**
Physical Function	-23	± 23	-9	± 18	9	**0.01**
Physical Problems**	-30	± 37	-10	± 20	20	**0.02**
Bodily Pain	-14	± 27	-1	± 16	13	**0.05**
General Health	-22	± 21	-16	± 20	6	0.18
Vitality	-38	± 21	-21	± 22	17	**0.00**
Social Functioning	-14	± 22	-12	± 22	2	0.72
Emotional Problems**	-30	± 38	-14	± 32	2	**0.07**
Mental Health	-24	± 22	-11	± 20	13	**0.00**
MCS	-8	± 8	-3	± 6	5	**0.01**
PCS	-16	± 23	-7	± 10	9	**0.04**

Table 8 Impact of treatment on SF-36 scales (mean differences ± standard deviation from gender and age-matched norm *) in young hyperthyroid patients. Mean deviations from the age- and gender-matched normal population at baseline (T1) and after six months after initiation of treatment at follow-up (T2). Significant changes ($p < 0.05$) from baseline to follow-up are indicated in bold. *German norm-based dataset of the SF-36. ** Role limitations due to physical problems or emotional problems.

	Patient 1		Patient 2		Patient 3	
	Baseline	**Follow-up**	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**
Physical Function	-14	-29	-59	6	-59	-14
Physical Problems**	-67	-92	-42	-17	-67	-17
Bodily Pain	-17	9	9	9	-60	-7
General Health	-30	-35	-40	-35	-45	-18
Vitality	-33	-53	-43	-33	-58	-18
Social Functioning	-18	-6	-68	-31	-31	-6
Emotional Problems**	-63	-96	-96	-63	-63	4
Mental Health	-22	-18	-62	-34	-30	2
MCS	-10	-11	-6	4	-25	-8
PCS	-14		-34	-24	-14	

Table 9 Impact of treatment on SF-36 scales (mean differences from gender and age-matched norm *) in three older hyperthyroid patients. Deviations from the age- and gender-matched normal population at baseline and six months after initiation of treatment (follow-up). *German norm-based dataset of the SF-36. ** Role limitations due to physical problems or emotional problems.

4.3.2 Disease-specific QoL measured by ThyPRO in hyperthyroid patients

Young patients with GD significantly benefited from treatment of hyperthyroidism regarding their disease-specific QoL; however there was no significant change in goitre symptoms, depressivity, or cosmetic complaints (Table 10).

Young Hyperthyroid Patients (n = 27)							
	Baseline (T1)		**Follow- up (T2)**		**Change**		**p-value**
Goitre symptoms	31	±11	27	±11	4	±11	0.15
Hyperthyroid symptoms	59	±15	35	±9	24	±13	**0.00**
Hypothyroid symptoms	31	±11	29	±11	2	±12	0.36
Eye symptoms	35	±13	30	±12	5	±11	**0.02**
Tiredness	63	±13	55	±10	8	±12	**0.00**
Cognitive problems	47	±22	34	±15	13	±18	**0.00**
Anxiety	61	±23	40	±23	22	±24	**0,00**
Depressivity	52	±15	48	±13	4	±15	0.16
Emotional susceptibility	60	±15	49	±15	30	±14	**0,00**
Social impairment	37	±20	27	±13	9	±16	**0.01**
Impaired day life	49	±25	35	±21	13	±30	**0.03**
Impaired sex life	50	±27	34	±18	16	±26	**0.01**
Cosmetic complaints	33	±17	31	±19	1	±10	0.50

Table 10 Impact of treatment on ThyPRO scales (mean ± standard deviation) in young hyperthyroid patients. Mean (SD) scale scores and mean changes (SD) in the ThyPRO questionnaire at baseline (T1) and six months (T2) after initiation of treatment. Significant changes ($p < 0.05$) from baseline to follow-up are indicated in bold. Higher scores indicate more health problems (worse = QoL)

With regard to the disease-specific QoL of the 3 older patients with overt hyperthyroidism, Patient 1 reported an improved QoL in the areas of Tiredness, Cognitive Problems, Anxiety, and Depressivity. The scales Goitre Symptoms, Eye Symptoms, Emotional susceptibility, and Social Impairment did not change over the

course of six months. QoL unexpectedly worsened for the scales Impaired Day Life, Impaired Sex Life and Cosmetic Complaints. Patient 2 reported improvement in a majority of of the areas of disease-specific QoL measured by the ThyPRO. However, QoL worsened for the scales Tiredness, Cognitive Problems and Cosmetic Complaints. Patient 3 additionally reported improvements in many areas of disease-specific QoL. The patient did not experience improvements concerning Tiredness, Depressivity and Social Impairment. This patient additionally reported more Cosmetic Complaints after treatment than other two patients did (see Table 11).

	Patient 1		Patient 2		Patient 3	
	Baseline (T1)	**Follow-up (T2)**	**Baseline (T1)**	**Follow-up (T2)**	**Baseline (T1)**	**Follow-up (T2)**
Goitre symptoms	27	27	27	24	64	31
Hyperthyroid symptoms	x	48	40	20	65	30
Hypothyroid symptoms	30	25	35	25	45	20
Eye symptoms	35	35	25	23	70	33
Tiredness	71	66	31	40	54	54
Cognitive problems	50	40	30	40	40	30
Anxiety	57	37	73	33	60	30
Depressivity	51	37	54	34	37	37
Emotional susceptibility	56	56	51	36	49	44
Social impairment	20	20	65	25	20	20
Impaired day life	23	27	57	33	73	43
Impaired sex life	40	80	40	x	80	60
Cosmetic complaints	23	37	37	40	20	31

Table 11 Impact of treatment on ThyPRO scales in three patients with hyperthyroidism (>60 years of age). Mean scale scores in the ThyPRO questionnaire at baseline (T1) and six months after the initiation of treatment (T2) in patients with hyperthyroidism. Higher scores indicate more health problems (worse QoL). X = missing data

4.4 QoL and HRQL in Younger and Older Overt Hypothyroid Patients

7 patients with overt hypothyroidism entered this study. The data of these patients (5 young and 2 old patients) were described for two thyroid patient groups: patients with overt hypothyroidism, <40 years of age (“young patients”, n=5; male: 1, female: 4) and patients >60 years of age (“old patients”, n=2; male: 1, female: 1). Age, mean arterial blood pressure, and thyroid function tests are presented in Table 12. Since the older patient group included data from two patients, data from each patient is presented. Due to the small sample size, an interference statistical analysis was not carried out.

	Baseline		**Follow-up**	
	Old Patients (n =2)	Young Patients (n= 5)	Old Patients (n =2)	Young Patients (n= 5)
Age	62 (61-64)	29 (21-34)	62 (61-64)	30 (22-35)
MAD	95 (95)	89 (83-96)	86 (95-103)	86 (71-106)
Heart rate	66 (64-68)	69 (57-87)	60 (80-70)	73 (60-116)
TSH	62(50-74)	49 (12-150)	3 (3)	2 (1-3)
fT4	8 (8)	9 (4-10)	16 (16-18)	17 (15-17)
fT3	4 (3-4)	4 (1-5)	4 (4-5)	5 (4-5)

Table 12 Age, heart rate, mean arterial blood pressure (MAD), and thyroid function parameters in the overt hypothyroid patients before and six months after initiation of treatment (Mean data; (range)).

4.4.1 Differences in generic QoL compared to age and standard specific norm in overt hypothyroid patients

Young Overt Hypothyroid Patients (N= 5)					
	Baseline (T1)		**Follow- up (T2)**		**Change**
Physical Function	-14	± 12	-8	± 14	6
Physical Problems**	-22	± 32	-5	± 20	17
Bodily Pain	-15	± 32	1	± 12	14
General Health	-12	± 25	-2	± 12	10
Vitality	-17	± 22	-13	± 9	4
Social Functioning	-7	± 20	5	± 5	2
Emotional Problems**	-12	± 28	4	± 0	8
Mental Health	-15	± 17	-7	± 8	8
MCS	-6	± 8	-3	± 6	3
PCS	-14	± 12	-1	± 3	13

Table 13 Impact of treatment on SF-36 scales (mean differences ± standard deviation from gender and age-matched norm *) in young overt hypothyroid patients. Mean deviations from the age- and gender-matched normal population at baseline (T1) and six months after initiation of levothyroxine substitution (T2).*German norm-based dataset of the SF-36. ** Role limitations due to physical problems or emotional problems.

Young patients with overt hypothyroidism experienced higher generic QoL after six months of levothyroxine substitution (see Table 13).

Old Overt Hypothyroid Patients (N = 2)				
	Patient 1		Patient 2	
	Baseline (T1)	Follow-up (T2)	Baseline (T1)	Follow-up (T2)
Physical Function	6	11	3	-2
Physical Problems**	8	8	-16	-16
Bodily Pain	9	9	11	11
General Health	-13	-3	-8	-23
Vitality	-3	-3	-46	-31
Social Functioning	7	7	-29	-41
Emotional Problems**	4	4	-27	6
Mental Health	14	6	-39	-35
MCS	-1	2	5	0
PCS	5	2	-23	-17

Table 14 Impact of treatment on SF-36 scales (mean differences from gender and age- matched norm *) in two old hypothyroid patients. Mean deviations from the age- and gender- matched normal population at baseline (T1) and six months after initiation of levothyroxine substitution (T2). *German norm-based dataset of the SF-36. ** Role limitations due to physical problems or emotional problems.

Patient 1 of the old patient group had, in general, less deviation from the age and sex-matched standard sample. There was no change in five scales at T2: Physical Problems, Bodily Pain, Social Functioning, Emotional Problems and Vitality. General and Mental health improved at T2 as well as the subscales PCS and MCS. Patient 2 experienced an improvement in six scales at T2. Two subscales of the generic QoL were not affected after six months: Physical Problems and Bodily Pain (see Table 14). Higher deviations from the standard sample, that is, worse QoL was reported for GH and the SF at T2.

4.4.2 Disease-specific QoL measured by ThyPRO in overt hypothyroid patients

Young Overt Hypothyroid Patients (N = 5)					
	Baseline (T1)		**Follow- up (T2)**		**Change**
Goitre symptoms	29	± 12	27	± 7	2
Hyperthyroid symptoms	42	± 18	32	± 9	10
Hypothyroid symptoms	26	± 4	25	± 5	1
Eye symptoms	32	± 10	27	± 8	5
Tiredness	56	± 6	57	± 5	1
Cognitive problems	42	± 25	29	± 11	13
Anxiety	45	± 14	28	± 6	17
Depressivity	48	± 11	38	± 1	10
Emotional susceptibility	60	± 8	49	± 10	11
Social impairment	31	± 13	23	± 4	8
Impaired day life	36	± 9	27	± 9	9
Impaired sex life	24	± 9	26	± 9	2
Cosmetic complaints	41	± 22	29	± 14	12

Table 15 Impact of treatment on ThyPRO scales (mean ± standard deviation). Mean (SD) scale scores in the ThyPRO questionnaire shown at baseline (T1) and six months (T2) after initiation of treatment in young patients with overt hypothyroidism. Higher scores indicate more health problems (worse = QoL)

Young overt hypothyroid patients reported, in general, lower scores in the ThyPRO, indicating fewer health problems at T2. The scales hypothyroid symptoms only changed by one point, and tiredness unexpectedly worsened. This might have been due to the small sample size in this subgroup (see Table 15).

Old overt hypothyroid Patients (n = 2)				
	Patient 1		**Patient 2**	
	Baseline (T1)	**Follow-up (T2)**	**Baseline (T1)**	**Follow-up (T2)**
Goitre symptoms	20	24	20	20
Hyperthyroid symptoms	28	38	20	20
Hypothyroid symptoms	25	35	20	20
Eye symptoms	33	35	28	25
Tiredness	66	40	71	46
Cognitive problems	27	20	20	20
Anxiety	57	30	27	x
Depressivity	51	46	37	37
Emotional susceptibility	44	38	42	42
Social impairment	30	30	20	25
Impaired day life	33	30	30	30
Impaired sex life	20	20	60	20
Cosmetic complaints	23	23	27	27

Table 16 Impact of treatment on ThyPRO scales in older overt hypothyroid patients. Mean scale scores in the ThyPRO questionnaire shown at baseline (T1) and six months (T2) after initiation of treatment. Higher scores indicate more health problems (worse = QoL). X= missing Data

Patient 1 reported lower scores, indicating fewer health problems for the scales of Tiredness, Cognitive problems, Anxiety, Depressivity, Emotional susceptibility, and Impaired day life. A larger number of health problems were reported for the Goitre symptom scale, the Hyperthyroid symptom scale, and the Hypothyroid symptom scale after treatment. No change was reported in Social impairment, Impaired sex life, and Cosmetic complaints (see Table 16).

Patient 2 perceived higher disease-specific QoL in Eye symptoms, Tiredness, and Impaired sex life. QoL in the scale Social impairment was lower at T2. Patient 2 did not report any change for the other scales (see Table 16).

5 DISCUSSION

In this prospective study, generic (SF-36) and disease-specific (ThyPRO) QoL was assessed using validated questionnaires for young and elderly patients with newly diagnosed, untreated sHT in Germany (TSAGE). Furthermore, the impact of age on QoL due to the effects of LT4 substitution was investigated. Additionally, the HRQL was compared with age- and sex-adjusted normative values from a general German population sample for the SF-36. TSAGE showed that patients with untreated sHT at TSH concentrations >8 mU/l benefited from LT4 substitution in terms of HRLQ and thyroid disease-specific QoL. This was, in part, more pronounced in old patients and a distinct pattern of QoL changes was observed under LT4 substitution in old compared to young patients. Significantly, serum TSH status did not differ between the old and young patient group.

Unlike the TRUST study published by Stott et al. in 2017, the TSAGE cohort showed an improvement in most areas of general and disease-specific QoL. The strongest change was seen in disease-related tiredness. Interestingly, the Tiredness score (ThyPRO) in the TRUST cohort was 25.5 for the placebo and 25.9 for the LT4 group before treatment (scale from 0–100, with higher scores indicating more symptoms). This is low compared to other populations. For example, in a Danish general population sample (N = 739, average age of 50 years), the baseline Tiredness score was 35 (Cramon P. et al., 2015). Furthermore, in TRUST, the cutoff for sHT was a TSH value >4.60 mU/l; the average of the TRUST cohort was 6.4 mU/l whereas in TSAGE, a cutoff of 8 mU/l was used. Given this discrepancy, it is not surprising that Tiredness scores did not show further improvement in the TRUST cohort on LT4 treatment (28.6 in the placebo group and 28.7 in the LT4 group) (Stott et al., 2017). In the TSAGE cohort, old, subclinically hypothyroid patients reported an average Tiredness score of 62, with young patients reporting a score of 57, both groups improved on LT4. Other studies reported Tiredness scores of 61 in cohorts with sHT and an average age of 45 (Watt et al., 2014; Winther et al., 2016).

Another important aspect that should be taken into consideration when evaluating studies examining the QoL of thyroid patients is the adequate selection of questionnaires. The ThyPRO questionnaire was designed to specifically display disease-related QoL in thyroid patients and thereby to incorporate the complex concept of QoL (Watt et al., 2006). Furthermore, high-quality psychometric criteria, that is, of sufficient reliability and validity, have to have been previously demonstrated for questionnaires. TSAGE used the well-established, high-quality questionnaires SF-36 and all scales of the ThyPRO in order to investigate a broad spectrum of QoL in young and old sHT patients. Winther and colleagues (2016) used the same instruments and additionally compared their results to a healthy population sample. However, their study was not designed for the comparison of young and old patients (the average age of their study population was 47) (See Table 12).

TSAGE enabled an analysis of QoL before and after LT4 substitution, with special regard to distinct age groups: young (<40) and old (>60) years. Furthermore, since TSAGE is a prospective and longitudinal study, there was enough time for tissue equilibration after initiation of LT4 substitution. Similar to Winther et al. (2016), in this study, health-related QoL was impaired in hypothyroid patients and improved by LT4 substitution. Based on the TSAGE, improvement under LT4 substitution accounts for young and old patients with TSH concentrations of >8 mU/l.

One interesting and unexpected finding in TSAGE was that sHT had a larger impact on HRLQ in older than in younger patients. This was consistent after correction for age- and gender-matched HRQL of the normal population. Older patients reported significantly lower scores in all areas of HRQL than younger patients, excluding for BP and emotional problems. On LT4 treatment, the differences in HRQL between younger and older patients were reduced, again illustrating that both old and young patients with sHT benefit from LT4 substitution in terms of QoL. Of note is the physical dimension of QoL, which significantly improved in old patients, particularly, physical role function (that is, accomplishing things, performing activities, and only doing specific activities) demonstrated the largest change. Furthermore, vitality significantly improved. Older patients reported disease-specific impairment in the scales

Tiredness, Anxiety, Depressivity and Emotional susceptibility. A remarkable effect of therapy was found in the amelioration of the disease-specific Tiredness as well as notably less Impaired day life in older people. This reflects as well in significantly higher scores in Vitality and Physical Problems (SF-36).

Although a recent meta-analysis did not find a statistically significant association between sHT and cognitive impairment (Akintola et al., 2015), patients of the TSAGE cohort perceived their cognitive functioning to be less impaired at T2 compared to T1. Notably, a significant change in the disease-specific physical hypothyroid symptoms scale, which included items such as “Have you had dry skin?” and “Have you been sensitive to cold?”, was not observed. This is in agreement with findings by Winther et al. (2016) who suggested that the physical hypothyroidism symptoms scale may belong to an independent entity requiring separate evaluation (Winther et al., 2016).

Disease-specific (ThyPRO), as well as generic QoL (SF-36), improved under LT4 substitution; however, full recovery was not obtained in the TSAGE in sHT groups. These results are consistent with the results of Winther et al. (2016) and Bektas et al. (2016) who found improvement but not full recovery of QoL in patients with previously hypothyroid hormone concentrations under LT4 substitution (after euthyroidism was achieved). Some studies suggest QoL may be independent of the direct influence of the level of TH themselves, and that autoimmunity could be another key player influencing QoL (Bektas Uysal et al., 2016; Bianchi et al., 2004; Watt et al., 2012). Patients with higher anti-TPO and anti-Tg levels report significantly lower scores in QoL questionnaires independent of their TH levels; hence, it has been suggested that, apart from hypothyroidism, high thyroid antibody levels could be another contributing factor for the development of AIT associated symptoms, leading to a lower QoL (Bektas, Uysal & Ayhan, 2016). Since AIT in combination with sHT increases the risk for development of overt hypothyroidism, the measurement of TPO antibodies is recommended when evaluating the need or decision to use LT4 substitution in subclinically hypothyroid patients (Pearce et al., 2013; Ross et al., 2016; Vanderpump et al., 1995).

A shortcoming of the TSAGE is its small sample size, which is due to its strict inclusion criteria. Furthermore, since a control group (for example, with a placebo administered instead of LT4) was not included in this study, a distortion of the data on QoL cannot be ruled out, for example, the influence of comorbidities or positive or negative life events that increased the likelihood that the patients sought medical advice in the first place.

TSAGE is, however, the first controlled follow-up study in which the QoL of older patients with new-onset, untreated sHT was compared to the QoL of younger patients with sHT and healthy individuals of the same sex and age. The strength of TSAGE is its application of very strict inclusion criteria. The focus was on two defined age groups: young patients below 40 years of age and old patients above 60 years of age. Furthermore, the presently discussed TSH cutoff of >8 mU/L was applied (Gharib et al., 2005; Grossman et al., 2016; Karmisholt et al., 2011; Pearce et al., 2013; Rosario et al., 2016; Ross et al., 2016) rather than the TSH concentration of >4.6 mU/L used in many epidemiological studies, including TRUST (Stott et al. 2017). Recent studies have suggested that reversal of sHT to normal thyroid function is less likely once TSH values are >8 mU/l (Rosario et al., 2016). In TSAGE, all patients had to be newly diagnosed and untreated. All patients had autoimmune thyroiditis, and a confounder effect of the underlying pathogenesis of hypothyroidism on QoL is, therefore, less likely. The measurements of the TSH value and TH were repeated in the Clinical Chemistry – Division of Laboratory Research at the University Hospital Essen in order to take into account fluctuations in TSH concentrations. Moreover, established questionnaires with solid psychometric properties to measure general and disease-specific aspects of QoL were used.

It may be argued that QoL is at least partly biased due to the subjects' awareness of treatment. Yet, a previous study showed that LT4-treated, previously hypothyroid patients blinded to their exact treatment status showed decrements in their perceived health status and mood when sHT was induced (Samuels et al., 2007).

TSAGE included a subgroup of young patients with GD and three old patients with GD. At baseline, young patients reported lower generic QoL compared to the German standard sample. Almost all areas of QoL as measured by the SF-36 improved significantly except for general health and social functioning (see Table 8) after six months of treatment initiation. Disease-specific QoL (ThyPRO) improved, with the exception of Goitre symptoms, Depressivity, and Cosmetic complaints. One possible explanation for this is that it might take longer than six months for depressive symptoms to resolve after euthyroidism has been reached. The scale General Heath (SF-36) includes items regarding future expectations, which might also additionally be negatively influenced by the presence of depressive symptoms. For patients, cosmetic issues due to goitre may be of minor concern in our study population. Watt (2014) observed similar results concerning Cosmetic complaints, including for patients with non-toxic goitre.

Since this study only included three older patients with hyperthyroidism, the results do not allow for conclusions to be made about the general population of older hyperthyroid patients. One interesting finding worth mentioning, however, is that Patient 1 reported a worsened generic QoL for all scales of the SF-36 whereas their disease-specific QoL (ThyPRO) improved; the other two patients reported a higher QoL for all scales of the SF-36 but reported a lower QoL in some areas of the ThyPRO. This is in line with previous studies showing higher responsiveness for disease-specific compared to generic questionnaires that measure patient-reported outcomes (Revickia et al., 2008; Watt et al., 2014).

The thyroid gland impacts many functions of the human body as well as mental functions (see Chapter 1). Thus, it is not surprising that dysfunctions in the thyroid homeostasis affect broad aspects of QoL. Analysis of generic and HRQL in TSAGE showed that sHT is associated with severe impairment in general and disease-specific QoL in young and old age. Furthermore, the study demonstrates that older patients with sHT and TSH concentration of >8 mU/l benefit from LT4 therapy in terms of QoL and show similar degrees of improvement as younger patients. A confirmation of the present concept of TH

homeostasis with regard to QoL in elderly patients was obtained that indicates that TSH concentration above 8-10 mU/l levels severely impact QoL. Hence, treatment should neither be withheld for the young nor for the old. Simultaneously, it is clear that there is a lack of large, placebo-controlled studies that are designed to examine different age groups with TSH values of >8–10 mU/L.

As a recommendation, the instruments for measuring QoL should be thoroughly selected; ideally, a comparison to a standard sample should be available.

TSAGE was not able to collect enough data on sHT or overt hyperthyroidism in older patients. The question of whether older patients experience a decrease of QoL although they show a paucity of symptoms is still unanswered. Considering that QoL should be integrated into the clinical decision process, particularly for older patients, the effect of treatment of sHY on QoL in older patients be of interest for further research (Brunner-La Rocca et al., 2012; Watt et al., 2014; Wong et al., 2016)

To conclude, there is sufficient evidence that QoL should be evaluated in clinical practice and is an important endpoint when it comes to the evaluation of treatment decisions for patients with thyroid dysfunction (Gulseren et al., 2006; Watt et al., 2014; Wong et al., 2016); this is particularly for situations where QoL is as or more valuable than longevity (Brunner-La Rocca et al., 2012).

	Winther et al. (2016)		TRUST Stott et al. (2017)		TSAGE		Jaeschke et al. (1996)	
	General Population	AIT	Placebo	LT4	Young Patients (< 40 years) AIT	Old Patients (> 60 years) AIT	Placebo	LT4
N	739	78	369	368	17	11	18	19
Age	50 (18–81)	47 (18–91)	74±6.8	74±5.8	27±6.4	66±6.4	68±9.4	68±6.4
TSH mU/l baseline	< 4.0	8.1 (5.5-12.2)	6.4±2	6.4±2	15.7±7.9	12.6±8.5	9.4±3.1	12.3±6.8
Tiredness*	35±16	58±24	25.5± 20.3	25.9± 20.6	57±10	62±8	n.d.	n.d.
Hypothyroid symptoms*	14±21	27±28	16.9±17.9	17.5±18.8	29±10	37±20	n.d	n.d.

Table 17 Studies on age-impact on change of hypothyroid symptoms under levothyroxine treatment. Autoimmune thyroiditis (AIT), N= sample size, Age (mean/median), TSH mU/l (median, mean TSH), *ThyPRO Scales Tiredness and Hypothyroidism ± standard deviation or range, n. d. = not determined.

6 ABSTRACT

Background: The European Thyroid Association recommends the treatment of hypothyroidism in the elderly only if thyroid-stimulating hormone (TSH) levels are consistently increased by >10 mU/l, as the available data does not suggest that the same benefits of treatment apply to young and older patients. The aim of this study was to prospectively investigate quality of life (QoL) and thyroid-related QoL in younger (<40 years) and older patients (>60 years) with elevated TSH concentrations due to autoimmune thyroiditis, before and after levothyroxine (LT4) treatment.

Material and Methods: Thyroid Study of Age in Germany (TSAGE): The study included male and female patients older than 18 years with newly diagnosed, untreated, overt endogenous hyperthyroidism (TSH < 0.3 mU/l and elevated free T4 or free triiodothyronine (fT3)), endogenous hypothyroidism (TSH > 8 mU/l, free T4 < 11.5 pmol/l or fT3 < 3.5 pmol/l), or subclinical hypothyroidism (TSH > 8 mU/l; free T4 and fT3 within reference range). Patients were evaluated by clinical assessment, blood sampling, and questionnaires that measured health-related QoL (SF-36 Version 2) and thyroid disease QoL (ThyPRO). Evaluations took place at the time of diagnosis (T1) and six months after initiation of treatment (intake of LT4), (T2).

Results: There were 43 patients with newly diagnosed subclinical hypothyroidism who completed the ThyPRO and SF-36 (Version 2) at baseline (T1). 28 patients completed the questionnaires six months after treatment initiation (> 60 years n = 11; <40 years n = 17). Significantly lower QoL in both young and old patients with subclinical hypothyroidism (sHT) compared to age-matched healthy individuals was found. All patients reported higher scores on follow-up for all SF-36 subscales, irrespective of age, indicating better QoL on levothyroxine therapy. Analysis of the ThyPRO questionnaire additionally showed an improvement, but thematic variation existed for thyroid-specific QoL for young and old patients.

Conclusion: Impairment in general and disease-specific QoL is associated with sHT in young and old age. These data confirm current recommendations for the initiation of LT4 substitution and underline that LT4 substitution should not be withheld in the treatment of elderly patients with TSH concentrations above 8–10 mU/l levels.

7 LITERATUR

1. Akintola, A. A., Jansen, S. W., van Bodegom, D., van der Grond, J., Westendorp, R. G., de Craen, A. J.,van Heemst, D. (2015). Subclinical hypothyroidism and cognitive function in people over 60 years: a systematic review and meta-analysis. Front Aging Neurosci 7, 150.

2. Atzmon, G., Barzilai, N., Hollowell, J. G., Surks, M. I.,Gabriely, I. (2009). Extreme longevity is associated with increased serum thyrotropin. J Clin Endocrinol Metab 94, 1251-1254.

3. Bektas Uysal, H.,Ayhan, M. (2016). Autoimmunity affects health-related quality of life in patients with Hashimoto's thyroiditis. Kaohsiung J Med Sci 32, 427-433.

4. Bianchi, G. P., Zaccheoni, V., Solaroli, E., Vescini, F., Verutti, R., Zoli, M.,Marchesini, G. (2004). Health-related quality of life in patients with thyroid disorders. A study based on Short-Form 36 and Nottingham Health Profile Questionnaires. Quality of Life Research 13, 45-54.

5. Biondi, B., Bartalena, L., Cooper, D. S., Hegedus, L., Laurberg, P.,Kahaly, G. J. (2015). The 2015 European Thyroid Association Guidelines on Diagnosis and Treatment of Endogenous Subclinical Hyperthyroidism. Eur Thyroid J 4, 149-163.

6. Biondi, B., Palmieri, E. A., Fazio, S., Cosco, C., Nocera, M., Sacca, L., Filetti, S., Lombardi, G.,Perticone, F. (2000). Endogenous Subclinical Hyperthyroidism Affects Quality of Life and Cardiac Morphology and Function in Young and Middle-Aged Patients. The Journal of Clinical Endocrinology & Metabolism 85, 4701-4705.

7. Blum, M. R., Bauer, D. C., Collet, T. H., Fink, H. A., Cappola, A. R., da Costa, B. R., Wirth, C. D., Peeters, R. P., Asvold, B. O., den Elzen, W. P., Luben, R. N., Imaizumi, M., Bremner, A. P., Gogakos, A., Eastell, R., Kearney, P. M., Strotmeyer, E. S., Wallace, E. R., Hoff, M., Ceresini, G., Rivadeneira, F., Uitterlinden, A. G., Stott, D. J., Westendorp, R. G., Khaw, K. T., Langhammer, A., Ferrucci, L., Gussekloo, J., Williams, G. R., Walsh, J. P., Juni, P., Aujesky, D., Rodondi, N.,Thyroid Studies, C. (2015). Subclinical thyroid dysfunction and fracture risk: a meta-analysis. JAMA 313, 2055-2065.

8. Boelaert, K., Torlinska, B., Holder, R. L.,Franklyn, J. A. (2010). Older subjects with hyperthyroidism present with a paucity of symptoms and signs: a large cross-sectional study. J Clin Endocrinol Metab 95, 2715-2726.

9. Brunner-La Rocca, H. P., Rickenbacher, P., Muzzarelli, S., Schindler, R., Maeder, M. T., Jeker, U., Kiowski, W., Leventhal, M. E., Pfister, O., Osswald, S., Pfisterer, M. E., Rickli, H.,Investigators, T.-C. (2012). End-of-life preferences of elderly patients with chronic heart failure. Eur Heart J 33, 752-759.

10. Bullinger, M. (1997). Gesundheitsbezogene Lebensqualität und subjektive Gesundheit. Überblick über den Stand der Forschung zu einem neuen Evaluationskriterium in der Medizin. Psychother Psychosom Med Psychol 47, 76-91.

11. Bullinger, M.,Kichberger, I. (1998): SF-36 Fragebogen zum Gesundheitszustand: Göttingen: Hogrefe.

12. Bullinger, M., Siegrist, J.,-Sieberer, U. R. (2000): Lebensqualitätsforschung aus medizinpsychologischer und - soziologischer Perspektive. Jahrbuch der medizinischen Psychologie Göttingen Hogrefe.

13. Canaris, G. J., Manowitz, N. R., Mayor, G.,Ridgway , E. C. (2000). The Colorado Thyroid Disease Prevalence study. Arch Intern Med, 526–534.

14. Chaker, L., Bianco, A. C., Jonklaas, J.,Peeters, R. P. (2017). Hypothyroidism. The Lancet 390, 1550-1562.

15. Chueire, V. B., Romaldini, J. H.,Ward, L. S. (2007). Subclinical hypothyroidism increases the risk for depression in the elderly. Arch Gerontol Geriatr 44, 21-28.

16. Cohen, J. (1988): Statistical power analysis for the behavioral sciences (2). New York Lawrence Erlbaum Associates

17. Cramon P., S., B., Bjorner JB, Ekholm O, Feldt-Rasmussen U, Frendl DM, Groenvold M, Hegedüs L, Rasmussen ÅK,T., W. (2015). Quality of life in patients with benign nontoxic goitre: impact of disease and treatment response, and comparison with the general population. Thyroid 25, 284-291.

18. de Jongh, R. T., Lips, P., van Schoor, N. M., Rijs, K. J., Deeg, D. J., Comijs, H. C., Kramer, M. H., Vandenbroucke, J. P.,Dekkers, O. M. (2011). Endogenous subclinical thyroid disorders, physical and cognitive function, depression, and mortality in older individuals. Eur J Endocrinol 165, 545-554.

19. Di Cosmo, C., Liao, X. H., Dumitrescu, A. M., Philp, N. J., Weiss, R. E.,Refetoff, S. (2010). Mice deficient in MCT8 reveal a mechanism regulating thyroid hormone secretion. J Clin Invest 120, 3377-3388.

20. Elberling, T. V., Rasmussen, A. K., Feldt-Rasmussen, U., Hørding, M., Perrild, H.,Waldemar, G. (2004). Impaired health-related quality of life in Graves' disease. A prospective study. European Journal of Endocrinology 151, 549-555.

21. Franklyn, J. A.,Boelaert, K. (2012). Thyrotoxicosis. The Lancet 379, 1155-1166.

22. Garmendia Madariaga, A., Santos Palacios, S., Guillen-Grima, F.,Galofre, J. C. (2014). The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. J Clin Endocrinol Metab 99, 923-931.

23. Gharib, H., Tuttle, R. M., Baskin, H. J., Fish, L. H., Singer, P. A.,McDermott, M. T. (2005). Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. J Clin Endocrinol Metab 90, 581-585; discussion 586-587.

24. Grossman, A., Weiss, A., Koren-Morag, N., Shimon, I., Beloosesky, Y.,Meyerovitch, J. (2016). Subclinical Thyroid Disease and Mortality in the Elderly: A Retrospective Cohort Study. Am J Med 129, 423-430.

25. Gulseren, S., Gulseren, L., Hekimsoy, Z., Cetinay, P., Ozen, C.,Tokatlioglu, B. (2006). Depression, anxiety, health-related quality of life, and disability in patients with overt and subclinical thyroid dysfunction. Arch Med Res 37, 133-139.

26. Hamburger, J. I. (1980). Evolution of toxicity in solitary nontoxic autonomously functioning thyroid nodules. J.Clin.Endocrinol Metab 50, 1089-1093.

27. Hintze, G.,Derwahl, M. (2010). [Hypothyreodism. From the latent functional disorder up to coma]. Internist (Berl) 51, 568,570-563.

28. Hollowell, J. G., Staehling, N. W., Flanders, W. D., Hannon, W. H., Gunter, E. W., Spencer, C. A.,Braverman, L. E. (2002). Serum TSH, T4, and Thyroid Antibodies in the United States Population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). The Journal of Clinical Endocrinology & Metabolism 87, 489-499.

29. J.Diez, J. (2002). Hypothyroidism in Patients Older Than 55 Years: An Analysis of the Etiology and Assessment of the Effectiveness of Therapy. Journal of Gerontology 57A, 315-320.

30. Jaeschke, R., Guyatt, G., Gerstein, H., Patterson, C., Molloy, W., Cook, D., Harper, S., Griffith, L.,Carbotte, R. (1996). Does treatment with l-thyroxine influence health status in milddle-aged and older adults with subclinical hypothyroidism? Journal of General Internal Medicine 11, 744-749.

31. Kahaly, G. J., Bartalena, L., Hegedus, L., Leenhardt, L., Poppe, K.,Pearce, S. H. (2018). 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. Eur Thyroid J 7, 167-186.

32. Karmisholt, J., Andersen, S.,Laurberg, P. (2011). Variation in thyroid function in subclinical hypothyroidism: importance of clinical follow-up and therapy. Eur J Endocrinol 164, 317-323.

33. Knudsen, N., Bulow, I. J., T., Laurberg, P. O., L.,Perrild, H. (2000). Comparative study of thyroid function and types of thyroid dysfunction in two areas in Denmark with slightly different iodine status. Eur J Endocrinol, 485–491.

34. Kovács, L. (2016). Die „Entstehung“ der Lebensqualität. 11-26.

35. Larisch, R., Kley, K., Nikolaus, S., Sitte, W., Franz, M., Hautzel, H., Tress, W.,Muller, H. W. (2004). Depression and anxiety in different thyroid function states. Horm Metab Res 36, 650-653.

36. Meisinger, C., Ittermann, T., Wallaschofski, H., Heier, M., Below, H., Kramer, A., Döring, A., Nauck, M.,Völzke, H. (2012). Geographic variations in the frequency of thyroid disorders and thyroid peroxidase antibodies in persons without former thyroid disease within Germany. European Journal of Endocrinology 167, 363-371.

37. Mendoza, A.,Hollenberg, A. N. (2017). New insights into thyroid hormone action. Pharmacol Ther 173, 135-145.

38. Mondal, S., Raja, K., Schweizer, U.,Mugesh, G. (2016). Chemistry and Biology in the Biosynthesis and Action of Thyroid Hormones. Angew Chem Int Ed Engl 55, 7606-7630.

39. Pearce, S. H., Brabant, G., Duntas, L. H., Monzani, F., Peeters, R. P., Razvi, S.,Wemeau, J. L. (2013). 2013 ETA Guideline: Management of Subclinical Hypothyroidism. Eur Thyroid J 2, 215-228.

40. Razvi, S., Ingoe, L. E., McMillan, C. V.,Weaver, J. U. (2005). Health status in patients with sub-clinical hypothyroidism. Eur J Endocrinol 152, 713-717.

41. Revickia, D., Hays, R. D., Cellac, D.,Soland, J. (2008). Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. Journal of Clinical Epidemiology 61, 102-109.

42. Rodondi, N., den Elzen, W. P., Bauer, D. C., Cappola, A. R., Razvi, S., Walsh, J. P., Asvold, B. O., Iervasi, G., Imaizumi, M., Collet, T. H., Bremner, A., Maisonneuve, P., Sgarbi, J. A., Khaw, K. T., Vanderpump, M. P., Newman, A. B., Cornuz, J., Franklyn, J. A., Westendorp, R. G., Vittinghoff, E., Gussekloo, J.,Thyroid Studies, C. (2010). Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA 304, 1365-1374.

43. Rosario, P. W.,Calsolari, M. R. (2016). Levothyroxine therapy in the subclinical hypothyroidism: a lifelong therapy? A long-term study. Clin Endocrinol (Oxf) 85, 819-820.

44. Rose, M., Fliege, H., Danzer, G.,Klapp, B. F. (2000). Gesundheitsbezogene Lebensqualität“ ein Teil „Allgemeiner Lebensqualität“? In: M. Bullinger, J. Siegrist, U. R. -Sieberer (Hrsg.): Lebensqualitätsforschung aus medizinpsychologischer und - soziologischer Perspektive. Jahrbuch der medizinischen Psychologie S. 206 - 221. Göttingen Hogrefe

45. Ross, D. S., Burch, H. B., Cooper, D. S., Greenlee, M. C., Laurberg, P., Maia, A. L., Rivkees, S. A., Samuels, M., Sosa, J. A., Stan, M. N.,Walter, M. A. (2016). 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid 26, 1343-1421.

46. Samuels, M. H., Schuff, K. G., Carlson, N. E., Carello, P.,Janowsky, J. S. (2007). Health status, mood, and cognition in experimentally induced subclinical hypothyroidism. J Clin Endocrinol Metab 92, 2545-2551.

47. Schouten, B. J., Brownlie, B. E., Frampton, C. M.,Turner, J. G. (2011). Subclinical thyrotoxicosis in an outpatient population - predictors of outcome. Clin Endocrinol (Oxf) 74, 257-261.

48. Smith, T. J.,Hegedus, L. (2016). Graves' Disease. N Engl J Med 375, 1552-1565.

49. Stott, D. J., Rodondi, N., Kearney, P. M., Ford, I., Westendorp, R. G., Mooijaart, S. P., Sattar, N., Aubert, C. E., Aujesky, D., Bauer, D. C., Baumgartner, C., Blum, M. R., Browne, J. P., Byrne, S., Collet, T. H., Dekkers, O. M., den Elzen, W. P., Du Puy, R. S., Ellis, G., Feller, M., Floriani, C., Hendry, K., Hurley, C., Jukema, J. W., Kean, S., Kelly, M., Krebs, D., Langhorne, P., McCarthy, G., McCarthy, V., McConnachie, A., McDade, M., Messow, M., O'Flynn, A., O'Riordan, D., Poortvliet, R. K., Quinn, T. J., Russell, A., Sinnott, C., Smit, J. W., Van Dorland, H. A., Walsh, K. A., Walsh, E. K., Watt, T., Wilson, R.,

Gussekloo, J.,Group, T. S. (2017). Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism. N Engl J Med

50. Surks, M. I.,Boucai, L. (2010). Age- and race-based serum thyrotropin reference limits. J Clin Endocrinol Metab 95, 496-502.

51. Testa, M. A.,Simonson, D. C. (1996). Assessment of Quality-of-Life Outcomes. The New England Journal of Medicine 334, 835-840.

52. Vanderpump, J., M. P., Tunbrldge, W. M. G., French, J. M., Appleton, D., Bates, D., Clark, F., Evans, J. G., Hasan, D. M., Rodgers, H., Tunbridge, F.,Young, E. T. (1995). The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clinical Endocrinology 43, 55-68.

53. Vanderpump, M. P. (2011). The epidemiology of thyroid disease. Br Med Bull 99, 39-51.

54. Verma, A.,Hasan, T. (2009). Thyroid disorders in older people. Reviews in Clinical Gerontology 19, 193.

55. Völzke, H., Lüdemann, J., Robinson, D. M., Knut W. Spieker, K. W., Schwahn, C., Kramer, A., John, U.,Wieland, M. (2003). The Prevalence of Undiagnosed Thyroid Disorders in a Previously Iodine-Deficient Area. Thyroid 13, 803-810.

56. Ware, J., Snow, K., Kosinski, M.,Gandek, B. (1993): SF-36 Health Survey: Manual and Interpretation Guide.: Boston, Mass.: The Health Institute, New England Medical Center.

57. Watt, T., Bjorner, J. B., Groenvold, M., Cramon, P., Winther, K. H., Hegedüs, L., Bonnema, S. J., Rasmussen, A. K., E. WareJr., J. E.,Feldt-Rasmussen, U. (2015). Development of a Short Version of the Thyroid-Related Patient-Reported Outcome ThyPRO. Thyroid 25, 1069–1079.

58. Watt, T., Cramon, P., Hegedus, L., Bjorner, J. B., Bonnema, S. J., Rasmussen, A. K., Feldt-Rasmussen, U.,Groenvold, M. (2014). The thyroid-related quality of life measure ThyPRO has good responsiveness and ability to detect relevant treatment effects. J Clin Endocrinol Metab 99, 3708-3717.

59. Watt , T., G., B., Jakob Bue Bjorner, J., Bonnema, S. J., Bukvic, B., Drummond, R., Groenvold, M., Hegedu¨s, L., Kantzer, V., Lasch, K. E., Marcocci, C., Mishra, A., Netea-Maier, R., Ekker, M., van Paunovic, I., Quinn, T. J., Rasmussen, A. K., Russell, A., Sabaretnam, M., Smit, J., Toerring, O., Zivaljevic, V.,Feldt-Rasmussen, U. (2015). Cross-cultural validity of the

thyroid-specific quality-of-life patient-reported outcome measure, ThyPRO. Quality of Life Research, 769–780.

60. Watt, T., Groenvold, M., Rasmussen, A. K., Bonnema, S. J., Hegedus, L., Bjorner, J. B.,Feldt-Rasmussen, U. (2006). Quality of life in patients with benign thyroid disorders. A review. Eur J Endocrinol 154, 501-510.

61. Watt, T., Hegedus, L., Bjorner, J. B., Groenvold, M., Bonnema, S. J., Rasmussen, A. K.,Feldt-Rasmussen, U. (2012). Is Thyroid Autoimmunity per se a Determinant of Quality of Life in Patients with Autoimmune Hypothyroidism? Eur Thyroid J 1, 186-192.

62. Watt, T., Hegedus, L., Groenvold, M., Bjorner, J. B., Rasmussen, A. K., Bonnema, S. J.,Feldt-Rasmussen, U. (2010). Validity and reliability of the novel thyroid-specific quality of life questionnaire, ThyPRO. Eur J Endocrinol 162, 161-167.

63. Wilson, S., Parle, J. V., Roberts, L. M., Roalfe, A. K., Hobbs, F. D., Clark, P., Sheppard, M. C., Gammage, M. D., Pattison, H. M., Franklyn, J. A.,Birmingham Elderly Thyroid Study, T. (2006). Prevalence of subclinical thyroid dysfunction and its relation to socioeconomic deprivation in the elderly: a community-based cross-sectional survey. J Clin Endocrinol Metab 91, 4809-4816.

64. Winther, K. H., Cramon, P., Watt, T., Bjorner, J. B., Ekholm, O., Feldt-Rasmussen, U., Groenvold, M., Rasmussen, A. K., Hegedus, L.,Bonnema, S. J. (2016). Disease-Specific as Well as Generic Quality of Life Is Widely Impacted in Autoimmune Hypothyroidism and Improves during the First Six Months of Levothyroxine Therapy. PLoS One 11, e0156925.

65. Wong, C. K., Lang, B. H. H.,Lam, C. L. K. (2016). A systematic review of quality of thyroid-specific health-related quality-of-life instruments recommends ThyPRO for patients with benign thyroid diseases. Journal of Clinical Epidemiology 78, 63-72.

8 APPENDIX

8.1 Abbreviation

GD: Graves´disease
HRQL: health related quality of life
KORA: Kooperative Gesundheitsforschung in der Region Augsburg
SHIP Study of Health in Pomerania
SF-36: Short Form Health Survey
sHT: subclinical hypothyroidism
sHY: subclinical hyperthyroidism
TSAGE: Thyroid Study of Age in Germany
ThyPRO: Quality of life questionnaire for patients with thyroid diseases
T3: 3',3,5-triiodothyronine
T4: thyroxine
TRs: Thyroid receptors
TH: thyroid hormone
TSH: thyroid stimulating hormone
QoL: quality of life
LT4: Levothyroxine

8.2 Index of Tables

Table 1 Symptoms of Hypothyroidism 4
Table 2 Symptoms of Hyperthyroidism 7
Table 3 Age, heart rate, mean arterial blood pressure (MAD) and thyroid function parameters in the study population 24
Table 4 Impact of age and levothyroxine substitution on SF-36 scales 25
Table 5 Impact of age and levothyroxine substitution on ThyPRO scales (mean ± standard deviation).....28
Table 6 Effect Size (mean change or SD baseline) of levothyroxine substitution in young and old patients with sHT 29
Table 7 Age, heart rate, mean arterial blood pressure (MAD) and thyroid function parameters in the hyperthyroid patients 31

Table 8 Impact of treatment on SF-36 scales (mean differences ± standard deviation from gender and age-matched norm *) in young hyperthyroid patients 32
Table 9 Impact of treatment on SF-36 scales (mean differences from gender and age-matched norm *) in three older hyperthyroid patients 33
Table 10 Impact of treatment on ThyPRO scales (mean ± standard deviation) in young hyperthyroid patients.....34
Table 11 Impact of treatment on ThyPRO scales in three patients with hyperthyroidism (>60 years of age).....36
Table 12 Age, heart rate, mean arterial blood pressure (MAD) 37
Table 13 Impact of treatment on SF-36 scales (mean differences ± standard deviation from gender and age-matched norm *) in young overt hypothyroid patients 38
Table 14 Impact of treatment on SF-36 scales (mean differences from gender and age- matched norm *) in two old hypothyroid patients 39
Table 15 Impact of treatment on ThyPRO scales (mean ± standard deviation) after initiation of treatment in young patients with overt hypothyroidism 40
Table 16 Impact of treatment on ThyPRO scales in older overt hypothyroid patients 41
Table 17 Studies on age-impact on change of hypothyroid symptoms under levothyroxine treatment.. 48

8.3 Index of Figures

Figure 1 Flow-chart presenting the process of including participants into the study sample.....23
Figure 2: Newly diagnosed untreated hypothyroidism (T1).....26

8.4 Questionnaires used

8.4.1 ThyPRO

Lebensqualität
Fragebogen für Patienten mit Schilddrüsenerkrankungen

-ThyPROde-

Dieser Fragebogen befasst sich damit, wie Ihre Schilddrüsenerkrankung Ihr Leben beeinflusst hat.

Bitte beantworten Sie jede Frage mit einem ☒ bei der Antwort, die für Sie am besten zutrifft. Wenn Sie sich unsicher sind, wie Sie eine Frage beantworten sollen, geben Sie bitte die Ihrer Meinung nach beste Antwort.

Copyright © Torquil Watt, Copenhagen University Hospital Rigshospitalet, Denmark

Der erste Abschnitt des Fragebogens bezieht sich auf Symptome, Ermüdung, Gedächtnis, Stimmung und Gesundheit.

Bitte beziehen Sie Ihre **Antworten darauf, wie Sie sich** innerhalb der letzten 4 Wochen **insgesamt gefühlt haben**.

1. ***Die ersten Fragen beziehen sich auf Symptome.***

Hatten Sie innerhalb der letzten vier Wochen	Gar nicht	Ein bisschen	Etwas	Viel	Sehr viel
1a - das Gefühl, dass etwas Ihnen Platz im Hals wegnimmt?	☐	☐	☐	☐	☐
1b - eine sichtbare Schwellung im Vorderbereich Ihres Halses?	☐	☐	☐	☐	☐
1c - einen Druck in Ihrer Kehle?	☐	☐	☐	☐	☐
1d - Schmerzen im Vorderbereich Ihrer Kehle?	☐	☐	☐	☐	☐
1e - Schmerzen in Ihrem Hals, die bis in Ihre Ohren gefühlt wurden?	☐	☐	☐	☐	☐
1f - das Gefühl, dass ein Kloß in Ihrem Hals sitzt?	☐	☐	☐	☐	☐
1g - das Verlangen, sich regelmäßig zu räuspern?	☐	☐	☐	☐	☐
1h - Unbehagen beim Schlucken?	☐	☐	☐	☐	☐
1i - Schwierigkeiten beim Schlucken?	☐	☐	☐	☐	☐
1j - ein Erstickungsgefühl?	☐	☐	☐	☐	☐
1k - Heiserkeit?	☐	☐	☐	☐	☐
1l - zitternde Hände?	☐	☐	☐	☐	☐
1m - die Tendenz, viel zu Schwitzen?	☐	☐	☐	☐	☐
1n - Herzklopfen (einen beschleunigten Herzschlag)?	☐	☐	☐	☐	☐
1o - Kurzatmigkeit?	☐	☐	☐	☐	☐
1p - Hitzeempfindlichkeit?	☐	☐	☐	☐	☐
1q - Kälteempfindlichkeit?	☐	☐	☐	☐	☐

→

Copyright © Torquil Watt, Copenhagen University Hospital Rigshospitalet, Denmark

	Hatten Sie innerhalb der letzten vier Wochen	Gar nicht	Ein bisschen	Etwas	Viel	Sehr viel
1r	- einen verstärkten Appetit?	☐	☐	☐	☐	☐
1s	- Durchfall?	☐	☐	☐	☐	☐
1t	- eine Magenverstimmung?	☐	☐	☐	☐	☐
1u	- feuchte oder wässrige Augen?	☐	☐	☐	☐	☐
1v	- Schwellungen unter den Augen oder geschwollene Augenlider?	☐	☐	☐	☐	☐
1w	- das Gefühl von Trockenheit oder „Sand“ in Ihren Augen?	☐	☐	☐	☐	☐
1x	- ein beeinträchtigtes Sehvermögen?	☐	☐	☐	☐	☐
1y	- Druck in (oder hinter) Ihren Augen?	☐	☐	☐	☐	☐
1z	- doppelt gesehen?	☐	☐	☐	☐	☐
1aa	- Augenschmerzen?	☐	☐	☐	☐	☐
1bb	- starke Lichtempfindlichkeit?	☐	☐	☐	☐	☐
1cc	- geschwollene Hände oder Füße?	☐	☐	☐	☐	☐
1dd	- trockene Haut?	☐	☐	☐	☐	☐
1ee	- Juckreiz der Haut?	☐	☐	☐	☐	☐

2. ***Die folgenden Fragen beziehen sich auf Ermüdung.***

	Hatten Sie innerhalb der letzten vier Wochen	Gar nicht	Ein bisschen	Etwas	Viel	Sehr viel
2a	- Ermüdungszustände?	☐	☐	☐	☐	☐
2b	- Ermattungszustände?	☐	☐	☐	☐	☐
2c	- Schwierigkeiten, sich für etwas zu motivieren?	☐	☐	☐	☐	☐
2d	- das Gefühl, ausgebrannt zu sein?	☐	☐	☐	☐	☐

Copyright © Torquil Watt, Copenhagen University Hospital Rigshospitalet, Denmark

3. ***Die folgenden Fragen beziehen sich auf Ihre Vitalität.***

Hatten Sie innerhalb der letzten vier Wochen	Gar nicht	Ein bisschen	Etwas	Viel	Sehr viel
3a - das Gefühl, voller Leben zu sein?	☐	☐	☐	☐	☐
3b - ein energiegeladenes Gefühl?	☐	☐	☐	☐	☐
3c - sich in der Lage gefühlt, die Anforderungen des Lebens zu bewältigen?	☐	☐	☐	☐	☐

4. ***Die folgenden Fragen beziehen sich auf Ihre Erinnerung und Ihre Konzentration.***

Hatten Sie innerhalb der letzten vier Wochen	Gar nicht	Ein bisschen	Etwas	Viel	Sehr viel
4a - Schwierigkeiten, sich zu erinnern?	☐	☐	☐	☐	☐
4b - langsames oder unklares Denkvermögen?	☐	☐	☐	☐	☐
4c - Wortfindungsstörungen?	☐	☐	☐	☐	☐
4d - das Gefühl, durcheinander zu sein?	☐	☐	☐	☐	☐
4e - Schwierigkeiten, etwas Neues zu lernen?	☐	☐	☐	☐	☐
4f - Konzentrationsprobleme?	☐	☐	☐	☐	☐

Copyright © Torquil Watt, Copenhagen University Hospital Rigshospitalet, Denmark

5. ***Die folgenden Fragen beziehen sich auf Nervosität und Anspannung.***

Hatten Sie innerhalb der letzten vier Wochen	Gar nicht	Ein bisschen	Etwas	Viel	Sehr viel
5a - das Gefühl, nervös zu sein?	☐	☐	☐	☐	☐
5b - das Gefühl, ängstlich oder unruhig zu sein?	☐	☐	☐	☐	☐
5c - das Gefühl, angespannt zu sein?	☐	☐	☐	☐	☐
5d - die Befürchtung, schwer krank zu sein?	☐	☐	☐	☐	☐
5e - ein unbehagliches Gefühl?	☐	☐	☐	☐	☐
5f - das Gefühl, ruhelos zu sein?	☐	☐	☐	☐	☐

6. ***Die folgenden Fragen beziehen sich auf ihr Gefühlsleben.***

Hatten Sie innerhalb der letzten vier Wochen das Gefühl,	Gar nicht	Ein bisschen	Etwas	Viel	Sehr viel
6a - traurig zu sein?	☐	☐	☐	☐	☐
6b - depressiv zu sein?	☐	☐	☐	☐	☐
6c - mutlos zu sein?	☐	☐	☐	☐	☐
6d - schnell weinen zu müssen?	☐	☐	☐	☐	☐
6e - unglücklich zu sein?	☐	☐	☐	☐	☐

Hatten Sie innerhalb der letzten vier Wochen das Gefühl,	Gar nicht	Ein bisschen	Etwas	Viel	Sehr viel
6f - glücklich zu sein?	☐	☐	☐	☐	☐
6g - selbstbewusst zu sein?	☐	☐	☐	☐	☐

Copyright © Torquil Watt, Copenhagen University Hospital Rigshospitalet, Denmark

7. *Die folgenden Fragen beziehen sich auf Stimmungsschwankungen oder Schwierigkeiten beim Bewältigen einer Situation.*

Hatten Sie innerhalb der letzten vier Wochen	Gar nicht	Ein bisschen	Etwas	Viel	Sehr viel
7a - Schwierigkeiten, alles zu bewältigen?	☐	☐	☐	☐	☐
7b - das Gefühl, nicht „Sie selbst zu sein“?	☐	☐	☐	☐	☐
7c - das Gefühl, schnell gestresst zu sein?	☐	☐	☐	☐	☐
7d - Stimmungsschwankungen?	☐	☐	☐	☐	☐
7e - das Gefühl, gereizt zu sein?	☐	☐	☐	☐	☐
7f - das Gefühl, frustriert zu sein?	☐	☐	☐	☐	☐
7g - das Gefühl, sich zu ärgern?	☐	☐	☐	☐	☐

	Gar nicht	Ein bisschen	Etwas	Viel	Voll-kommen
7h - das Gefühl, Ihr Leben unter Kontrolle zu haben?	☐	☐	☐	☐	☐
7i - das Gefühl, ausgeglichen zu sein?	☐	☐	☐	☐	☐

Copyright © Torquil Watt, Copenhagen University Hospital Rigshospitalet, Denmark

Der Rest dieses Fragebogens bezieht sich darauf, **wie Ihre Schilddrüsenerkrankung die unterschiedlichen Seiten Ihres Lebens beeinflusst**.

8. *Die folgenden Fragen betreffen Ihre Beziehungen mit anderen Menschen.*

War Ihre Schilddrüsenerkrankung innerhalb der letzten vier Wochen verantwortlich für	Gar nicht	Ein bisschen	Etwas	Viel	Sehr viel
8a - Schwierigkeiten beim Zusammensein mit anderen Menschen (z.B. Ehepartner, Kindern, Freund/Freundin, Bekannten, oder anderen)?	☐	☐	☐	☐	☐
8b - Ihr Gefühl, eine Last für andere Menschen zu sein?	☐	☐	☐	☐	☐
8c - Auseinandersetzungen mit anderen Personen?	☐	☐	☐	☐	☐

Innerhalb der letzten vier Wochen	Gar nicht	Ein bisschen	Etwas	Viel	Sehr viel
8d - haben Sie bemerkt, dass Leute in Ihrer Umgebung kein Verständnis für Ihre Schilddrüsenerkrankung aufgebracht haben?	☐	☐	☐	☐	☐

Copyright © Torquil Watt, Copenhagen University Hospital Rigshospitalet, Denmark

9. ***Die folgenden Fragen beziehen sich auf Ihre täglichen Aktivitäten.***

War Ihre Schilddrüsenerkrankung innerhalb der letzten vier Wochen der Grund für Ihre	Gar nicht	Ein bisschen	Etwas	Viel	Sehr viel
9a - Probleme bei der Bewältigung Ihres täglichen Lebens?	☐	☐	☐	☐	☐
9b - Einschränkungen der Freizeit-aktivitäten oder Hobbys?	☐	☐	☐	☐	☐
9c - Unfähigkeit am Leben um Sie herum teilzuhaben?	☐	☐	☐	☐	☐
9d - Schwierigkeiten herumzukommen, (z.B. Gehen, Joggen, Fahrradfahren oder Autofahren)?	☐	☐	☐	☐	☐
9e - Gefühle, dass alles etwas länger dauert?	☐	☐	☐	☐	☐

War Ihre Schilddrüsenerkrankung innerhalb der letzten vier Wochen der Grund für Ihre	Ich arbeite nicht	Gar nicht	Ein bisschen	Etwas	Viel	Sehr viel
9f - Schwierigkeiten bei der Bewältigung Ihres Jobs (z. B. eine Situation schwer zu bewältigen oder krank zu machen)?	☐	☐	☐	☐	☐	☐

Copyright © Torquil Watt, Copenhagen University Hospital Rigshospitalet, Denmark

10. ***Die folgenden Fragen beziehen sich auf Ihr Sexualleben.***

	Hatten Sie innerhalb der letzten vier Wochen	Gar nicht	Ein bisschen	Etwas	Viel	Sehr viel
10a	- das Gefühl, dass sich Ihre Schilddrüsenerkrankung negativ auf Ihr Sexualleben ausgewirkt hat?	☐	☐	☐	☐	☐
10b	- ein nachlassendes sexuelles Verlangen?	☐	☐	☐	☐	☐

11. ***Schilddrüsenerkrankungen (oder ihre Behandlung) können Ihr Äußeres beeinflussen. (Z.B. Schwellungen des Halses, des Gesichtes, der Hände oder der Füße, oder Veränderungen des Gewichtes oder der Augen.)***

	Innerhalb der letzten vier Wochen	Gar nicht	Ein bisschen	Etwas	Viel	Sehr viel
11a	- hat Ihre Schilddrüsenerkrankung Ihr Äußeres beeinflusst (z.B., Schwellung des Halses, Veränderungen der Augen, Veränderungen des Gewichts)?	☐	☐	☐	☐	☐
11b	- waren Sie mit Ihrem Aussehen aufgrund Ihrer Schilddrüsenerkrankung unzufrieden?	☐	☐	☐	☐	☐
11c	- haben Sie versucht sichtbare Merkmale Ihrer Schilddrüsenerkrankung zu verbergen oder zu maskieren (z.B. in dem Sie einen Schal oder eine Sonnenbrille getragen haben)?	☐	☐	☐	☐	☐
11d	- haben Sie die Blicke anderer Leute gestört?	☐	☐	☐	☐	☐
11e	- hat Sie Ihre Schilddrüsenerkrankung bei der Kleidung, die Sie getragen haben, beeinflusst?	☐	☐	☐	☐	☐
11f	- haben Sie sich durch Ihre Schilddrüsen-erkrankung zu dick gefühlt?	☐	☐	☐	☐	☐

Copyright © Torquil Watt, Copenhagen University Hospital Rigshospitalet, Denmark

12. ***Die letzte Frage bezieht sich darauf, wie sehr Sie Ihre Schilddrüsenerkrankung insgesamt innerhalb der letzten 4 Wochen beeinflusst hat.***

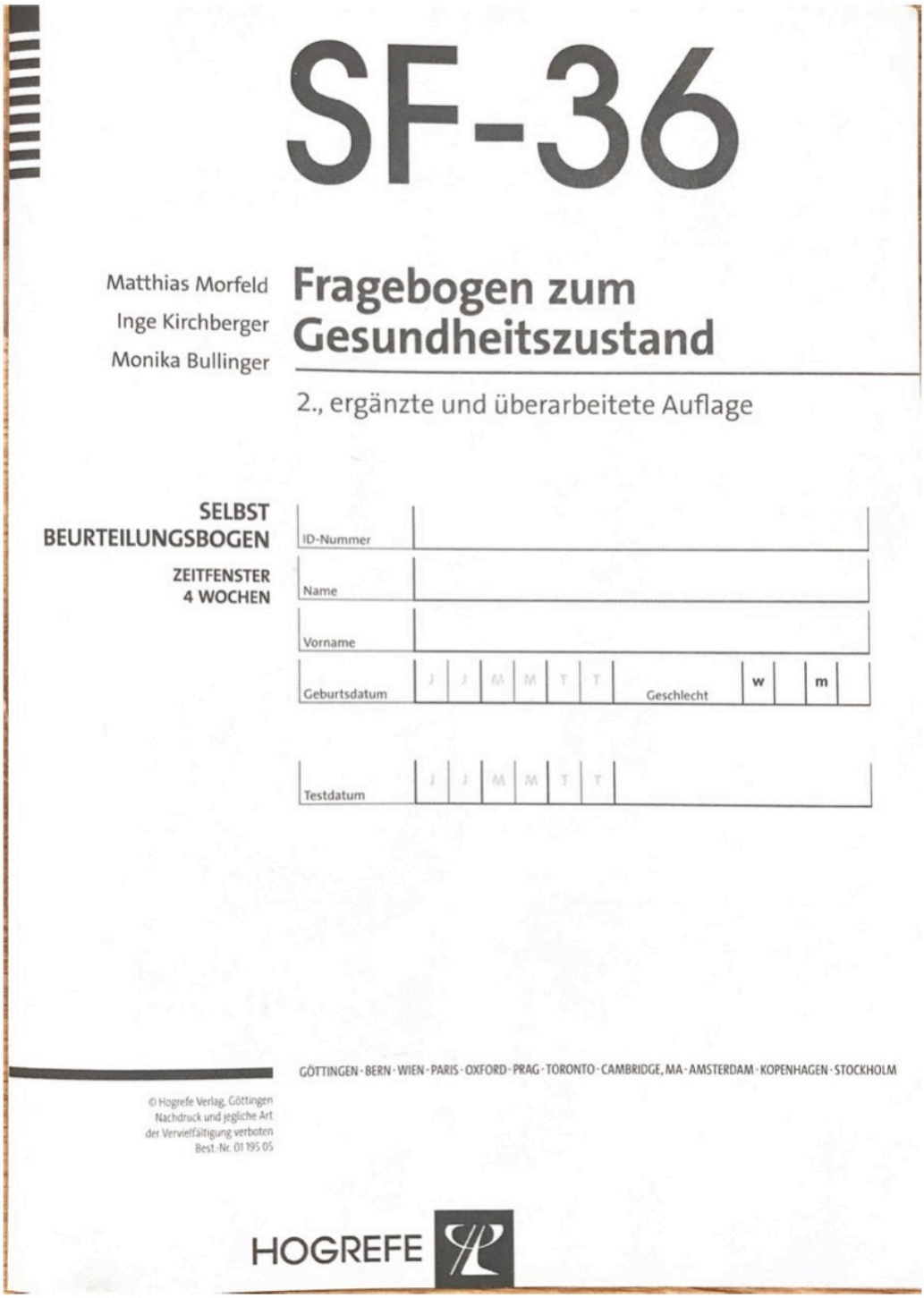
Innerhalb der letzten vier Wochen	Gar nicht	Ein bisschen	Etwas	Viel	Sehr viel
12 - hatte Ihre Schilddrüsenerkrankung eine negative Auswirkung auf Ihre Lebensqualität?	☐	☐	☐	☐	☐

Bitte vergewissern Sie sich, dass Sie alle Fragen beantwortet haben.

Vielen Dank, dass Sie diesen Fragebogen beantwortet haben!

Copyright © Torquil Watt, Copenhagen University Hospital Rigshospitalet, Denmark

8.4.2 SF-36



SF-36

Matthias Morfeld
Inge Kirchberger
Monika Bullinger

Fragebogen zum Gesundheitszustand

2., ergänzte und überarbeitete Auflage

SELBST BEURTEILUNGSBOGEN

ZEITFENSTER 4 WOCHEN

ID-Nummer

Name

Vorname

Geburtsdatum J J M M T T Geschlecht w m

Testdatum J J M M T T

GÖTTINGEN · BERN · WIEN · PARIS · OXFORD · PRAG · TORONTO · CAMBRIDGE, MA · AMSTERDAM · KOPENHAGEN · STOCKHOLM

© Hogrefe Verlag, Göttingen
Nachdruck und jegliche Art der Vervielfältigung verboten
Best.-Nr. 01 195 05

HOGREFE

In diesem Fragebogen geht es um die Beurteilung Ihres Gesundheitszustandes. Der Bogen ermöglicht es, im Zeitverlauf nachzuvollziehen, wie Sie sich fühlen und wie Sie im Alltag zurechtkommen.

Bitte beantworten Sie jede Frage, indem Sie bei den Antwortmöglichkeiten die Zahl ankreuzen, die am besten auf Sie zutrifft.

	Ausgezeichnet	Sehr gut	Gut	Weniger gut	Schlecht
1. Wie würden Sie Ihren Gesundheitszustand im Allgemeinen beschreiben?	1	2	3	4	5

	Derzeit viel besser	Derzeit etwas besser	Etwa wie vor einem Jahr	Derzeit etwas schlechter	Derzeit viel schlechter
2. Im Vergleich zum *vergangenen Jahr*, wie würden Sie Ihren derzeitigen Gesundheitszustand beschreiben?	1	2	3	4	5

Im Folgenden sind einige Tätigkeiten beschrieben, die Sie vielleicht an einem normalen Tag ausüben. *Sind Sie durch Ihren derzeitigen Gesundheitszustand* bei diesen Tätigkeiten *eingeschränkt*? Wenn ja, wie stark?

	Ja, stark eingeschränkt	Ja, etwas eingeschränkt	Nein, überhaupt nicht eingeschränkt
3.a **anstrengende Tätigkeiten**, z. B. schnell laufen, schwere Gegenstände heben, anstrengenden Sport treiben	1	2	3
3.b **mittelschwere Tätigkeiten**, z. B. einen Tisch verschieben, staubsaugen, kegeln, Golf spielen	1	2	3
3.c Einkaufstaschen heben oder tragen	1	2	3
3.d **mehrere** Treppenabsätze steigen	1	2	3
3.e **einen** Treppenabsatz steigen	1	2	3
3.f sich beugen, knien, bücken	1	2	3
3.g **mehr als 1 Kilometer** zu Fuß gehen	1	2	3
3.h **mehrere** Straßenkreuzungen weit zu Fuß gehen	1	2	3
3.i **eine** Straßenkreuzung weit zu Fuß gehen	1	2	3
3.j sich baden oder anziehen	1	2	3

Hatten Sie in den *vergangenen 4 Wochen aufgrund Ihrer* ***körperlichen*** *Gesundheit* irgendwelche Schwierigkeiten bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause?

	Ja	Nein
4.a Ich konnte nicht **so lange** wie üblich tätig sein.	1	2
4.b Ich habe **weniger geschafft** als ich wollte.	1	2
4.c Ich konnte **nur bestimmte Dinge** tun.	1	2
4.d Ich hatte **Schwierigkeiten** bei der Ausführung.	1	2

Hatten Sie in den *vergangenen 4 Wochen aufgrund* ***seelischer*** *Probleme* irgendwelche Schwierigkeiten bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause (z.B. weil Sie sich niedergeschlagen oder ängstlich fühlten)?

	Ja	Nein
5.a Ich konnte nicht **so lange** wie üblich tätig sein.	1	2
5.b Ich habe **weniger geschafft** als ich wollte.	1	2
5.c Ich konnte nicht so **sorgfältig** wie üblich arbeiten.	1	2

	Überhaupt nicht	Etwas	Mäßig	Ziemlich	Sehr
6. Wie sehr haben Ihre körperliche Gesundheit oder seelischen Probleme in den *vergangenen 4 Wochen* Ihre normalen Kontakte zu Familienangehörigen, Freunden, Nachbarn oder zum Bekanntenkreis beeinträchtigt?	1	2	3	4	5

	Keine Schmerzen	Sehr leicht	Leicht	Mäßig	Stark	Sehr stark
7. Wie stark waren Ihre Schmerzen in den *vergangenen 4 Wochen*?	1	2	3	4	5	6

	Überhaupt nicht	Ein bisschen	Mäßig	Ziemlich	Sehr
8. Inwieweit haben die Schmerzen Sie in den *vergangenen 4 Wochen* bei der Ausübung Ihrer Alltagstätigkeiten zu Hause und im Beruf behindert?	1	2	3	4	5

In diesen Fragen geht es darum, wie Sie sich fühlen und wie es Ihnen in den *vergangenen 4 Wochen* gegangen ist. (Bitte kreuzen Sie in jeder Zeile die Zahl an, die Ihrem Befinden am ehesten entspricht).

Wie oft waren Sie *in den vergangenen 4 Wochen* ...

	Immer	Meistens	Ziemlich oft	Manch-mal	Selten	Nie
9.a ... voller Schwung?	1	2	3	4	5	6
9.b ... sehr nervös?	1	2	3	4	5	6
9.c ... so niedergeschlagen, dass Sie nichts aufheitern konnte?	1	2	3	4	5	6
9.d ... ruhig und gelassen?	1	2	3	4	5	6
9.e ... voller Energie?	1	2	3	4	5	6
9.f ... entmutigt und traurig?	1	2	3	4	5	6
9.g ... erschöpft?	1	2	3	4	5	6
9.h ... glücklich?	1	2	3	4	5	6
9.i ... müde?	1	2	3	4	5	6

	Immer	Meistens	Manchmal	Selten	Nie
10. Wie häufig haben Ihre körperliche Gesundheit oder seelischen Probleme in den *vergangenen 4 Wochen* Ihre Kontakte zu anderen Menschen (Besuche bei Freunden, Verwandten usw.) beeinträchtigt?	1	2	3	4	5

Inwieweit trifft *jede* der folgenden Aussagen auf Sie zu?

	trifft ganz zu	trifft weitgehend zu	weiß nicht	trifft weitgehend nicht zu	trifft überhaupt nicht zu
11.a Ich scheine etwas leichter als andere krank zu werden.	1	2	3	4	5
11.b Ich bin genauso gesund wie alle anderen, die ich kenne.	1	2	3	4	5
11.c Ich erwarte, dass meine Gesundheit nachlässt.	1	2	3	4	5
11.d Ich erfreue mich ausgezeichneter Gesundheit.	1	2	3	4	5

Vielen Dank.

9 ACKNOWLEDGEMENTS

Mein ganz besonderer Dank gilt Frau Prof. Dr. Dr. D. Führer Direktorin der Klinik für Endokrinologie, Diabetologie und Stoffwechsel am Essener Universitätsklinikum für ihre große unermüdliche Unterstützung.

Für Fragen, die Durchsicht meiner Arbeit und wertvollen Verbesserungsvorschläge möchte ich mich außerdem bei Prof. Dr. Karin Frank-Raue, Prof. Rainer Görges, Dr. Sebastian Lederbogen, PD. Dr. Gudrun Leidig-Bruckner, Prof Dr. Lars Möller, MD PhD DMSc Torquil Watt und Dr. Denise Zwanziger bedanken.

Zudem gilt Prof. Dr. Karin Frank-Raue, Prof. Görges, Dr. Sebastian Lederbogen, PD Dr. Gudrun Leidig-Bruckner, Dr. Dieter Graf mein Dank für das große Engagement in der fortwährenden Rekrutierung von Patienten für TSAGE.

Bei Karin Dunschen möchte ich mich für Ihre engagierte technische Unterstützung bei der Blutprobenanalyse und die große Hilfsbereitschaft bei organisatorischen Fragen bedanken.

Frau Dr. Viehmann vom Institut für IMIBE bedanke ich mich für die Geduld und Unterstützung bei speziellen statistischen Fragen.

Auch meiner Familie und Freunden bin ich dankbar für das Verständnis und die Unterstützung in meinem Bestreben noch ein Medizinstudium aufzunehmen.

10 CURRICULUM VITAE

Der Lebenslauf ist in der Online-Version aus Gründen des Datenschutzes nicht enthalten.