Dissertation

Diagnostic characteristics and clinical course of thyroid dysfunction in various clinical settings

submitted by

Dr.med.univ. Eva Steinberger

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Department of Internal Medicine

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Assoz. Prof. Priv.-Doz. Dr.med.univ. Stefan PILZ, PhD

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Statutory Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the "Guidelines of the Medical University of Graz on Good Scientific Practice".

Disclosures

Part of this thesis has been published in

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I confirm that all co-authors have explicitly agreed to the use of their data in the thesis and that I have obtained permission to reproduce figures and tables published in Melmed S, Koenig R, Rosen C, Auchus R, and Goldfine A. *Williams Textbook of Endocrinology E-Book*. 14th. Elsevier Health Sciences, Nov. 14, 2019. 1792 pp. ISBN: 978-0-323-71154-8, Steinberger E, Pilz S, Trummer C, Theiler-Schwetz V, Reichhartinger M, Benninger T, Pandis M, Malle O, Keppel MH, Verheyen N, Gruebler MR, Voelkl J, Meinitzer A, and Maerz W. "Associations of Thyroid Hormones and Resting Heart Rate in Patients Referred to Coronary Angiography". In: *Hormone and Metabolic Research = Hormon- Und Stoffwechselforschung = Hormones Et Metabolisme* 52.12 (Dec. 2020), pp. 850–855. ISSN: 1439-4286. DOI: 10.1055/a-1232-7292.

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Contents

Acronyms

AAS anabolic androgenic steroid. 26, 30

ACS acute coronary syndrome. 16

ADHD attention deficit hyperactivity disorder. 48

ALP alkaline phosphatase. 11

ANOVA analyses of variance. 17

ARDS acute respiratory distress syndrome. 26, 29, 30

AST acute suppurative thyroiditis. 25–31

ATA American Thyroid Association. 43, 45–49

AVP arginine vasopressin. 9

BMI body mass index. 17, 18, 21, 39

BMR basal metabolic rate. 10, 11

BPM beats per minute. 19

CAD coronary artery disease. 16, 38

CATS Controlled Antenatal Thyroid Screening. 48

CCK cholecystokinin. 9

CI confidence interval. 20

CK creatine kinase. 11, 41

CRP C-reactive protein. 25, 27, 28

CT computed tomography. 25, 28, 29, 31

D1 type 1 deiodinase. 7

D2 type 2 deiodinase. 7

D3 type 3 deiodinase. 7

DIT diiodotyrosine. 4, 5

DNA deoxyribonucleic acid. 7

DUOX1 dual oxidase 1. 5

DUOX2 dual oxidase 2. 5

ENT otorhinolaryngology. 26–28

ER endoplasmic reticulum. 4

ESR erythrocyte sedimentation rate. 31

fT3 free triiodothyronine. 10, 11, 15–23, 27, 34–36, 39, 40, 50, 51

fT4 free thyroxine. 10, 11, 15–23, 27, 33–35, 38–40, 44, 48, 50, 51

GLP1 glucagon-like peptide 1. 9

GRP gastrin-releasing peptide. 9

H2O2 hydrogen peroxide. 5

hCG human chorionic gonadotropin. 9, 44, 45, 49

HNF3 hepatocyte nuclear factor 3. 5

HPT axis hypothalamic-pituitary-thyroid axis. 8

hTg-Ab human thyroglobulin antibod. 13

hTPO-Ab human thyroid peroxidase antibody. 13

ICU intensive care unit. 29, 30

IDDM insulin-dependent diabetes mellitus. 13

IL-1β interleukin 1β. 9

IL-6 interleukin 6. 9

IQ intelligence quotient. 48

IVF in vitro fertilization. 45

JTI Jostel's TSH index. 16, 17, 20, 22, 23

LAT1 L-type amino acid transporter 1. 7

LAT2 L-type amino acid transporter 2. 7

LDH lactate dehydrogenase. 41

LDL low-density lipoprotein. 11

LT3 liothyronine. 39–42

LT4 levothyroxine. 35, 38–42, 45–49, 51, 52

MCT10 monocarboxylate transporter 10. 7

MCT8 monocarboxylate transporter 8. 5, 7

MIT monoiodotyrosine. 4, 5

mRNA messenger ribonucleic acid. 7

MSH melanocyte-stimulating hormone. 8

NIS sodium-iodide symporter. 4, 5

NPY neuropeptide Y. 8, 9

NTI nonthyroidal illness syndrome. 15, 16, 18, 23, 36

OATP1C1 organic anion transporting polypeptide 1C1. 7

PAX8 paired box 8. 5

PPII pyroglutamyl peptidase II. 9

PTU propylthiouracil. 7

PVN paraventricular nuclei. 8, 9

RAIU radioactive iodine uptake test. 13

RCT randomized controlled trial. 23, 39, 41, 45, 48

RCTs randomized controlled trials. 43, 46–48, 52

RHR resting heart rate. 15–24

rT3 reverse triiodothyronine. 5, 7

RTHβ resistance to thyroid hormoneβ. 11

SAT subacute thyroiditis. 25–29, 31

SD standard deviation. 17

SE standard error. 20

T3 triiodothyronine. 5–12, 15, 16, 36, 39–41, 45

T4 thyroxine. 4–12, 22, 39–41, 45, 46

T4-G T4-glucuronide. 7

TBG thyroxine-binding globulin. 6, 11, 44

Tg thyroglobulin. 4, 5, 7, 11, 36

Tg-Ab thyroglobulin antibodies. 13, 48, 49

TNFα tumor necrosis factor α. 9

TPO thyroid peroxidase. 5, 11, 36, 45

TPO-Ab thyroid peroxidase antibodies. 13, 44, 45, 47–49, 51, 52

TRα thyroid hormone receptor α. 7

TRα1 thyroid hormone receptor α1. 7

TRβ thyroid hormone receptor β. 7

TRβ1 thyroid hormone receptor β1. 7

TRβ2 thyroid hormone receptor β2. 7

TRβ3 thyroid hormone receptor β3. 7

TRAbs thyrotropin receptor antibodies. 46, 47, 50, 51

TRH thyrotropin releasing hormone. 8, 9, 33

TRs thyroid hormone receptors. 7

TSH thyrotropin. 5, 8–12, 15–23, 26, 27, 33–36, 38–40, 42, 44–49, 51, 52

TSHR thyrotropin receptor. 5, 11

TSHR-Ab thyrotropin receptor antibodies. 13

TTF1 thyroid transcription factor 1. 5

TTF2 thyroid transcription factor 2. 5

TTR transthyretin. 6

UDPGTs uridine diphosphate glucuronyl transferases. 7

UDPGTs uridine diphosphate glucuronyl transferases. 7

Abstract in German:

Schilddrüsenerkrankungen gehören aufgrund ihrer hohen Prävalenz zu den häufigsten Krankheiten in der Allgemeinbevölkerung. In dieser Arbeit befassen wir uns mit der Diagnose und Behandlung von Schilddrüsendysfunktionen aus verschiedenen Blickwinkeln. Wir gehen speziell auf die neuesten Entwicklungen in der Behandlung von Schilddrüsenerkrankungen ein, ziehen statistische Schlussfolgerungen und berichten über das klinische Umfeld. Wir beginnen mit einer allgemeinen Einführung in die Pathophysiologie der Schilddrüse sowie der Diagnostik von Schilddrüsenerkrankungen und bilden so die Grundlage für eine weiterführende Diskussion.

Im Hauptteil der Arbeit untersuchen wir den Zusammenhang zwischen Schilddrüsenhormonen und Ruheherzfrequenz (RHR) und zeigen einen statistisch signifikanten Zusammenhang zwischen freiem Trijodthyronin (fT3) sowie freiem Thyroxin (fT4) und RHR bei Patienten, die zur Koronarangiographie überwiesen werden und bei denen RHR als Risikofaktor für negative klinische outcomes gilt. Wir stellen fest, dass für Thyreotropin (TSH) keine solche Korrelation gefunden werden konnte. Dieses Ergebnis steht weitgehend im Einklang mit anderen Untersuchungen. Basierend darauf ergeben sich mehrere zukünftige Forschungs- und potenzielle Behandlungsmöglichkeiten. Zum Beispiel die Verwendung der RHR, die heutzutage leicht mit einer intelligenten Uhr (smartwatch) überwacht werden kann, als erster Hinweis für die Notwendigkeit einer Anpassung des aktuellen Behandlungsplans oder als Früherkennungszeichen für das Auftreten von Schilddrüsenerkrankungen. Aufgrund der Einfachheit der Messung der RHR, könnte ein solcher Ansatz leicht in eine telemedizinische Einrichtung integriert werden.

Im Anschluss berichten wir über den Fall einer akut eitrigen Thyreoiditis durch Streptococcus anginosus, die zu einer Sepsis mit akutem Atemnotsyndrom führte. Darin zeigen wir, wie schwierig diese Diagnose in der klinischen Praxis sein kann, insbesondere wenn die Abgrenzung zur subakuten Thyreoiditis nicht eindeutig ist.

Um die Kluft zwischen der theoretischen Analyse und dem klinischen Umfeld vollständig zu überbrücken, betrachten wir die Hypothyreose sowie auch Schilddrüsenerkrankungen mit Fokus auf Fruchtbarkeit, Schwangerschaft und Stillzeit aus einer breiteren Perspektive, die Leitlinien, neue Erkenntnisse und die damit verbundene klinische Praxis beinhaltet. Die Indikation zur Behandlung einer latenten Hypothyreose wurde in den letzten Jahren zunehmend in Frage gestellt, auch innerhalb der Schwangerschaft, was darauf hindeutet, dass eine übermäßige Therapie der latenten Hypothyreose vermieden werden sollte. Wir beobachten somit einen Trend weg von der aggressiven Therapie der latenten Hypothyreose, wobei wir die Wichtigkeit der Diagnose und Behandlung einer manifesten Schilddrüsenfehlfunktion hervorheben möchten.

Insgesamt liefert die Dissertation eine Reihe wissenschaftlicher Daten, die wir mit der klinischen Praxis durch Leitlinien und einer Fallstudie verknüpfen und damit hoffen, dass die gesamte Arbeit für Kliniker, die sich um Patienten mit Schilddrüsenerkrankungen kümmern hilfreich ist.

Abstract in English:

Thyroid disorders are among the most common diseases due to their high prevalence in the general population. In this thesis, we investigate the diagnosis and treatment of thyroid dysfunctions from various angles and focus on the clinical setting. We especially look into recent developments in the treatment of thyroid disorders, draw statistical conclusions with easily accessible measurements, and report about the clinical settings. We start with a general introduction on the pathophysiology of the thyroid gland and its diagnostic evaluation, forming the basis for more in-depth discussions.

In the main part of the thesis, we evaluate at the association of thyroid hormones with resting heart rate (RHR), showing that there is a statistically significant association between free triiodothyronine (fT3) as well as free thyroxine (fT4) and RHR in patients referred to coronary angiography, where RHR is considered a risk factor for adverse clinical outcomes. We note that no such correlation could be found for thyrotropin (TSH). This finding is at large in line with other research. Based on these findings, multiple future research directions and potential treatment opportunities are revealed. For example, using RHR, which can nowadays easily be monitored with a smart watch, as first indication for the potential need for readjustment of a current treatment plan or the early detection of signs for the onset of thyroid disorders. Due to the ease of measurement of RHR and the ability to perform such measurements continuously and without the help of physicians, such an approach could easily be integrated into a tele-medicine setup.

In the following chapter, we turn our attention to the clinical setting, providing a case report on an acute suppurative thyroiditis (AST) due to Streptococcus anginosus, which led to sepsis and acute respiratory distress syndrome. In this case report, we show how challenging the diagnosis of AST can be in practice, especially when the distinction from subacute thyroiditis (SAT) is not straight-forward.

To fully bridge the gap between theoretical analysis to the clinical setting, we look at hypothyroidism as well as thyroid disorders with a focus on fertility, pregnancy and lactation from a broader perspective, covering guidelines, new evidence and the related clinical practice. The indication for treatment of subclinical hypothyroidism also within pregnancy has been increasingly questioned in recent years, suggesting that excessive diagnosis and therapy for subclinical hypothyroidism should be avoided. Thus, we observe trends away from aggressive therapies of subclinical hypothyroidism, while still putting emphasis on the importance of the diagnosis and treatment of overt thyroid dysfunctions.

Overall, the thesis provides a string of scientific data that have a clear focus on clinical science. We also connect these scientific data with clinical practice through guidelines and a case study and thus hope the entirety of this thesis is useful for clinicians taking care of patients with thyroid disorders.

Chapter 1

Introduction

Contents

Thyroid disorders are among the most common diseases due to their high prevalence in the general population. Both, treatment improvements on a general population level, as well as, for severe cases can thus be highly beneficial. In this thesis, we set out to shed light on recent developments in the treatment of thyroid disorders, draw statistical conclusions about thyroid disorders with easily accessible measurements, and report about the clinical implications. The specific aim of this thesis is to provide scientific data that have a clear focus on clinical science and are therefore, hopefully, useful for clinicians taking care of patients with thyroid disorders. In this context, we wish to point out that it is very common that physicians—who are not endocrinologists by training—are frequently confronted with patients suffering from thyroid diseases. Providing useful guidance for these clinicians by easy to read and clinically oriented reviews covering frequent clinical questions and topics in this area was therefore another major goal of this work. The clinical orientation of this thesis is further underlined by the inclusion of a case report.

The thesis is based on the four published articles, including one original article, one case report and two literature reviews:

- Steinberger E, Pilz S, Trummer C, Theiler-Schwetz V, Reichhartinger M, Benninger T, Pandis M, Malle O, Keppel MH, Verheyen N, Gruebler MR, Voelkl J, Meinitzer A, and Maerz W. "Associations of Thyroid Hormones and Resting Heart Rate in Patients Referred to Coronary Angiography". In: *Hormone and Metabolic Research = Hormon- Und Stoffwechselforschung = Hormones Et Metabolisme* 52.12 (Dec. 2020), pp. 850–855. ISSN: 1439-4286. DOI: 10.1055/a-1232-7292

- Trummer C, Theiler-Schwetz V, Steinberger E, Reisinger AC, Hassler E, Valentin T, Reinisch S, and Pilz S. "Acute suppurative thyroiditis due to Streptococcus anginosus leading to sepsis and acute respiratory distress syndrome: a case report." In: *Archives of endocrinology and metabolism* 65.6 (Nov. 24, 2021). Place: Brazil, pp. 846–851. ISSN: 2359-4292 2359-3997. DOI: 10.20945/2359-3997000000420

- Pilz S, Theiler-Schwetz V, Malle O, Steinberger E, Pandis M, Lerchbaum E, and Trummer C. "Schilddruese: Fertilitaet, Schwangerschaft und Laktation". In: *Journal für Klinische Endokrinologie und Stoffwechsel* 13.3 (Sept. 1, 2020), pp. 106–114. ISSN: 1998-7781. DOI: 10.1007/s41969-020-00107-8. URL: https://doi.org/10.1007/s41969-020-00107-8 (visited on 05/19/2021)

- Pilz S, Theiler-Schwetz V, Malle O, Steinberger E, and Trummer C. "Hypothyreose: Guidelines, neue Erkenntnisse und klinische Praxis". In: *Journal für Klinische Endokrinologie und Stoffwechsel* 13.3 (Sept. 1, 2020), pp. 88–95. ISSN: 1998-7781. DOI: 10.1007/s41969-020-00114-9. URL: https://doi.org/10.1007/s41969-020-00114-9

The remainder of the thesis is structured as follows: Section 1.1 gives an overview of the pathophysiology and the diagnostic evaluation of the thyroid gland—experienced readers on the topic of the thyroid gland and thyroid disorders may thus skip this introductory chapter. Chapter 2 focuses on the association of thyroid hormones with resting heart rate in patients referred to coronary angiography and is based on our original article [1]. Chapter 3 presents a case report on acute suppurative thyroiditis [2]. Chapter 4 and 5 focus on hypothyroidism and the influence of the thyroid on fertility, pregnancy and lactation, rounding out the thesis with discussions and recent developments that are relevant in the clinical practice. Finally, we summarize and discuss our main findings in chapter 6 and provide a future outlook.

1.1 Thyroid gland

The following summary of the thyroid gland is to a large extend based on the textbook by Melmed et al. [5]. For more details the interested reader is referred to section 3 of the textbook [5].

1.1.1 Pathophysiology of the thyroid gland

The thyroid anatomy and histology, as well as the thyroid hormones and the regulation of the thyroid function are well established.

1.1.1.1 Thyroid anatomy

A normal thyroid gland consists of two lobes that are connected by the isthmus, a thin band of tissue. In healthy adults, each lobe is approximately 2 cm to 2.5 cm wide and thick and has a length of about 4 cm. The isthmus measures 0.5 × 2 × 1–2 cm. It connects to the lobes at the inferior pole, which is typically blunt, opposing the superior pole, which is pointed. Comparing the two lobes, the right lobe is often larger, may be more vascular and also has the tendency to enlarge easier in patients with disorders that cause an increased thyroid gland size. In healthy adults, the entirety of the thyroid weighs about 15 g to 20 g, making the thyroid the largest purely endocrine organ.[5]

The blood supply of the thyroid comes from the superior and inferior thyroid artery. The first arising from the external carotid artery, the latter from the subclavian artery. Together they achieve a blood flow of 4 mL min^{-1} g^{-1} to 6 mL min^{-1} g^{-1}. Interestingly, that is well in excess of the kidney's blood flow of 3 mL min^{-1} g^{-1}. As a cause of Graves' disease (with a diffuse toxic goiter) blood flow can reach and even exceed 1 L min^{-1}. In such a case the blood flow may even be palpable and audible.[5]

Throughout the gland, blood flow is established through a rich capillary network that supplies the thyroid follicles.[5]

1.1.1.2 Thyroid histology

The follicles are the structural and functional units of the thyroid gland. They are spherical and tightly packed, with an average diameter of 200 nm; however, their size varies strongly, not only across patients, but even within a single gland. Their walls are made up of cuboidal cells, named the follicular cells. When active, the cells increase in height and turn columnar instead of cuboidal. The thyroid follicles form a compartment for a clear proteinaceous substance called the colloid, which makes up the majority of the thyroid's overall mass. The follicles are separated from the surrounding capillaries by the basement membrane which is rich in glycoproteins. 20 to 40 follicles typically form a lobule that is delineated by connective tissue and supplied by one artery.[5]

At or close to the surface of the cell, where numerous microvilli elongate into the colloid, iodination, exocytosis and colloid resorption take place. While the nucleus

shows typical features, the cytoplasm is filled with lysosomes, mitochondria and loads of endoplasmic reticulum (ER) stuffed with microsomes and a network of wide irregular tubules which contain the precursor of thyroglobulin (Tg). In the apically located Golgi apparatus the carbohydrate component of Tg is added.[5]

The parafollicular cells (C cells) are located among the cells of the follicular epithelium or in the thyroid interstitium, never bordering on the follicular lumen. They are rich in mitochondria and represent the source of calcitonin.[5]

1.1.1.3 Thyroid hormones

To create the amount of necessary thyroid hormones to meet the demands of the peripheral tissue, a thyroidal uptake of about 60 µg to 75 µg exogenous **iodine** daily is needed. The daily fecal loss is merely about 10 µg to 20 µg iodine, whereas the urinary loss is about 100 µg to 150 µg iodine in a iodine-sufficient population.[6] The daily intake of iodine depends on the iodine content of soil and water and on dietary practice, which obviously varies around the world. To avoid iodine deficiency, at least 100 µg of iodine per day is required. The largest pool of body iodine lies within the thyroid gland with approximately 8000 µg, mainly in form of diiodotyrosine (DIT) and monoiodotyrosine (MIT), which has a slow turnover about 1% daily.[5] The large store of thyroid hormones within the gland, about 250 µg thyroxine (T4) per gram of wet weight or 5000 µg of T4 in a 20 g gland, provides protection against depletion of circulation hormones in case of reduction of synthesis and is able to maintain an euthyroid state for a minimum of 50 days.[7, 5] The peripheral pool holds approximately 250 µg, where iodide is manly found in the extracellular fluid with a concentration of about 10 $\mu g\,L^{-1}$ to 15 $\mu g\,L^{-1}$ ($\approx 10^{-7}\,mol\,L^{-1}$), but also in red blood cells and the intraluminal fluids of the gastrointestinal tract.[5]

Due to the low plasma concentration of iodide, it is necessary to concentrate the required amount via **iodide trapping**, where the sodium-iodide symporter (NIS) (a 643–amino acid glycoprotein with 13 membrane-spanning domains expressed at the basolateral membrane of the thyroid cell, encoded by the SLC5A gene) performs the uptake of iodide via a sodium gradient across the basal membrane of the thyroid cell, where against an electrochemical gradient two Na+ ions are being transported outside in exchange of one iodide entering the follicle. NIS is also found in other iodide-concentrating cells, that is the salivary gland, choroid plexus, gastric mucosa and in the cytotrophoblast and syncytiotrophoblast.[8, 9] Furthermore its presence in the lactating mammary gland is important for the iodide supply for the thyroid hormone

synthesis of the newborns by concentrating iodide in the milk.[10, 11]

In the follicular lumen iodide is rapidly **oxidized** and transferred to tyrosine appearing in an organic combination with **Tg**, which is mediated by the thyroid peroxidase (TPO) (a heme-containing protein, which is oriented in the apical membrane of the thyroid cell and contains a membrane-spanning region near the carboxy-terminus) and requires the hydrogen peroxide (H2O2) generated by the calcium-dependent dual oxidase 1 (DUOX1) and dual oxidase 2 (DUOX2) enzymes.[12]

In a next step **organification** occurs at the apical border of the thyroid cell, where specific tyrosine residues of Tg homodimers are iodinated to form the hormonally inactive iodotyrosines MIT and DIT.[13, 14, 12]

For the synthesis of T4, TPO catalyzes the fusion of two molecules of DIT and one MIT and one DIT for triiodothyronine (T3), which are then still part of the Tg stored within the colloid.[13, 14]

For the thyroid hormone **release**, which is stimulated by thyrotropin (TSH), phagolysosomes are formed via pinocytosis and on the way of the colloid droplets toward the basal area of the cell, specific proteases digest Tg to release T4, T3, DIT and MIT. While T4 and T3 are transported out of the the phagolysosomes and across the basolateral cell membrane (partially by monocarboxylate transporter 8 (MCT8)) and exit the cell to enter circulation, DIT and MIT are deiodinated (by iodotyrosine dehalogenase (DEHAL1) for recycling the iodide.[13, 14]

The inhibition of thyroid hormone release is induced by several agents, most importantly by iodide.[15]

For the efficient synthesis of thyroid hormones the expression of numerous thyroid cell-specific proteins are required. Besides Tg and TPO, the thyrotropin receptor (TSHR) is needed to transduce the extracellular TSH effects. Additionally, for the functional differentiation of the thyroid follicular cells and the onset of hormonogenesis, numerous transcription factors are needed, including thyroid transcription factor 1 (TTF1), thyroid transcription factor 2 (TTF2), paired box 8 (PAX8) and hepatocyte nuclear factor 3 (HNF3), as well as TSH.[13, 14]

Plenty of **iodothyronines** and their metabolic derivatives are found in plasma. The highest in concentration is **T4**, which is also the only one with a direct origin by the thyroid gland. In contrast, **T3** is also released by the thyroid gland, but about 80% derived by the enzymatic removal of a single 5′ iodine atom (outer ring or 5′ monodeiodination) from T4 in the peripheral tissue.[16] For the key data of T4 and T3 see Table 1.1.

Table 1.1: Comparison of T3 and T4 in Humans. Table reproduced from Melmed et al. [5], with permission of the publisher (Elsevier).

Parameter	T3	T4
Production rate ($\mathrm{nmol\,d^{-1}}$)	50	110
Fraction from thyroid	0.2	1.0
Relative metabolic potency	1.0	0.3
Serum concentration		
Total ($\mathrm{nmol\,L^{-1}}$)	1.8	100
Free ($\mathrm{pmol\,L^{-1}}$)	5	20
Fraction of total hormone in free form ($\times 10^2$)	0.3	0.02
Distribution volume (L)	40	10
Fraction intracellular	0.64	0.15
Half-life (d)	0.75	6.7

The rest of the iodothyronines and their derivatives are developed from T4 and T3 in the peripheral tissue, which are mainly $3,3',5'$-triiodothyronine (reverse triiodothyronine (rT3)) and $3,3'$-diiodo-l-thyronine ($3,3'$-T2), and in low concentrations other diiodothyronines, monoiodothyronines, and conjugates thereof with glucuronic or sulfuric acid as well as deaminated derivatives of T4 and T3 with acetic acid rather than an alanine side chain (tetrac and triac).[17, 18]

Because iodothyronines are poorly soluble in water, they reversibly bind to plasma proteins. T4 is mainly bound to thyroxine-binding globulin (TBG), transthyretin (TTR) and albumin, whereas T3 is about 75 to 80% bound to TBG and the residual to TTR and albumin.[5]

TBG is a glycoprotein (molecular mass approximately 54 kDa) with a plasma concentration of about $270\,\mathrm{nmol\,L^{-1}}$ ($21\,\mathrm{\mu g\,dL^{-1}}$) and a half-life of about 5 days.[19, 5] One TBG molecule has one iodothyronine binding site, meaning its concentration equals its binding capacity. As TBG is the main binding-protein of T4 and T3 (with a 20-fold higher affinity for T4), changes in its concentration show changes in total plasma T4 and T3, although the hormone production is hardly changed.[5] The binding is inhibited by various medication (e.g. phenytoin, salicylate, salsalate, furosemide, fenclofenac, and mitotane).[20, 21, 5] Because the glycosylation of TBG affects its plasma clearance (slower clearance of highly sialylated TBG, due to their inhibited hepatic uptake), estrogen-treated patients, pregnant women and women receiving oral contraceptives as well as and patients with acute hepatitis show higher levels.[5]

TTR is a transport protein mainly for T4 and retinol-binding protein bound to

retinol (vitamin A) (consisting of four identical polypeptide chains (molecular mass approximately 55 kDa)) with a plasma concentration of about 4 mmol L^{-1} (250 µg mL^{-1}) and a half-life of about 2 days. One mole of TTR binds one mole of T4 with high affinity, while only at high concentrations it binds one more with lower affinity.[22]

Albumin is a plasma protein and binds approximately 10% of the plasma thyroid hormones (due to its high concentration, although its binding affinity for T4 and T3 is way lower than that of TBG and TTR).[5]

All three proteins are synthesized in the liver and hepatic failure or nephrotic syndrome cause a decrease in their plasma concentration.[5]

For the **transport** of iodothyronines across the plasma membrane into and out of the cell, a number of transporter proteins are known (MCT8, monocarboxylate transporter 10 (MCT10), organic anion transporting polypeptide 1C1 (OATP1C1), L-type amino acid transporter 2 (LAT2), L-type amino acid transporter 1 (LAT1)).[23, 24, 25]

The **iodothyronine deiodination** is catalyzed by type 1 deiodinase (D1), type 2 deiodinase (D2) and type 3 deiodinase (D3), all homodimeric integral membrane proteins. For the catalysis they need a thiol cofactor and in their active catalytic center they hold the amino acid selenocysteine (which is with its nucleophilic properties well suitable for the catalysis of this oxidoreductive reaction).[26, 27] The location of their active center are intracellular of D1 and D2, while outside of the cell of D3.[28] D1 and D2 catalyze the most important pathway for the metabolism of T4 with its outer ring (5′) monodeiodination to the active thyroid hormone T3, while D3 catalyzes the inner ring deiodination, which inactivates T3 and converts T4 to rT3 (preventing its activation by that).[16, 29] In human Tg the ratio of T4 to T3 are 15:1 and for T4 to rT3 100:1.[30]

There are some pharmacologic agents which influence the thyroid hormone deiodination, e.g. propylthiouracil (PTU) inhibits D1, amiodarone (with its structural similarity with T4) inhibits deiodination of T4 and rT3 by D1 and potentially by D2 and high dosages of short-termed glucocorticoids suggest with their reduced ratio of T3 to T4 and the increased ratio of rT3 to T4 that the action of D3 is increased.[31, 32, 5]

There are also other pathways involved in iodothyronine metabolism, e.g. T4 and little of T3 undergo glucuronidation of the phenolic hydroxyl by the uridine diphosphate glucuronyl transferases (UDPGTs), which is of clinical importance because some pharmacotherapeutic agents (phenobarbital, phenytoin, rifampin and some serotonin reuptake inhibitors (such as sertraline)) might increase the biliary excretion of T4-glucuronide

(T4-G) into the intestine via the uridine diphosphate glucuronyl transferases (UDPGTs). In euthyroid patients thyroid hormone homeostasis will adjust, while hypothyroid patient need an adjustment of their therapy (increased levothyroxine).[33, 5]

The **thyroid hormone action** works via binding to specific nuclear thyroid hormone receptors (TRs), which then bind to deoxyribonucleic acid (DNA). There are the thyroid hormone receptor α (TRα) (found on chromosome 17) and the thyroid hormone receptor β (TRβ) (found on chromosome 3), which then show in several active and inactive spliced gene products. The active proteins are thyroid hormone receptor α1 (TRα1) (its messenger ribonucleic acid (mRNA) is found in the brain, brown adipose tissue, skeletal muscle, gastrointestinal tract, lungs and heart) and thyroid hormone receptor β1 (TRβ1) (in all tissues, but in high quantities in the kidney and liver), thyroid hormone receptor β2 (TRβ2) (in the hypothalamus and pituitary, also in the cochlea and retina), and thyroid hormone receptor β3 (TRβ3) (very low levels in the liver, kidneys and lungs).[34, 35] The binding affinity for T3 to the TRs is about 15 times higher than for T4, which explains its active thyroid hormone function.[5]

1.1.1.4 Regulation of the thyroid function

The **hypothalamic-pituitary-thyroid axis (HPT axis)** operates in a classic negative feedback mechanism, where the hypothalamus, the anterior pituitary, the thyroid gland and even higher centers of the brain, react to the availability of thyroid hormones (see Figure 1.1). This axis is also affected by other hormones and neuropeptides.[5] Additionally autoregulatory mechanisms within the thyroid gland stabilize the hormone synthesis rate in spite of changes of iodine availability to keep the thyroid hormones in a tight physiologic range. Also, the higher the iodine level in the thyroid gland is, the less hormones are produced and vice versa. Usually the large intraglandular hormone store secures a stable hormone availability despite fluctuations in hormone synthesis.[36]

The **TRH** is an altered tripeptide (pyroglutamyl-histidyl-proline amide) derived from a prepro-TRH molecule and moves through the median eminence in the axons of the peptidergic neurons, to then be released near the hypothalamic-pituitary portal plexus. TRH is expressed in various organs (the hypothalamus, brain, thyroid gland (C cells), pancreas (beta cells), myocardium, reproductive organs and spinal cord), whereas the one from the hypothalamus (parvocellular region of the paraventricular nuclei (PVN)) controls the secretion of TSH. The prepro-TRH molecule synthesis is altered by catecholamines, leptin, neuropeptide Y (NPY), melanocyte-stimulating hormone (MSH) and somatostatin-containing axons (which innervate the neuron bodies

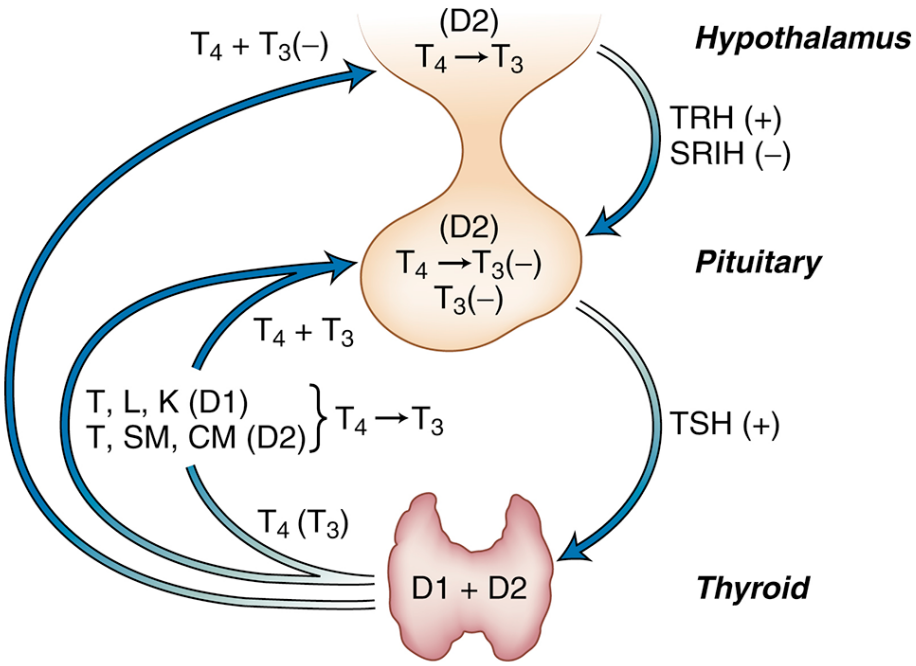

Figure 1.1: Roles of T4 and T3 in the feedback regulation of secretion of TRH and TSH. To produce its effects, secreted T4 is converted to T3 either in the liver (L), kidney (K), or thyroid (T) catalyzed by the type 1 iodothyronine deiodinase (D1) or in the thyroid (T), skeletal muscle (SM), possibly the cardiac muscle (CM) and the pituitary and hypothalamus by type 2 (D2). Figure reproduced from Melmed et al. [5], with permission of the publisher (Elsevier).

producing TRH).[37, 38] For the negative feedback mechanism T3 suppresses the levels of prepro-TRH mRNA in the hypothalamus, thyroid hormones activate the TRH-inactivating pyroglutamyl peptidase II (PPII) in the hypothalamic tanycytes (only in the parvocellular division of the PVN) and additionally they inhibit the ability of TRH to induce the release of TSH from the thyrotrophs.[39, 40, 38, 5]

TSH is a glycoprotein secreted by the thyrotrophs (in the anteromedial portion of the adenohypophysis), made of an α-subunit of 14 kDa with 92 amino acids (common to the luteinizing hormone, follicle-stimulating hormone and human chorionic gonadotropin (hCG)) and a specific β-subunit with 112 amino acids (merely synthesized in the thyrotrophs). TSH is responsible for the morphologic and functional states of the thyroid gland, while its synthesis is regulated mostly by TRH (increase of its subunits) and thyroid hormones (decrease of its subunits).[5] For the full biologic activity of TSH glycosylation is required, which also prevents its subunits from intracellular degradation and allows standard folding of the protein chains for proper forming of the internal disulfide linkages.[41, 42] The normal serum concentration of TSH is $0.4\,\mathrm{mU\,L^{-1}}$ to $4.2\,\mathrm{mU\,L^{-1}}$, which is increased in primary hypothyroidism and decreased in thyrotoxicosis. About $40\,\mathrm{mU\,d^{-1}}$ to $150\,\mathrm{mU\,d^{-1}}$ of TSH is produced, its half-life is approximately 30 minutes and it shows pulsatile and circadian fluctuations. The pulsatile variation lasts about 1 to 2 hours, while the TSH amplitude is decreased during fasting and illness or after surgery.[43] The circadian variation shows a nocturnal rise which precedes the onset of sleep and is independent of the serum concentration changes of T4 and T3 as well as the cortisol rhythm.[44] Additionally there is a seasonal alteration (decrease in summer, increase in winter).[45]

The feedback mechanism of the TSH secretion is mediated by T4 and T3, while its set-point is determined by TRH. To evaluate the thyroid state, the serum TSH concentration is a sensitive marker of the thyroid state, as there is an inverse relationship between the log of TSH and the free serum concentration of T4.[46]

The secretion of TSH is influenced by several endogenous or exogenous agents, while some are stimulating (TRH, α-adrenergic agonists, opioids, arginine vasopressin (AVP), glucagon-like peptide 1 (GLP1), galanin, leptin, glucocorticoids (in vitro)) others are inhibiting (thyroid hormones and analogues, dopamine and dopamine agonists, biotin, glucocorticoids (in vivo, high dose), serotonin, cholecystokinin (CCK), gastrin or gastrin-releasing peptide (GRP), AVP, NPY, interleukin 1β (IL-1β) and interleukin 6 (IL-6), tumor necrosis factor α (TNFα), bexarotene (retinoid receptor agonist), phenytoin, somatostatin and somatostatin analogues, mitotane).[5]

1.1.2 Diagnostic evaluation of the thyroid gland

To diagnose a thyroid disorder, the patient's history, a physical evaluation as well as the evaluation of the results of laboratory tests are mandatory. Additionally ultrasound can improve the diagnosis (with especially higher sensitivity for the detection and characterization of thyroid nodules).[47, 48, 5]

1.1.2.1 Physical evaluation of the thyroid gland

For the physical evaluation the neck should be inspected and the thyroid palpated, especially while swallowing, to inspect the typical movement of the thyroid gland due to its sheathing in the pretracheal fascia (which differentiates a goiter from most other neck masses). With the palpation physicians should examine the shape, size (in relation to normal) and consistency (which normally should be a bit more than adipose tissue but less than muscle, but softer in diffuse goiter and patient with Graves' disease and firm in patients with Hashimoto disease) of the gland as well as the presence and characteristics of nodules. During this examination a vascular thrill might be noticed and auscultation of the neck can enhance this finding (systolic or permanent bruit at increased vascularity of an hyperactive gland e.g. with Graves' disease, when other causes (transmitted murmur from the heart, venous hum in young patients with high cardiac output or patients with severe anemia) can be ruled out). Additionally the regional lymph nodes along the jugular vein, posterior to the sternocleidomastoids and in the supraclavicular region should be inspected. Furthermore other features can extend the diagnosis (e.g. hoarseness or inspiratory stridor might suggest compression or infiltration of the recurrent laryngeal nerve (mostly caused by malignancies)) and extended by laryngoscopy.[5]

1.1.2.2 Laboratory Assessment of the thyroid status

The laboratory assessment of the thyroid status includes tests of the hypothalamic-pituitary-thyroid axis (TSH), tests that estimate the serum thyroid hormone concentrations (T4 and T3), tests that assess the (metabolic) impact of thyroid hormones on tissues (basal metabolic rate (BMR)), tests that screen for autoimmune thyroid disease (thyroid autoantibodies) and tests that give information about the thyroidal iodine metabolism (radioiodine uptake).[5]

For measuring **TSH** an immunometric assay is more specific, sensitive, and rapid than a radioimmunoassay. It uses TSH antibodies bound to an inert surface, where

TSH attaches and links with a second antibody (against a different TSH epitope) which is labeled with a detectable marker (125I, an enzyme, or a chemiluminescent reagent), hence showing the TSH concentration. The reference range is 0.4 mU L^{-1} to 4.2 mU L^{-1} and TSH shows diurnal fluctuations with peak values in the late evening and a nadir in the afternoon.[49, 5]

Patients with primary hyperthyroidism (higher thyroid hormone secretion) or thyrotoxicosis (higher thyroid hormone due to any reason) show TSH values below 0.4 mU L^{-1}. Patients with values between the lower limit of the reference range and 0.1 mU L^{-1} might be asymptomatic (subclinical hyperthyroidism), whereas patients with values below 0.1 mU L^{-1} usually show typical symptoms and a significant elevation in free thyroxine (fT4).[41, 42] Patients with primary hypothyroidism show values above 4.2 mU L^{-1}, where the magnitude usually correlates with the clinical severity. Patients with values up to approximately 15 mU L^{-1} usually have low concentrations of fT4 and free triiodothyronine (fT3) within the reference range and show few or no symptoms (subclinical hypothyroidism).[5]

For measuring **total T4 and T3** sensitive and specific radioimmunoassays are available with a reference range for healthy adults (with normal TBG concentrations) for fT4 of 64 nmol L to 142 nmol L (5 µg dL^{-1} to 11 µg dL^{-1}) and for fT3 of 1.1 nmol L^{-1} to 2.9 nmol L^{-1} (70 ng dL^{-1} to 190 ng dL^{-1}). Approximately 0.02% of T4 and 0.3% of T3 is free or unbound. Direct measurements of **fT4 and fT3** have mostly replaced the T4 index.[50, 5] The reference range for fT4 is 9 pmol L^{-1} to 30 pmol L^{-1} (0.7 ng dL^{-1} to 2.5 ng dL^{-1}) and for fT3 it is 3.5 pmol L^{-1} to 6.5 pmol L^{-1} (0.22 ng dL^{-1} to 0.43 ng dL^{-1}).[5] The validity of these tests are limited by endogenous antibodies to the thyroid hormones, abnormal binding proteins, severe illness or in pregnant women.[51, 52, 53, 54] For causes of abnormal TSH or thyroid hormone concentrations, see Table 1.2.

The **BMR** might be useful in patients where TSH is not a correct marker of the thyroid status (e.g. patients with resistance to thyroid hormoneβ (RTHβ)), as alterations in thyroid hormone availability accompany changes in various metabolic processes (thyroid hormones increase energy expenditure which manifests in various clinical aspects). It measures basal oxygen consumption (resting energy expenditure) with an energy equivalent of 1 L oxygen for 4.83 kcal. Under basal conditions values usually range from −15% to +5% (calculated as percentage of established normal means for sex and age). With thyroid disorders, they can range from −40% in hypothyroid patients to +25% to +50% in thyrotoxic patients. Abnormal increased values may

Table 1.2: Causes of Abnormal TSH or Thyroid Hormone Concentrations. Arrows indicate the nature of the abnormality, N stands for no change. Parentheses indicate unusual result but may occur. Table reproduced from Melmed et al. [5], with permission of the publisher (Elsevier).

	Expected TSH (mU/L)	Clinical Thyroid Status	fT3	fT4
Thyrotropin Reduced				
Hyperthyroidism of any cause	< 0.1	↑	↑	↑
Euthyroid Graves' disease	$0.2 - 0.5$	N,(↑)	N	N,(↑)
Autonomous nodule or multinodular goiter	$0.2 - 0.5$	N,(↑)	N	↑
Exogenous thyroid hormone excess	$< 0.1 - 0.5$	N,↑	N,↑	↑
Thyroiditis (subacute or painless)	$< 0.1 - 0.5$	N,↑	N,↑	↑,(N)
Recent thyrotoxicosis due to any cause	$< 0.1 - 0.5$	↑,N,↓	N,↓	N,↓
Illness with or without dopamine infusion	$< 0.1 - 5.0$	N	↑,N,↓	↓
First trimester of pregnancy	$0.2 - 0.5$	N,(↑)	N,(↑)	↑
Hyperemesis gravidarum	$0.2 - 0.5$	N,(↑)	↑,(N)	↑
Hydatidiform mole	$0.1 - 0.4$	↑	↑	↑
Acute psychosis or depression (rare)	$0.4 - 10$	N	N,(↑)	N,(↓or↑)
Elderly (small fraction)	$0.2 - 0.5$	N	N	N
Glucocorticoids (acute, high dose)	$0.1 - 0.5$	N	N	↓
Biotin	↓	N	N	N
Congenital TSH deficiency				
a.Combined pituitary hormone deficiency (POU1F1/PIT1, PROP1, LHX3, HESX1)	$0-$ ↓	↓	↓	↓
b.TSH beta gene mutations	$0-$ ↓	↓	↓	↓
Thyrotropin Elevated				
Primary hypothyroidism	$6 - 500$	↓	↓	N,↓
Recovery from severe illness	$5 - 30$	N,(?)	N,↓	N,↓
Iodine deficiency	$6 - 150$	N,↓	↓	N
Thyroid hormone resistance	$1 - 20$	↑,N,↓	↑	↑
Thyrotroph tumor	$0.5 - 50$	↑	↑	↑
Hypothalamic-pituitary disease	$1 - 20$	↓	↓	N,↓
Psychiatric illnesses	$0.4 - 10$	N	N	N,↓
Adrenal insufficiency	$5 - 30$	N	N	N,↓
Artifact (endogenous antimouse γ-globulin antibodies)	$10 - 500$	N	N	N

also be found during recovery of burn patients and in patients with various systemic disorders (febrile illnesses, pheochromocytoma, myeloproliferative disorders, anxiety and disorders with involuntary muscular activity).[55, 5]

There are also some **biochemical markers** which show alterations accompanying thyroid disease. In thyrotoxicosis some markers can be increased (osteocalcin, urine pyridinium collagen cross-links, alkaline phosphatase (ALP) (bone or liver), atrial natriuretic hormone, sex hormone-binding globulin, ferritin, von Willebrand factor) as well as decreased (low-density lipoprotein (LDL) cholesterol, lipoprotein(a)). Also in hypothyroidism they can show an increase (creatine kinase (CK) (MM isoform), LDL cholesterol, lipoprotein(a), plasma norepinephrine) or decrease (vasopressin).[56, 5]

The serum **Tg** concentrations are up to $50\,\mathrm{ng\,mL^{-1}}$, with most assays having mean normal values of about $20\,\mathrm{ng\,mL^{-1}}$.[57] It can be used in the management of differentiated thyroid carcinomas, but not for diagnosis, as it is increased in benign and malignant tumors with levels correlating with the thyroid size as well as neoplastic mass.[58, 59] In general, Tg shows higher values in women (then in men), even more in pregnant women as well as in newborns. Also various thyroid disorders increase (goiter, hyperthyroidism, inflammatory or physical injury to the thyroid, differentiated follicular cell-derived thyroid tumors as well as consumptive hypothyroidism) or transiently increase (subacute thyroiditis, after thyroid surgery or 131I therapy) as well as decrease (thyrotoxicosis factitia) its concentration.[60, 5] In case of auto-Tg antibodies, measurements can show wrong results, thus screening should be performed with immunoassays sensitive for those antibodies.[5]

Measurements for **thyroid autoantibodies** include TPO, Tg and TSHR, which are present in most patients with autoimmune thyroid disorders.[5]

Tests for **thyroid peroxidase antibodies (TPO-Ab) and thyroglobulin antibodies (Tg-Ab)** directly measure the interaction between autoantibody and autoantigen, hence they have a high accuracy. As quite some euthyroid people within the normal population show low levels of autoantibodies, the quantity of these antibodies is important, as shown in Table 1.3.[61] They appear in nearly all patients with autoimmune thyroiditis, with an even higher affinity and therefor higher concentration of TPO-Ab. They are also elevated in patients with Graves' disease, goiter, isolated thyroid nodules and cancer (pointing towards the histologically detectable associated thyroiditis), as well as transiently in patients with subacute (de Quervain) thyroiditis or patients with other autoimmune diseases (especially insulin-dependent diabetes mellitus).[5]

Tests for **thyrotropin receptor antibodies (TSHR-Ab)** are useful in the as-

Table 1.3: Prevalence of Thyroid Autoantibodies. Table reproduced from Melmed et al. [5], with permission of the publisher (Elsevier).. IDDM: insulin-dependent diabetes mellitus; hTg-Ab: human thyroglobulin antibod; hTPO-Ab: human thyroid peroxidase antibody; TSHR-Ab: thyrotropin receptor antibodies.

Group	TSHR-Ab %	hTg-Ab %	hTPO-Ab %
General population	0	$5-20$	$8-27$
Patients with Graves' disease	$80-95$	$50-70$	$50-80$
Patients with autoimmune thyroiditis	$10-20$	$80-90$	$90-100$
Relatives of patients	0	$40-50$	$40-50$
Patients with IDDM	0	40	40
Pregnant women	0	14	14

sessment of hyperthyroid patients, where it is the significant autoantigen in Graves' disease.[5]

The **radioiodine uptake** uses radioactive iodine isotopes for the direct measurement of thyroid function. 131I (8.1 days half-life) and 123I (0.55 day half-life) are physiologically indistinguishable from the body's naturally occurring stable form of iodine (127I), thus suitable to find and quantify the location of accumulation. For the radioactive iodine uptake test (RAIU), the (orally or intravenously) administered tracer quantities of inorganic radioiodine mix with the endogenous iodide in the extracellular fluid and start getting removed by the thyroid (with a normal iodide clearance of about $0.4\,\mathrm{L\,h^{-1}}$) and the kidneys (with a normal iodide clearance of about $2.0\,\mathrm{L\,h^{-1}}$), thus usually showing a thyroidal uptake of the isotopes of about 20% of the administered dose. The thyroidal isotope amount increases quickly over the first hours and more slowly until the reach of its plateau, while plasma levels decrease exponentially, minimal levels are already reached by 24 hours and virtual nothing is detectable after 72 hours. Because 123I has a shorter half-life, its delivered radiation is only approximately 1% of that of by 131I, thus its favored use. Apart from that, 131I also emits beta radiation, which makes it valuable in the therapy of patients with Graves' disease, hyperfunctioning nodules, and well-differentiated thyroid cancer. There are several factors which influence the 24 h thyroid iodide uptake. Factors that increase the uptake can occur with increased hormone synthesis (hyperthyroidism, response to glandular hormone depletion (recovery from thyroid suppression or subacute thyroiditis, antithyroid agents), excessive hormone losses (nephrotic syndrome, chronic diarrheal states, soybean ingestion)) as well as with normal hormone synthesis (iodine deficiency (dietary insufficiency, excessive

loss (dehalogenase defect, pregnancy)), hormone biosynthetic defects). Factors that decrease the uptake can occur with decreased hormone synthesis (primary hypofunction (primary hypothyroidism, antithyroid agents, hormone biosynthetic defects, Hashimoto disease, subacute thyroiditis), secondary hypofunction, exogenous thyroid hormones) as well as without any change in synthesis (increased availability of iodine (diet or drugs, cardiac or renal insufficiency), increased hormone release (very severe hyperthyroidism (rare))).[5]

Chapter 2

Associations of thyroid hormones and resting heart rate in patients referred to coronary angiography

Contents

2.1 Introduction

Cardiovascular and cerebrovascular diseases are common causes of morbidity and mortality. Resting heart rate (RHR) is an easily accessible clinical parameter that is associated with both [62, 63, 64]. Elevated RHR is related to increased sympathetic activity with its adverse cardiovascular consequences and may cause various other deleterious effects, including increased myocardial oxygen demand [62, 63, 64].

It is well established that thyroid hormones target the cardiovascular system [65, 66, 67]. For example, overt hyperthyroidism causes an increase in RHR. Among the thyroid hormones fT3 is considered the main driver for the complex cardiac effects rather than fT4 [65, 66]. While thyroid hormones outside the normal range are considered to have an influence on the cardiovascular system, there is little to no knowledge about the clinical relevance of subclinical thyroid dysfunctions or thyroid hormones within the normal range on the cardiovascular system [65, 66, 67, 68].

Some studies in general populations showed that a positive correlation between thyroid hormones and RHR exists, while others did not find a correlation, pointing towards

a need for more specific studies [68, 69, 70, 71, 72]. A specifically interesting group are patients undergoing coronary angiography, as RHR may be a causal cardiovascular risk factor and in view of frequently observed changes in thyroid hormone metabolism, i.e., nonthyroidal illness syndrome (NTI) [73, 74]. In these patients NTI is characterized by low T3 levels without increases in TSH. Thus, NTI represents a therapeutic challenge with many open questions, including the effects of T3 supplementation [73, 74]. To the best of our knowledge, no study exists for patients undergoing coronary angiography that specifically addresses the association between thyroid hormones and RHR.

In this chapter we specially look into this group of patients and investigate whether thyroid hormone measurements are associated with RHR in patients undergoing coronary angiography. We derive our data from the Ludwigshafen Risk and Cardiovascular Health Study (LURIC Study) [75]. For this data set, it was previously shown that RHR, high fT4 and low fT3 are all associated with increased mortality [63, 76].

2.2 Subjects and Methods

The LURIC Study is a prospective cohort study including patients undergoing coronary angiography [75]. Patients have been included if they were clinically stable except for acute coronary syndrome (ACS) and a coronary angiogram was performed. To limit genetic heterogeneity only patients with German ancestry were included. Patients were excluded if they had (1) any acute illness other than ACS, (2) any non-cardiac chronic disease that was predominant, (3) or a history of malignancy within the past five years. For a detailed description on the study design please see [75]. Written informed consent was obtained from all study participants and the study was approved by the ethics committee of the "Ärztekammer Rheinland-Pfalz" (Mainz, Germany).

For the LURIC Study, 3316 participants were recruited between July 1997 and January 2000 from the Cardiac Centre Ludwigshafen in Southwest Germany. The RHR measurement was carried out with an automated oscillometric device (Omron MX4, Omron Healthcare GmbH, Hamburg, Germany). Two measurements (30 seconds apart) were taken in the morning following a rest of 10 minutes in the supine position. The average of the two measurements was recorded as RHR and used in our analyses. Patients were diagnosed with coronary artery disease (CAD) if at least 1 stenosis $\geq 20\%$ in at least 1 of 15 coronary segments was present. Blood samples were taken after an overnight fast in the morning before coronary angiography. The thyroid markers used in our analysis were determined using an electrochemiluminescence enzyme immunoassay

on an Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany): serum fT3 with a reference range of 2.8 pmol L^{-1} to 7.1 pmol L^{-1}, fT4 with a reference range of 13 pmol L^{-1} to 23 pmol L^{-1}, and TSH with a reference range of 0.27 mU L^{-1} to 4.2 mU L^{-1}. Patients were diagnosed with NTI if fT3 was below the reference range ($<$ 2.8 pmol L^{-1}) and TSH was not elevated ($\leq$ 4.2 mU L^{-1}). To assess individual thyroid function, we computed Jostel's TSH index (JTI) and structure parameter inference approach - gain of thyroid (SPINA-GT) from the taken measurements. JTI measures the pituitary thyrotropic function and can take into account individual setpoints of thyroid hormones and SPINA-GT forms a measure for the maximum secretion rate of the thyroid gland under stimulated conditions [77, 78, 79]. Other measurements taken in the course of the LURIC Study are summarized in Winkelmann et al. [75].

In the following we describe the presented data and statistics. For normally distributed continuous data, we show mean and standard deviation (SD). For continuous data that is not normally distributed, we report medians with 25th to 75th percentile. For categorical data we provide percentages. As is common practice, for parametric analyses, we applied a $\log_e$ transformation for non-normally distributed variables. We show clinical and laboratory characteristics for the entire study cohort as well as stratified according to gender. We use analyses of variance (ANOVA) to test for associations between thyroid hormones (TSH, fT3, and fT4) grouped in to quartiles with RHR as a continuous outcome (dependent) variable.

For a more detailed analysis, we compute linear regressions using the thyroid hormones as continuous explanatory (independent) variables and RHR again as continuous outcome (dependent) variable. We run the linear regression in five variants. First as a crude analysis without adjustment (model 0), with adjustment (forced entry) for age (in years) and sex (women/men) (model 1), with additional adjustment for use of beta-blockers (yes/no) and digitalis (yes/no) (model 2), with additional adjustment for body mass index (BMI) (in kg m^{-2}), active smoking (yes/no), and C-reactive protein (CRP) (in mg L^{-1}) (model 3), and with additional adjustment for the prevalence of arterial hypertension (yes/no), the prevalence of diabetes mellitus (yes/no), N-terminal pro B-type natriuretic peptide (NT-proBNP) (in pg mL^{-1}) and CAD (yes/no) (model 4). We chose these covariates as they were associated with RHR in previous investigations and several of them have been used for related analyses [63, 69, 70, 71].

We compute sensitivity analyses stratified by gender and in patients who did not take medications known to interfere with thyroid hormone metabolism, i.e., thyroxine, triiodothyronine, iodine supplements, antithyroid drugs including carbimazole, thiama-

zole, propylthiouracil and perchlorate, amiodarone and lithium, and in patients with TSH, fT3 and fT4 within the reference range. As mentioned before, we also evaluated JTI and SPINA-GT. We calculate an univariate regression analyses of both with RHR. However, we do not run a multivariate analysis with these calculated parameters to avoid spurious correlations. We use two-sided tests and use the standard p-value cutoff of 0.05 to identify statistical significance. For all statistical analyses we use SPSS version 25.0 (IBM Corporation).

Table 2.1: Baseline characteristics of the LURIC Study population. Continuous data are given as means ± standard deviation for normally distributed values and median with 25th and 75th percentile for non-normally distributed values. Categorical data is given in percent. HbA1c: haemoglobin A1c; HDL: high-density lipoprotein; LDL: low-density lipoprotein; GFR-MDRD: glomerular filtration rate - modification of diet in renal disease. Table reproduced from Steinberger et al. [1], with permission from Georg Thieme Verlag KG.

Variable	All	Women	Men
Numbers	2795	842	1953
Age (years)	62.8 ± 10.7	65.0 ± 10.1	61.8 ± 10.7
BMI ($kg\,m^{-2}$)	27.5 ± 4.1	27.3 ± 4.7	27.2 ± 3.8
RHR (beats/minute)	68.8 ± 11.7	69.5 ± 11.4	68.5 ± 11.9
Systolic blood pressure (mmHg)	141.0 ± 23.8	140.6 ± 24.5	141.1 ± 23.5
Diastolic blood pressure (mmHg)	80.9 ± 11.5	79.2 ± 11.5	81.7 ± 11.5
Arterial hypertension (%)	73.0	75.5	71.9
Diabetes mellitus (%)	40.8	40.7	40.8
Fasting glucose ($mg\,dL^{-1}$)	114 ± 36	115 ± 41	113 ± 34
HbA1c ($mmol\,mol^{-1}$)	42 (38 – 49)	43 (39 – 51)	42 (38 – 49)
Current smoker (%)	19.7	14.7	21.8
HDL-cholesterol ($mg\,dL^{-1}$)	39 ± 11	43 ± 12	37 ± 10
LDL-cholesterol ($mg\,dL^{-1}$)	116 ± 35	122 ± 37	113 ± 33
Triglycerides ($mg\,dL^{-1}$)	146 (110 – 200)	142 (106 – 199)	148 (111 – 200)
Serum potassium ($mmol\,L^{-1}$)	4.2 ± 0.3	4.2 ± 0.3	4.2 ± 0.3
Serum sodium ($mmol\,L^{-1}$)	141 ± 3	141 ± 3	141 ± 3
GFR-MDRD ($mL/min/1.73m^2$)	80.6 ± 19.0	74.1 ± 18.0	83.4 ± 18.7
CRP ($mg\,L^{-1}$)	2.7 (1.1 – 7.2)	2.8 (1.2 – 6.9)	2.7 (1.1 – 7.4)
NT-proBNP ($pg\,mL^{-1}$)	294 (107 – 879)	309 (135 – 837)	289 (99 – 894)
CAD (%)	78.2	64.9	75.2
ACS (%)	32.2	28.7	33.7
Atrial fibrillation (%)	12.3	11.8	12.5
Beta-blockers (%)	62.6	60.2	63.7
Digitalis (%)	16.1	16.7	15.9
TSH ($mU\,L^{-1}$)	1.25 (0.76 – 1.92)	1.23 (0.73 – 2.06)	1.26 (0.77 – 1.87)
fT3 ($pmol\,L^{-1}$)	4.8 (4.2 – 5.3)	4.7 (4.1 – 5.2)	4.8 (4.3 – 5.3)
fT4 ($pmol\,L^{-1}$)	17.1 (15.4-19.0)	17.2 (15.4 – 19.0)	17.1 (15.4 – 19.0)
NTI (%)	0.9	1.2	0.8

Table 2.2: Associations of fT3, fT4 and TSH with RHR in BPM computed using ANOVA and p-value for trend analysis. Data are given as ranges, medians with 25th and 75th percentile, and as means ± standard deviation. Table reproduced from Steinberger et al. [1], with permission from Georg Thieme Verlag KG.

	fT3 quartiles				p
	1st quartile	2nd quartile	3rd quartile	4th quartile	
Number	718	801	638	638	
fT3 ($\mathrm{pmol\,L^{-1}}$)	< 4.3 3.9 (3.6 – 4.1)	4.3 – 4.8 4.6 (4.4 – 4.7)	4.9 – 5.3 5.1 (5.0 – 5.2)	> 5.3 5.8 (5.5 – 6.1)	
RHR (BPM)	68.3 ± 11.9	68.0 ± 11.5	68.4 ± 11.9	70.6 ± 11.6	$< .001$
	fT4 quartiles				p
	1st quartile	2nd quartile	3rd quartile	4th quartile	
Number	714	687	722	672	
fT4 ($\mathrm{pmol\,L^{-1}}$)	< 15.5 14.3 (13.6 – 14.9)	15.5 – 17.1 16.4 (15.9 – 16.7)	17.2 – 19.0 18.0 (17.6 – 18.5)	> 19.0 20.6 (19.7 – 22.2)	
RHR (BPM)	67.2 ± 11.4	68.5 ± 10.9	68.8 ± 12.0	70.7 ± 12.3	$< .001$
	TSH quartiles				p
	1st quartile	2nd quartile	3rd quartile	4th quartile	
Number	702	696	702	695	
TSH ($\mathrm{mU\,L^{-1}}$)	< 0.77 0.48 (0.28 – 0.64)	0.77 – 1.25 1.01 (0.89 – 1.13)	1.26 – 1.92 1.55 (1.39 – 1.71)	> 1.92 2.64 (2.20 – 3.49)	
RHR (BPM)	68.4 ± 11.4	69.2 ± 11.6	69.1 ± 11.9	68.4 ± 12.0	.894

2.3 Results

We restrict our analysis to the subset of LURIC Study participants with complete data of RHR, TSH, fT3, fT4, which are 2795 individuals. Table 2.1 outlines the characteristics of those 2795 individuals. In Table 2.2 we present the associations between quartiles of TSH, fT3, and fT4 with RHR. We found an increase of RHR over the fT3 and fT4 quartiles, but no difference in the TSH quartiles. The difference in RHR (beats/min) between the lowest and the highest quartile for fT3 was statistically significant (2.30, 95% confidence interval (CI): 1.06 to 3.55; $p < .001$). Similarly, the difference in RHR (beats/min) between the lowest and the highest quartile for fT4 was statistically significant (3.48, 95% CI: 2.23 to 4.73; $p < .001$). There was no such difference for the lowest and highest TSH quartiles (-0.06, 95% CI: -1.29 to 1.17; $p = .924$). Table 2.3 shows the linear regression analyses of RHR as the dependent variable and thyroid hormones (TSH, fT3, and fT4) as explanatory variables with cumulative adjustments by various covariates. As can be seen in the table, for all models, fT3 and fT4 were significantly positively associated with RHR. In none of the models TSH was significantly associated with RHR. Note that the number of participants was decreased throughout the models as we excluded cases with missing values for covariates and did not perform any data imputation.

To provide more details, we performed sensitivity analyses using multiple linear regression for model 4 (the model that adjusts for most covariates). We report the unstandardized regression coefficients B (with standard error (SE) and p-values) and adjusted R^2 values. fT3 was significantly associated with RHR in men (B: 6.78 [SE: 1.46, $p < .001$]; $R^2 = 0.093$; $n = 1855$) and women (B: 5.06 [SE: 5.06, $p = .015$]; $R^2 = 0.084$; $n = 797$), while fT4 was significantly associated with RHR in men (B: 5.36 [SE: 1.49, $p < .001$]; $R^2 = 0.088$; $n = 1855$) but not in women (B: 3.09 [SE: 2.15, $p = 0.152$]; $R^2 = 0.080$; $n = 797$). For patients without use of medications known to interfere with thyroid hormone metabolism, fT3 (B: 5.27 [SE: 1.29, $p < .001$]; $R^2 = 0.085$; $n = 2404$) and fT4 (B: 4.74 [SE: 1.36, $p < .001$]; $R^2 = 0.083$; $n = 2404$) were significantly associated with RHR. When considering only participants with TSH within the normal range both fT3 (B: 8.08 [SE: 1.14, $p < .001$]; $R^2 = 0.092$; $n = 2388$) and fT4 (B: 5.58 [SE: 1.45, $p < .001$]; $R^2 = 0.085$; $n = 2388$) were significantly associated with RHR. When considering only participants with fT3 ($n = 2599$) or fT4 ($n = 2427$) within the normal range we obtained similar significant results for fT3 and fT4. Across all subgroup analyses TSH did not show a significant association with

Table 2.3: Linear regression analyses of fT3, fT4 and TSH (explanatory variable) with RHR (outcome variable). Model 1 adjusts for age (years) and sex (women/men). Model 2 additionally adjusts for beta-blockers (yes/no) and digitalis (yes/no). Model 3 additionally adjusted for BMI ($\mathrm{kg\,m^{-2}}$), active smoking (yes/no), and C-reactive protein* ($\mathrm{mg\,L^{-1}}$). Model 4 additionally adjusted for arterial hypertension (yes/no), diabetes mellitus (yes/no), N-terminal pro B-type natriuretic peptide* ($\mathrm{pg\,mL^{-1}}$), and coronary artery disease (yes/no). * Logarithmically transformed variables using the natural logarithm. Table reproduced from Steinberger et al. [1], with permission from Georg Thieme Verlag KG.

	fT3*	fT4*	TSH*
	Unstandardized Beta coefficients (with standard error), p-value; adjusted R squared		
Crude ($n = 2795$)	3.54 (1.12), $p = .002$; $R^2 = 0.003$	6.69 (1.21), $p < .001$; $R^2 = 0.011$	−0.19 (0.23), $p = .406$; $R^2 = 0.000$
Model 1 ($n = 2795$)	3.57 (1.15), $p = .002$; $R^2 = 0.005$	6.72 (1.22), $p < .001$; $R^2 = 0.012$	−0.21 (0.23), $p = .363$; $R^2 = 0.001$
Model 2 ($n = 2795$)	3.53 (1.13), $p = .002$; $R^2 = 0.035$	5.90 (1.21), $p < .001$; $R^2 = 0.040$	−0.22 (0.23), $p = .335$; $R^2 = 0.032$
Model 3 ($n = 2728$)	6.15 (1.16), $p < .001$; $R^2 = 0.068$	6.00 (1.20), $p < .001$; $R^2 = 0.067$	−0.30 (0.23), $p = .192$; $R^2 = 0.059$
Model 4 ($n = 2652$)	6.34 (1.19), $p < .001$; $R^2 = 0.092$	4.70 (1.23), $p < .001$; $R^2 = 0.087$	−0.26 (0.23), $p = .252$; $R^2 = 0.082$

RHR. Furthermore, JTI did not emerge as a significant predictor of RHR throughout the entire cohort either (B: 0.41 [SE: 0.24, $p = .088$]; $R^2 = 0.001$), albeit it can be seen as a non-significant trend. However, SPINA-GT was significantly associated with RHR (B: 0.58 [SE: 0.28, p = .040]; $R^2 = 0.002$).

We validated all regression models. All residuals were normally distributed, homoscedasticity was not violated and there were no significant collinearity and interaction (note that this also means that the interaction term of fT4 and gender was not significant).

2.4 Discussion

In a large group of patients referred to coronary angiography, we found that fT3 and fT4 concentrations are positively associated with RHR. However, TSH does not show a statistically significant association with RHR. It is especially interesting that the association of fT3 and fT4 with RHR remained statistically significant in multivariate adjusted analyses and in subgroups restricted to participants with thyroid hormone concentrations within the normal range. We only found one subgroup where the association between fT4 and RHR turned insignificant: for fT4 in women. Note that our study population was skewed towards men, with a ratio of 2.3 : 1. Thus, it cannot be ruled out that such an association could show up with a larger population. In any case, fT3 was still significant in that subgroup.

To the best of our knowledge, we are the first to show that free thyroid hormones within the normal range are positively associated with RHR in a large cohort of patients referred to coronary angiography. Similar results have been shown in the population-based Asklepios study with 2078 participants, where fT3 was positively associated with RHR in participants who were free from overt cardiovascular disease and had TSH levels within the reference range [69]. The study was unable to show that fT4 or TSH could predict RHR [69]. In the population-based study of Health in Pomerania with 3610 participants it was also shown that TSH does not predict RHR; fT3 and fT4 were not considered [71]. In the Third National Health and Nutrition Examination Survey (NHANES III) with 5990 participants a significant association for total T4 and RHR was found in men, but only a non-significant trend in women [70]. Again, TSH did not show a significant association with RHR in either gender [70]. These findings from the NHANES III data set on sex-specific differences for T4 and RHR fit our findings on fT4 and RHR. Even though NHANES III has a 1 : 1 between men and women, the authors

state that the gender-specific effects require confirmation [70]. With our data, we can only restate that point, given that there was a trend that allows to describe RHR with fT4 in women, but these result have a 15% chance to be an accidental finding.

In general it is not surprising that the free thyroid hormones fT3 and fT4 are associated with RHR and TSH is not: fT3 and fT4 may exert rapid effects that can either be thyroid hormone receptor dependent or independent, while TSH is not a perfect mirror of the thyroid hormone status [79, 80]. The meta-analysis by Fitzgerald et al. [81] has also shown that thyroid hormones are better correlated to various clinical parameters than TSH. The systematic review and individual participant meta-analysis by Baumgartner et al. [82] in euthyroid individuals found that fT4 but not TSH is associated with increased risk of incident atrial fibrillation, again underlining the importance of the free thyroid hormone over TSH. Similarly, Müller et al. [77] and Chaker et al. [83] documented that fT4 but not TSH was significantly associated with an increased risk of ventricular arrhythmias and sudden cardiac death. Our finding that the SPINA-GT was significantly associated with RHR and JTI only showed a non-significant trend, could be interpreted that an impending primary hyperthyroidism rather than an elevated set point of thyroid homeostasis is driving associations with RHR in our data. Still, it should be noted that both SPINA-GT and JTI include both TSH and fT4 just in a different combination. Thus, our results could also simple indicate that it is easier to extract fT4 — which is significantly associated with RHR — from SPINA-GT than from JTI. In any case, further investigation is needed in this respect. Our results are particularly interesting as we found that clinical implications from fT3 and fT4 can be drawn even if they are largely in the normal range and thyroid function can be considered largely normal. Still, we want to note that other studies have largely, but not consistently, shown that subclinical and overt hyperthyroidism is associated with RHR compared to conditions with euthyroidism [65, 66, 68, 84, 85]. Because tachycardia is one of the most prominent features in symptom rating scales for hyperthyroidism it is scientifically sound to postulate a link between thyroid hormones and RHR even if thyroid hormones are within the normal range as in our study [86].

As we are working with observational data, we cannot derive causal inference, however, there is compelling evidence that thyroid hormones may directly increase RHR [65, 66]. Thyroid hormones upregulate the β1-adrenergic receptors and modulate sodium, potassium and calcium channels through genomic and non-genomic pathways and thus exert chronotropic effects on the heart [65, 66]. Additionally, thyroid hormones may also exert a chronotropic effect on the peripheral circulation, e.g., through a decrease

of systemic vascular resistance [65, 66]. Finally, a link between hyperthyroidism and increased risk of atrial fibrillation is well established [65, 66, 82].

Up to this point we focused on the existence of a link between thyroid hormones and RHR. While we — alongside previous work — argue that such a link exists, we also need to consider the strength of such a potential influence. Typically, one can only argue that only a very small part of the variation in RHR can be explained through thyroid hormones. Still, even small effects on an individual level may have a significant impact on a population level. Thus, we believe that our findings of an association between free thyroid hormones and RHR may have certain therapeutic and diagnostic implications in clinical practice. It is well established that RHR is a risk factor of adverse cardiovascular events and mortality. Thus, chronotropic effects of thyroid hormones might in part mediate the increased risk of adverse outcomes reported by studies for patients with subclinical and overt hyperthyroidism [87, 88, 89, 90, 91]. Given a link between thyroid hormones — even within the reference range — and RHR, one should potentially be cautious with thyroid hormone replacement therapy in older patients with increased cardiovascular risk [92]. On the other hand, it has been reported that thyroid hormone replacement in NTI, such as in patients with myocardial infarction or heart failure, may show beneficial cardiovascular effects [93, 94, 95]. Again, further randomized controlled trials (RCTs) may be needed. Finally, given the association of thyroid hormones with RHR, measuring (changes) in RHR could potentially be used to draw conclusions about the thyroid hormone status. Thus, monitoring RHR may be a useful, noninvasive tool for the potential detection of a (re-)emerging hyperthyroidism and for guiding treatment decisions of antithyroid drug titration, especially in patients with hyperthyroidism [96, 97].

We want to note that our study is limited by its observational design. Furthermore, we focused on a specific patient group, which does not permit a wider generalization of our findings. Still, the strength of our study is its large and well-characterized patient cohort, which allowed us to consider various potential confounders in analyses.

In summary, we found that free thyroid hormones are significantly and positively associated with RHR in patients referred to coronary angiography. While our design does not allow for the observation of a causal effect, consideration towards causation are sensible and might have therapeutic implications for treatment of thyroid dysfunctions. Especially when considering the progress in digital medicine, where measurements of RHR are nowadays possible with off the shelf smart watches, our findings may be useful for the development of decision support systems to guide, e.g., the dose titration of

antithyroid drugs for the treatment of hyperthyroidism or for the early detection of hyperthyroid episodes.

Chapter 3

Case report on acute suppurative thyroiditis due to Streptococcus anginosus leading to sepsis and acute respiratory distress syndrome

Contents

3.1 Introduction

Acute suppurative thyroiditis (AST) is a potentially lethal thyroid disease which occurs rarely [98]. The estimated prevalence of AST is low with 0.1 to 0.7% among all thyroid disorders and affects women and men in equal proportions [99, 100]. AST is an acute infection of the thyroid gland, which in the vast majority of cases is caused by bacterial pathogens [98]. In case of pre-existing diseases or structural variants of the thyroid, e.g., piriform sinus fistulas, goiter, nodule, and others, the risk of infection is significantly higher — which was found in about 70% of AST [101]. Neck swelling, localized pain and erythema, fever, hoarseness, and dysphagia are typical signs of AST [98, 101]. Biochemically, elevated inflammation parameters such as CRP and increased serum thyroglobulin as a marker for destructive thyroiditis are associated with AST [98, 102]. Thyrotoxicosis may serve as an indication to distinguish between other causes of destructive thyroiditis, like, subacute thyroiditis (SAT) or postpartum thyroiditis, as thyrotoxicosis only occurs in less than 20% of AST cases. In acute cases, thyroid

sonography and computed tomography (CT) should be used for imaging studies [103]. As AST has a high mortality, immediate empiric antibiotic therapy is mandatory in all cases. It is also advised to obtain blood cultures, abscess fluid or tissue samples [98]. In severe cases when the patient status deteriorates despite antimicrobial therapy and/or minimal-invasive drainage, surgical drainage or subtotal/total thyroidectomy is necessary [98, 104].

The diagnosis of AST is often challenging, mostly due to its rarity. However, differentiation from other thyroid disorders with higher prevalence such as SAT is of utmost clinical importance due to the potentially dramatic or even lethal courses of AST [98]. In this chapter, we describe the case of a 22-year-old man with AST, who was initially treated with glucocorticoids for suspected SAT. The patient eventually developed sepsis with acute respiratory distress syndrome (ARDS) due to Streptococcus anginosus bacteremia. We contrast the case findings with current recommendations for the diagnosis and treatment of AST and especially focus on the differentiation from other thyroid disorders.

3.2 Case Presentation

A 22-year-old male was admitted to the otorhinolaryngology (ENT) outpatient clinic of a tertiary care hospital in October 2019. The patient complained of cervical supraclavicular and prelaryngeal pain lasting for two weeks aggravated by swallowing as well as increased sweating and palpitations. The patient reported symptoms of an upper respiratory tract infection prior to the onset of the cervical discomfort. The inspection of nose, larynx and pharynx in the ENT was inconspicuous. However, the right thyroid lobe was prominent on palpation and sonography revealed an inhomogeneous enlargement. As a result, the patient was referred to the endocrine outpatient clinic with suspected thyroiditis.

At the time of admission, the patient reported that there was no specific medical therapy; however, he reported regular anabolic androgenic steroid (AAS) abuse for muscle gain. Thyroid function tests revealed a thyrotoxicosis (TSH: $0.04\,\mu U\,mL^{-1}$, reference range 0.10 to 4.00, fT4: $30.7\,pmol\,L^{-1}$, reference range 9.5 to 24.0, fT3: $8.7\,pmol\,L^{-1}$, reference range 3.0 to 6.3). There was no elevation in thyroid-specific antibodies (thyroperoxidase antibodies, thyroglobulin antibodies, TSH-receptor antibodies). The serum thyroglobulin concentration was significantly elevated ($231\,ng\,mL^{-1}$, reference range 0 to 30) — a marker for destructive thyroiditis. Although the patient

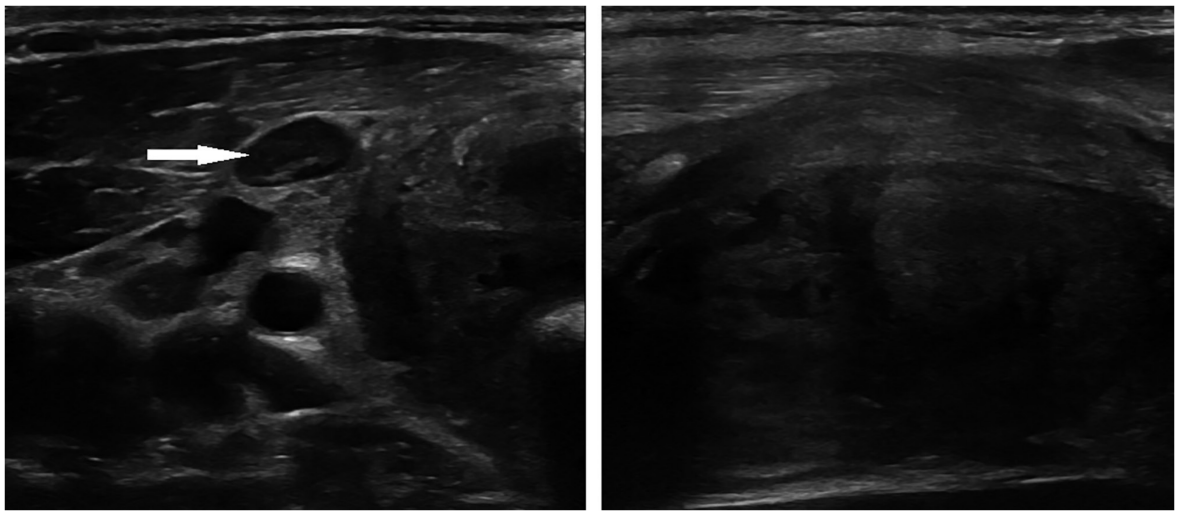

Figure 3.1: Sonography of the right thyroid lobe at initial presentation of the patient (left image: transverse axis, right image: sagittal axis, arrow: prominent lymph node). Images in this figure were published by Trummer, Theiler-Schwetz, and Pilz [105] and Trummer et al. [2] under the CC BY license.

was afebrile, inflammation parameters were moderately elevated (white blood count: 11.42 μL^{-1}, reference range 4.4 to 11.3, CRP: 38.5 mg L^{-1}, reference range 0 to 5), liver parameters (including aspartate aminotransferase and alanine aminotransferase) were within the normal range. Following the first ENT sonography, a detailed sonography was carried out, showing a significantly enlarged right thyroid lobe ($2.6 \times 2.8 \times 5.8$ cm in diameter) with inhomogeneous structure (indicated in the figure), reduced echogenicity and decreased vascularization in color-coded Doppler imaging (Figure 3.1, Figure 3.2). Additionally, a prominent oval-shaped lymph node with a longitudinal diameter of 1.11 cm was found adjacent to the right interior jugular vein (see Figure 3.1). In contrast to the right thyroid lobe, the left thyroid lobe was normal in size, showed normal echogenicity and a homogeneous structure. No cystic or nodular thyroid lesions were found.

The differential diagnosis of AST and SAT, pointed towards SAT at this point: thyrotoxicosis was found clinically and biochemically (AST leads to thyrotoxicosis in only 20% of cases), the right thyroid lobe was affected (AST more often affects the left thyroid lobe), and there was no fever (fever is typical in AST). Thus, treatment for SAT was initiated with 50 mg of prednisolone once daily and 10 mg of propranolol three times per day. The differential diagnosis between SAT and AST was discussed with the patient and the importance of immediately returning to the outpatient clinic in

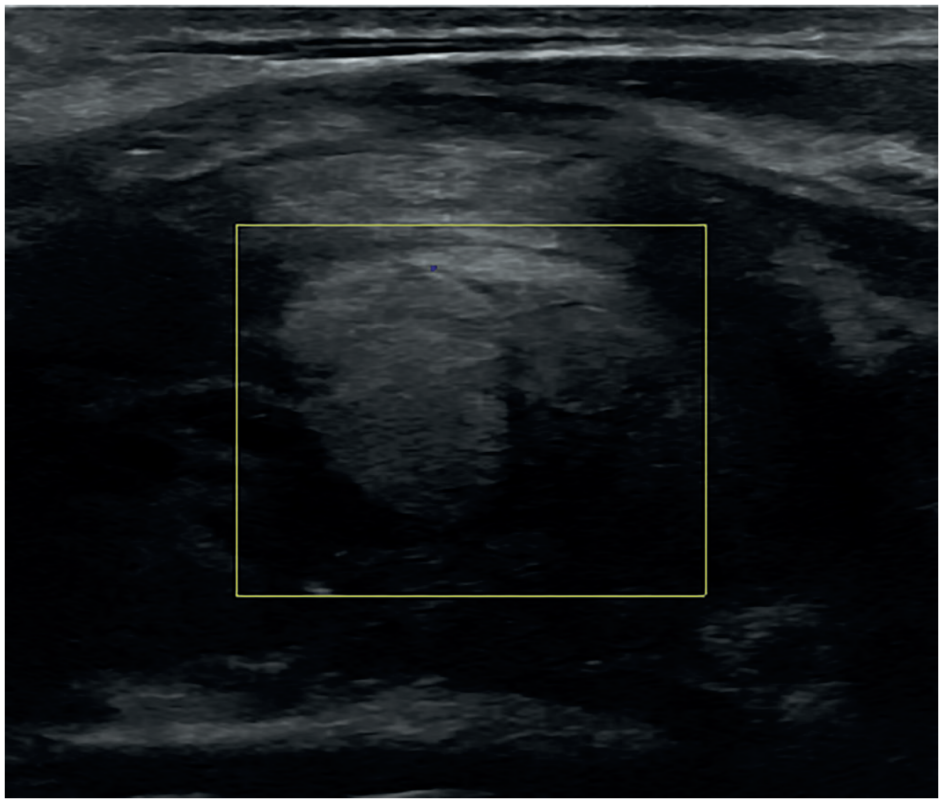

Figure 3.2: Color-coded Doppler sonography of the right thyroid lobe at initial presentation of the patient (sagittal axis). Figure originally published in Trummer et al. [2] under the CC BY license.

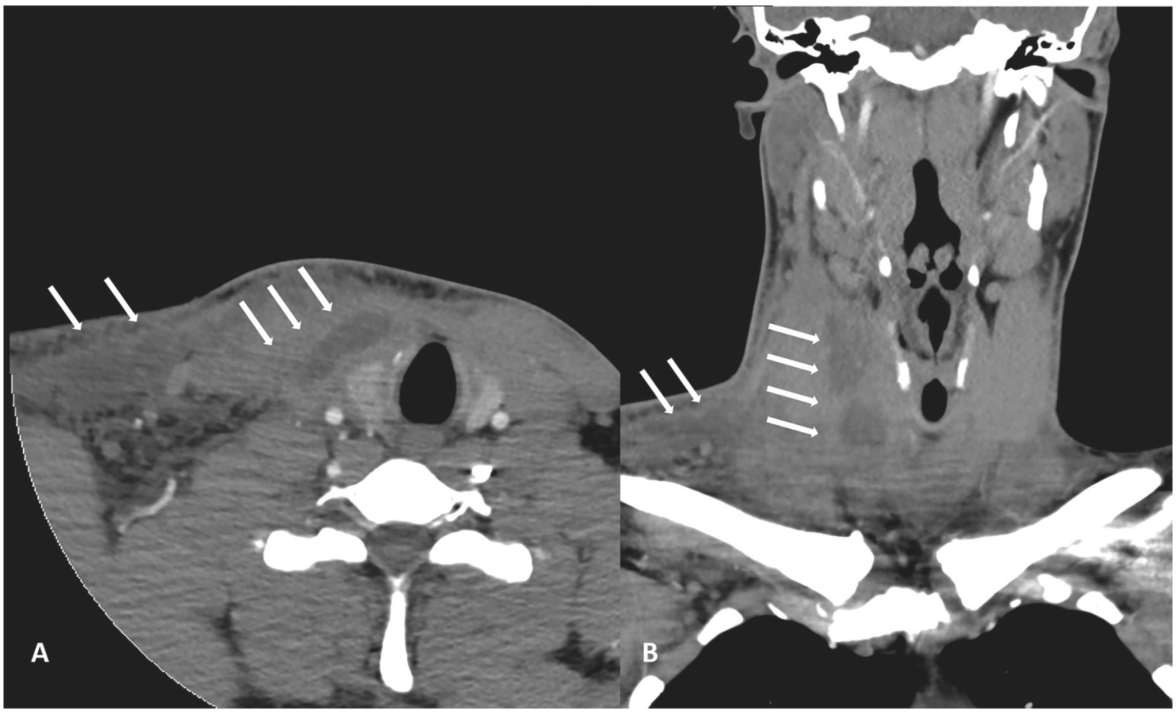

Figure 3.3: Contrast-enhanced computed tomography of the neck, showing large confluent central hypodense contrast formation (arrows) starting from the right thyroid lobe and extending to the subcutis ventral of the sternocleidomastoid muscle in axial (left) and frontal (right) orientation. Figure originally published in Trummer et al. [2] under the CC BY license.

case of no clinical improvement within the next few days was underlined. Following the initiation of glucocorticoid and beta-blocker treatment, the patient status was checked during a phone call with the treating physician, during which the patient reported rapid and significant amelioration of pain and symptoms of thyrotoxicosis. However, one week later, the patient noticed recurrence of cervical pain and localized erythema extending from the right thyroid lobe to the pectoral region. Additionally, fever emerged and the patient returned to the medical emergency department. In comparison to the initial checks, the inflammation parameters were significantly increased (white blood count: $36.64\,\mu L^{-1}$, CRP: $192.3\,mg\,L^{-1}$, procalcitonin: $2.98\,ng\,mL^{-1}$, reference range: 0 to 0.5). Immediately, a CT of the neck and thorax was scheduled, which showed a phlegmonous process of $8 \times 4 \times 9\,cm$ in diameter with abscess formation, reaching from the hyoid to the infraclavicular space with compression of the right internal jugular vein (see Figure 3.3). Blood cultures were taken and parenteral antibiotic treatment with piperacillin/tazobactam was started. The patient was also referred to the ENT department for surgical intervention. The surgical drainage of several abscesses was successful. Still, the patient developed progressive dyspnea during the first postoperative days, which resulted in hypoxemic respiratory failure. Thus, the patient was referred to the medical intensive care unit (ICU). Another CT revealed bilateral inflammatory pulmonary infiltrates, concordant with moderate ARDS (paO2/FiO2 ratio 152). Echocardiography showed no signs of heart failure or endocarditis. Streptococcus anginosus was found in both blood and abscess fluid cultures. At the ICU, the patient initially received non-invasive ventilation support. The ICU physicians continued the parenteral antimicrobial treatment with piperacillin/tazobactam. In addition, the patient received moxifloxacin and methylprednisolone. Also, regular lavages of the cervical drainages were performed. The patient's clinical status improved in accordance with the decrease of inflammation parameters. The patient could be discharged from ICU care after 10 days and from inpatient care after a total of 19 days.

During subsequent routine outpatient visits, a normalization of thyroid function parameters was recorded while inflammation parameters remained within the normal range. Confirmed by sonography, both thyroid lobes were of normal size with homogeneous parenchyma and without any nodal or cystic lesions. The adjacent cervical lymph nodes were also of normal size. At this point it was found that there was no evidence of anatomic or cervical structural variants that may represent a predisposition for AST.

3.3 Discussion

In this chapter, we present a rare case of AST that led to Streptococcus anginosus sepsis with ARDS requiring ICU treatment. This case clearly underlines that AST is a possibly life-threatening disease, especially considering the patient's young age and lack of relevant medical history.

The ability to differentiate between AST and other thyroid disorders, especially between SAT, is of utmost importance in the diagnostic process [98]. SAT is the most common granulomatous thyroid disease with a probable viral or post-viral etiology. It has an incidence of about 12.1 cases per 100.000 individuals per year [106, 107, 108]. In contrast to AST, thyrotoxicosis as a consequence of destructive thyroiditis is common in SAT [107]. Occasionally, SAT leads to abnormal liver function tests, including elevated concentrations of transaminases, alkaline phosphatase, and gamma-glutamyl transpeptidase [109]. Sonography of the thyroid may help to establish a diagnosis between AST and SAT: as AST is usually found unilaterally (mainly in the left thyroid lobe), while SAT commonly affects both thyroid lobes [103, 110]. Note that in the early inflammatory stage of AST, abscess formation typically does not show up in sonography, while a unilateral hypoechoic area is frequently found [103]. Thus, SAT is a common misdiagnosis in the acute setting [103]. This also happened in our patient, where no clear abscess was found during the first thyroid ultrasound. The initial diagnosis was further complicated by the presence of thyrotoxicosis, whereas liver function tests were normal, all pointing towards SAT rather than AST. Furthermore — like in our patient — glucocorticoid treatment initiated for the treatment of SAT may also lead to rapid and significant amelioration of symptoms in case of AST. Thus, dangerous misdiagnosis may be supported by such transient treatment successes [111]. After an initial positive clinical response under glucocorticoids, it is tempting to omit invasive procedures. However, considering the potential deleterious outcomes of a missed AST, we would like to emphasize that liberal fine needle aspiration biopsy should be performed in all doubtful cases, especially if diagnostic uncertainty remains after sonographic imaging [98, 112, 113]. It should also be noted that AST must also be differentiated from aggressive thyroid carcinomas, e.g., anaplastic or medullary thyroid carcinomas. While such aggressive thyroid carcinomas are rarely observed, they may also cause local infections and necrosis and may thus be confused with AST [98].

Streptococcus anginosus is a common pathogen in AST; it has been found that around 40% of cases may be attributed to gram-positive aerobes [98, 99, 100, 114].

Streptococcus anginosus belongs to the Streptococcus milleri group and is one of three genetically distinct microorganisms from this group which is involved in pyogenic processes in humans [115]. A distinct association of Streptococcus anginosus with AST was described by Wu et al. [116] and Desai, Mbachi, and Singh [117]. As in our case, all reported patients were treated with parenteral antibiotics and received interventional drainage [116, 117]. In our patient, empiric antibiotic therapy with piperacillin/tazobactam was started after AST was suspected clinically. Testing from blood and abscess fluid cultures showed that the strain was susceptible to the chosen antibiotics. As mentioned previously, the treating ICU physicians added moxifloxacin to the antibiotic regimen due to the persistent bilateral pneumonic infiltrates and due to persistent need for respiratory support.

Due to its low incidence the exact morbidity and mortality of AST is currently unknown. It undoubtedly remains a potentially life-threatening disease with increased mortality in the absence of immediate intervention [98]. Previously reported cases almost always required parenteral antibiotic treatment, surgical drainage and inpatient care [101, 118, 119]. However, our case showed a particularly severe course with sepsis and ARDS leading to ICU admission. The self-reported regular abuse of parenteral AAS is a potential risk for aggravated forms of AST: AAS may lead to local infections and abscess formation due to intramuscular application and more importantly, systemic effects of AAS may adversely affect the course of infectious diseases [120]. At the same time, study data in general suggest an immunosuppressive effect of male sex hormones, which may lead to an increased susceptibility for bacterial and viral infections [121, 122, 123]. One explanation for this effect may be the reduced antibody concentrations in plasma under testosterone influence [124, 125]. Additionally, testosterone increases anti-inflammatory lymphokine secretion and decreases pro-inflammatory lymphokine production [126, 127, 128]. Thus, in our patient, the regular parenteral injections may have played a significant role in the etiology of AST, especially when considering that there was no predisposing anatomic or immunologic condition. As a side note, it should also be considered that AST has been reported in intravenous drug users [129, 130].

Our case report is interesting due to the rarity of AST and the particularly difficult differentiation from SAT according to the clinical features presented during the first examination. Additionally, our patient showed a serious case of AST in an otherwise healthy young patient, underlining the potential threat of AST. The shortcomings of our case report include the lack of long-term follow-up data as well as the lack of the patient's perspective on the received treatment. Additionally, we did not assess

erythrocyte sedimentation rate (ESR), although this would have been indicated in our opinion. Thus, a better distinction between AST and SAT may have been possible early on using ESR.

In conclusion, we can emphasize that AST represents a rare but potentially life-threatening bacterial thyroid infection, which should be treated with immediate medical attention, empiric antibiotic therapy and interventional abscess drainage. However, differential diagnosis between AST and other thyroid disorders, especially SAT, can be difficult. Especially as the absence of fever as well as prompt clinical improvement in response to glucocorticoid treatment points towards SAT, but can also be observed in AST, as illustrated by our case. This fact is especially important due to the probably high mortality associated with unrecognized and thus untreated AST. Thus, in uncertain cases, liberal additional diagnostic measures such as CT scans of the neck region and fine needle aspiration biopsy are strongly advised. In severe cases, surgical intervention and drainage are necessary.

Chapter 4

Hypothyroidism: guidelines, new evidence and clinical practice

Contents

4.1 Introduction

Hypothyroidism is defined as a thyroid hormone deficiency, which is present in approximately 5% of the population in Europe, with women and the elderly being more commonly affected [131, 132, 133]. We distinguish between primary hypothyroidism (pathologies of the thyroid gland), secondary hypothyroidism (pituitary pathologies) and tertiary hypothyroidism (TRH deficiency), which collectively are referred to as central hypothyroidism, and peripheral hypothyroidism (e.g., consumptive hypothyroidism or genetic forms) [131, 132, 133]. In most cases of primary hypothyroidism, which is the main focus of this chapter — for other forms of hypothyroidism, please refer to the relevant literature —, a distinction is made between overt hypothyroidism with elevated TSH and reduced fT4 and subclinical hypothyroidism with elevated TSH but fT4 in the normal range. In subclinical hypothyroidism, a mild form (TSH $> 4.0\,\mathrm{mU\,L^{-1}}$ to $10.0\,\mathrm{mU\,L^{-1}}$) is distinguished from a severe form (TSH $> 10.0\,\mathrm{mU\,L^{-1}}$) depending on

the TSH value, with approximately 90 % of patients with subclinical hypothyroidism having a TSH $< 10.0\,\mathrm{mU\,L^{-1}}$. The clinical symptoms of hypothyroidism range from the severe life-threatening myxedema coma to asymptomatic cases, with the most common symptoms regularly listed in the literature being fatigue, lethargy, cold intolerance, weight gain, constipation, voice change, and dry skin.

In this chapter, we will address the practically relevant diagnosis and therapy of hypothyroidism based on current guidelines, but we will also highlight new and forward-looking findings related to hypothyroidism [134].

4.2 Diagnosis of hypothyroidism

The diagnosis of hypothyroidism is based on laboratory measurements of TSH and fT4, where the reference ranges (or standard values) are defined as between the 2.5 to 97.5 percentile of an apparently healthy population. However, this definition of the standard values has recently been discussed intensively and critically, especially due to the realization that TSH alone does not carry enough information about the homeostasis and allostasis of the thyroid hormones, which is also supported by the fact that, e.g., fT4 correlates better with clinical parameters than TSH [135, 136, 78, 79, 137, 81]. Appropriate mathematical modeling allows a much better representation of individual thyroid function, taking into account individual setpoints or adaptive mechanisms of the HPT axis, than TSH measurements alone. Relying on such mathematical models which take into account kinetic properties, TSH, fT4, and fT3 can be used to compute combined parameters such as SPINA-GT or the JTI. The former indicates the (primary) secretion capacity of the thyroid gland while the latter reflects the central (pituitary) stimulation of the thyroid gland [135, 136, 78, 79, 137]. Although these parameters are not yet established in the clinical practice and are the subject of active research, they may help us in the future to establish a more individualized and thus better diagnosis and therapy of thyroid dysfunction, which goes beyond our simple, linear and TSH-centered thinking.

With regard to the current mainly TSH-centered approach, it should be kept in mind that the upper limit of the normal range — which is typically considered at $4.0\,\mathrm{mU\,L^{-1}}$ — increases especially in the elderly and that TSH concentration has a circadian rhythm with a nadir in the afternoon and higher concentrations at night. However, the intraindividual variation of TSH is relatively small, which is why one sometimes speaks of an individual ‘TSH-setpoint’ [138, 139, 140, 141, 142, 143, 144,

145]. This largely genetically determined 'TSH-setpoint' shifts somewhat upward with age, which is why, for example, mild TSH elevations of 4.0 mU L^{-1} to 7.0 mU L^{-1} in > 80-year-old humans are considered physiological [134]. The relationship between TSH and fT4 is characterized in a way that small changes in fT4 have large effects on TSH levels (log-linear relationship). Thus, for example, a decrease in fT4 from 1.0 to 0.5 ng dL^{-1} may cause an increase in TSH from approximately 0.5 to 50.0 mU L^{-1}, whereas an increase in TSH from 1.0 to 5.0 mU L^{-1} indicates only a decrease in fT4 from about 1.0 to 0.9 ng dL^{-1}.

In clinical practice a controversial discussion often incurs over the indication for measuring TSH (and potentially fT4, and fT3). In contrast, in many fields overdiagnosis is common practice, while many professional societies also do not issue a clear recommendation in this respect [138, 139, 140, 141, 142, 143, 144, 145]. It is also not clear whether only TSH should be measured initially or whether TSH plus fT4 is preferred, since TSH alone is sufficient in most cases, but isolated cases of, e.g., central/pituitary dysfunction can be overlooked [144, 145]. Of course, the decision most often comes down to cost effectiveness, whereas a simultaneous TSH-/fT4- (and possibly fT3-) measurement is increasingly suggested [144, 145]. However, general screening for thyroid dysfunction in everyone is not recommended by most professional societies (or no statement is made in this regard). Symptom-based testing is often advised, but this leaves open many questions and room for interpretation [138]. Certain complaints attributed to hypothyroidism, such as fatigue, overweight/obesity, or (subjectively) hair loss, are so common in the general population (at least one of these complaints is present in at least half of the general population) that this makes targeted thyroid diagnosis difficult or nearly impossible [143]. Since the connection between obesity and thyroid hormones is frequently discussed and many professional societies recommend TSH screening in connection with obesity, it should also be mentioned that TSH levels are often elevated in cases of pronounced obesity, but a decrease in TSH is regularly observed when weight is lost (leptin, among other things, is suspected for this effect of obesity on TSH levels). Conversely, the current literature cannot (!) confirm that subclinical hypothyroidism causally leads to weight gain or that levothyroxine (LT4) therapy in subclinical hypothyroidism causes weight loss [134].

For specific constellations, such as women with a desire to become pregnant or an intact pregnancy, general testing is recommended by many experts, but this is not the consensus everywhere. Annual TSH screening is often recommended for diseases such as type 1 diabetes mellitus, since a connection with hypothyroidism/Hashimoto thyroiditis

is common, as well as for osteoporosis or tachycardia (but with regard to possible hyperthyroidism) and hyperlipidemia, since hypothyroidism can lead to changes in lipid metabolism [134]. However, some professional societies recommend — especially with increasing age (e.g. from 50 to 60 years) — to determine TSH with partial repetition every 5 years, whereas other professional societies are diametrically opposed to this stance. In summary, there is unfortunately no international consensus on the indications and frequency of diagnosis/screening for thyroid dysfunction. Regarding the testing of pre-existing specific thyroid diseases such as carcinomas, we refer to the relevant literature. However, it is epidemiologically interesting to look at publications which report that, e.g., in the adult population in Great Britain approximately 18 % to 25 % are subjected to a TSH tests annually or that LT4 is one of the most prescribed drugs. In many countries about 3 % of the population, or even more, take thyroid hormone replacement therapy on a daily basis and those numbers are increasing [138].

In general, it is recommended to repeat TSH measurements after 2 to 3 months in patients with elevated TSH and fT4 in the normal range before deciding on a possible therapy, as there may be different causes for transient TSH elevations and many slightly elevated TSH measurements return to normal during the next check-up. About half of all elevated TSH levels between $4\,\mathrm{mU\,L^{-1}}$ to $10\,\mathrm{mU\,L^{-1}}$ normalize without therapy at follow-ups within 5 years. It is also important to note that especially in critically ill patients TSH may be reduced partly by cytokines in the course of the so-called 'Euthyroid Sick Syndrome' ('NTI' or 'low T3-syndrome') which typically also reduces fT3, followed by a rebound and partly increased TSH in the recovery phase. Thus, hypothyroidism in critically ill patients should only be diagnosed after complete recovery [133]. Furthermore, various medications can also influence TSH or thyroid function. Again, we refer to the relevant literature, but would like to note that glucocorticoids in particular can reduce TSH [140].

Since Hashimoto thyroiditis (chronic lymphocytic thyroiditis or autoimmune thyroiditis) is the most common cause of hypothyroidism, TPO antibodies and Tg antibodies should also be measured if TSH levels are elevated [146]. Individuals with elevated TSH who show a spontaneous return to normal TSH levels in one of the follow-ups, no further diagnosis and/or therapy needs to be performed with regard to hypothyroidism if their antibodies are negative and they do not present a clinical goiter. In patients with persistent subclinical hypothyroidism who are not treated for it, TSH measurements should be performed every 6 months for the first 2 years and then annually, as a transition to an overt hypothyroidism which requires treatment is possible. Such

a transition becomes more likely with increased TSH levels and with positive TPO antibodies. The progression from subclinical to overt hypothyroidism is about 2 to 6% per year. With positive TPO antibodies this risk doubles compared to individuals with negative TPO antibodies. Note that a sonographic examination of the thyroid gland as part of the workup for hypothyroidism is not routinely recommended [132, 134]. However, because Hashimoto thyroiditis is associated with a somewhat increased risk of malignancy, thyroid ultrasonography is often performed to evaluate the possible Hashimoto thyroiditis (typically with a echo-deficient thyroid parenchyma) and repeated at long intervals, e.g., every 3 to 5 years in patients with this disease [147]. However, this procedure is based purely on expert opinion and has not been shown to be effective in improving patient outcome. In any case, thyroid scintigraphy is not indicated in the routine evaluation of hypothyroidism or Hashimoto thyroiditis.

4.3 Causes of hypothyroidism

Hashimoto thyroiditis is most often the cause of hypothyroidism and it is about 10 times more common in women than in men. TPO antibodies are positive in 90 % to 95 % of the cases and Tg antibodies are positive in 60 % to 80 % of the cases. Neither antibody is disease-causing, and there is no clear relationship between the level of these antibodies and disease severity, but particularly high antibody titers appear to correlate with disease activity. Repeated measurements of these antibodies are not recommended, although they can decrease in the course of the disease and sometimes even become negative. Complicating is the fact that these antibodies can also be negative in exceptional cases of Hashimoto thyroiditis (in this context, the sonographic image is decisive for the diagnosis). Additionally, these antibodies are also positive in many healthy people without Hashimoto thyroiditis. In the case of Hashimoto thyroiditis, it should also be kept in mind that this disease is associated with other autoimmune diseases in about 25 % of cases, i.e., routine laboratory findings and clinic should be carefully and regularly evaluated for indications of, e.g., Addison's disease, type 1 diabetes mellitus, pernicious anemia, or celiac disease. Other causes of hypothyroidism are mainly iatrogenic after thyroid surgery and radioiodine therapy. However, there are also passive hypothyroidism, which often improve spontaneously, e.g. in postpartum thyroiditis or thyroiditis de Quervain, as well as rare causes such as congenital hypothyroidism, which is why newborn screening is absolutely necessary (please see the relevant literature).

4.4 Symptoms and clinical consequences of hypothyroidism

While patients with overt hypothyroidism may have significant symptoms (e.g., fatigue, lethargy, cold intolerance, weight gain, constipation, voice changes, and dry skin), the overall quality of life is not altered in patients with subclinical hypothyroidism compared to euthyroid individuals [133, 148, 149, 150]. Meta-analyses of placebo-controlled trials also show that the quality of life is not improved by therapy for subclinical hypothyroidism [149, 150].

Diverse studies have examined the association between hypothyroidism and cardiovascular risk, although data on this remains inconsistent [133, 65, 151, 152, 153, 154]. However, many studies suggest that hypothyroidism, especially with increasing severity and thus very high TSH, is likely to be associated with increased cardiovascular risk. In this context, it has been shown that hypothyroidism leads to changes in lipid metabolism characterized by higher LDL cholesterol and higher triglycerides, which is why a diagnosis of hypothyroidism is also indicated in cases of hypercholesterolemia. Various studies have also partially shown an association between hypothyroidism and arterial hypertension and systolic and diastolic heart failure. In addition, meta-analyses of epidemiological cohort studies showed an association between hypothyroidism and all-cause mortality and — in some cases — cardiovascular events [152, 153]. Whether and to what extent these are causal relationships is still unclear. However, it should be noted that hypothyroidism in acute myocardial infarction indicates an increased cardiovascular risk, but therapy in this constellation has no significant beneficial effects [154].

The association between hypothyroidism and cognitive impairment and dementia has also been studied in detail. While overt hypothyroidism may well lead to cognitive impairment, studies do not prove that subclinical hypothyroidism also contributes to dementia or a decline in cognitive performance [155]. There are also associations of hypothyroidism with depression and various other pathologies, although the data is not clear, especially with regard to causality [156].

4.5 Therapy of hypothyroidism

In the treatment of hypothyroidism, we start by citing the recommendations of the European Thyroid Society before then critically discussing this 2013 guideline below

with reference to the recent literature and other recommendations [134, 157, 158, 159]. Overt hypothyroidism is a clear indication for therapy according to an international consensus. If subclinical hypothyroidism is detected for the first time (TSH elevated and fT4 in the normal range), no (!) therapy should be initiated initially, but — as already discussed in section 4.2 — a laboratory check should be performed to confirm the diagnosis after about 2 to 3 months. If a subclinical hypothyroidism is then confirmed, considerations regarding possible initiation of therapy will depend primarily on the TSH level, age, and concomitant symptoms/comorbidities. According to the guideline of the European Thyroid Society, a therapy with LT4 should be initiated in severe subclinical hypothyroidism with a TSH $> 10\,\mathrm{mU\,L^{-1}}$ and an age > 65 to 70 years, even if the patient is otherwise symptom-free. In younger patients with a TSH $\leq 10\,\mathrm{mU\,L^{-1}}$ or all older patients with a TSH $> 10\,\mathrm{mU\,L^{-1}}$, the decision for or against LT4 therapy should be based on hypothyroid symptoms, cardiovascular risk (higher risk tends to favor therapy), and patient preference, with therapy also more likely to be sought in the presence of goiter. In elderly patients with TSH $\leq 10\,\mathrm{mU\,L^{-1}}$, a watch-and-wait strategy without LT4 should be pursued.

Regarding therapy, the European Thyroid Society recommends taking an LT4 preparation daily approximately 30 min before breakfast or in the evening before going to bed at least 2 h after the last meal. The recommended dosage for subclinical hypothyroidism is about $1.5\,\mathrm{\mu g\,kg^{-1}\,d^{-1}}$, i.e. about 75 µg to 100 µg for women and about 100 µg to 125 µg for men. Various literature sources equate an LT4 dose of $1.6\,\mathrm{\mu g\,kg^{-1}\,d^{-1}}$ to a complete replacement of thyroid function, which is thus roughly equivalent to a dose for the therapy of overt hypothyroidism. Thus, the dosage recommendations of the European Thyroid Society for LT4 therapy in subclinical hypothyroidism are rather high. In contrast various experts recommend lower LT4 dosages of e.g. 25 µg to 75 µg daily in subclinical hypothyroidism, which are usually also sufficient for TSH normalization in these patients [133]. In this regard, an American guideline for the treatment of subclinical hypothyroidism also mentions that, according to studies, a daily LT4 dose of 25 µg at TSH $4.0\,\mathrm{mU\,L^{-1}}$ to $8.0\,\mathrm{mU\,L^{-1}}$, of 50 µg at TSH $8.0\,\mathrm{mU\,L^{-1}}$ to $12.0\,\mathrm{mU\,L^{-1}}$ and of 75 µg at TSH $> 12.0\,\mathrm{mU\,L^{-1}}$ usually led to TSH normalization or required only minimal dose adjustments. In principle, one should usually start right away with the full LT4 dosage. Patients with CAD should be started on a lower daily dosage of 25 µg to 50 µg and then increased to the target dose with increments of 25 µg every 2 to 3 weeks. In elderly patients > 70 years of age, slow up-dosing is also often recommended, although unless CAD is present, it is not mandatory to do so.

Serum TSH should be checked approximately 2 months (6 to 8 weeks) after initiation of therapy, and depending on laboratory findings, dose adjustment should then possibly be made, generally aiming for $0.4\,\mathrm{mU\,L^{-1}}$ to $2.5\,\mathrm{mU\,L^{-1}}$ as the TSH target range. In principle, no dose adjustment should be made if TSH is within the normal range. In elderly patients (> 70 to 75 years), a TSH target range of $1\,\mathrm{mU\,L^{-1}}$ to $5\,\mathrm{mU\,L^{-1}}$ is also acceptable. In patients initiated on LT4 therapy for presumed hypothyroid symptoms, treatment success should be evaluated approximately 3 to 4 months after reaching the TSH target range, and LT4 therapy should be discontinued if symptoms have not improved. Note that studies published in the meanwhile did not show any improvement of quality of life, fatigue etc. with LT4 therapy of subclinical hypothyroidism, thus, this recommendation has to be questioned very critically. In patients on stable LT4 therapy, long-term TSH monitoring should take place at least annually. Should TSH in clinically euthyroid patients and previously stable setting be minimally above the upper reference range during these checks, the dose does not necessarily have to be adapted immediately.

After discussing the current recommendation of the European Thyroid Society, we must, however, also refer to more recent data and recommendations, which in principle argue quite clearly against a therapy of subclinical hypothyroidism in most patients [149, 157]. Based on a recent systematic review article that failed to demonstrate a significant effect of LT4 therapy on quality of life, hypothyroid symptoms, fatigue, depressive symptoms, cognitive function, muscle strength, systolic blood pressure, BMI, mortality, and cardiovascular events in RCTs in subclinical hypothyroidism, a 2019 international guideline does not recommend LT4 therapy in most patients with subclinical hypothyroidism [149, 157]. However, it is explicitly mentioned that this recommendation does not apply to the following groups: women who wish to have children or have an unplanned pregnancy, patients with TSH $> 20\,\mathrm{mU\,L^{-1}}$, young patients (< 30 years), patients with severe symptoms, and patients already taking thyroid hormone replacement. In the treatment of hypothyroidism, it is a concern that in clinical practice many patients do not reach their TSH target range despite LT4 therapy, with the risk of both over- and under-treatment. For example, one study showed that after 5 years of LT4 therapy, 10% of patients had a LT4 $> 10\,\mathrm{mU\,L^{-1}}$ and 6% had a suppressed TSH $< 0.1\,\mathrm{mU\,L^{-1}}$ [132]. Over-substitution with LT4 must be avoided at all costs, as this causes iatrogenic hyperthyroidism, which, in addition to symptoms of hyperthyroidism, also leads to a significantly increased risk of atrial fibrillation and an increased incidence of fractures.

International guidelines and experts clearly recommend LT4 monotherapy for the initial therapy of hypothyroidism and not a LT4/liothyronine (LT3) combination therapy or bioidentical thyroid hormones [158, 159, 160, 161, 162, 163, 164, 165, 166, 167]. This recommendation is made despite the fact that LT4 monotherapy has possible side effects and is not physiological, due to the associated LT4 peaks after intake and the sometimes comparatively low fT3 levels under therapy [158, 159, 160, 161, 162, 163, 164, 165, 166, 167]. In this regard, it should be mentioned that LT4 has a half-life of about 1 week, during which it is deiodinated into active T3 in peripheral target organs, which also physiologically generate about 80% of T3 from T4 [158]. The thyroid gland itself secretes only approximately 20% of circulating T3, whereas the T4-to-T3 ratio is physiologically about 13:1 to 16:1 and T3 has a significantly shorter half-life than T4. After morning LT4 intake, about 80% of it is absorbed gastrointestinally, and there may be a 16 to 20% increase in fT4 after about 4 h, which is why it is often recommended not to take thyroid hormone substitution before laboratory determination. With regard to LT4/LT3 combination compounds, these often have the limitation that they do not have a physiological LT4/LT3 ratio (e.g. Novothyral® [Merck Healthcare KGaA, Darmstadt, Germany] contains 100 µg LT4 and 20 µg LT3, i.e. a ratio of 5:1) and thus also lead, among other things, to unphysiologically high T3 peaks after intake. Note: When switching from a T3-containing preparation to LT4 monotherapy, it should be remembered that T3 is approximately 3 to 4 times as biologically potent as T4, i.e., 20 µg of T3 is equivalent to approximately 60 µg to 80 µg of T4 [163]. Many guidelines oppose the use of LT4/LT3 combination therapy because, among other reasons, it has not shown significant benefits in studies, is often administered at nonphysiologic doses (compounds with, for example, LT4:LT3 ratios of 5:1, such as Novothyral®, should not be used in any case according to professional societies), and is more expensive than LT4 monotherapy [134, 161]. However, the European Thyroid Society and others have noted that in patients with persistent hypothyroid symptoms despite LT4 therapy and TSH in the normal range, LT4/LT3 combination therapy may be considered an 'experimental' therapy trial, with termination of this therapy if symptoms have not improved after 3 months [161]. Laboratory controls during ongoing LT4/LT3 therapy (which should follow an LT4:LT3 ratio between 13:1 and 20:1), should be guided by TSH and not by serum fT3, since this has a very short half-life and thus fluctuates strongly, i.e. may be increased 3 h after intake, but may again be reduced before the next intake (LT3 compounds should therefore also be administered (at least) 2× daily) [161].

Patients with ongoing LT4 therapy who still have elevated TSH levels despite

adequate full dosing and who are suspected of incompliance can be evaluated by means of an LT4 absorption test, in which, for example, seven times the daily dose is taken by the patient under supervision on an empty stomach in the morning [168]. Serum fT4 is then measured before and 2 h after intake with an expected increase of at least 54%. If the increase is significantly lower, this would be indicative of gastrointestinal absorption disorders, if it is higher, there was probably previous incompliance. Of course, one should also evaluate whether the intake modalities (fasted!) are adhered to or whether additional medications (e.g. calcium supplements taken at the same time reduce LT4 absorption) are not partly responsible for persistently elevated TSH levels despite LT4 substitution. If patients cannot take their LT4 therapy orally due to illness or surgery for more than 5 to 7 days, parenteral LT4 therapy should be initiated. The recommended parenteral dose is about 80% of the usual oral dose because about 80% of the orally given LT4 is also absorbed in the intestine. (For example L-Thyroxine Henning® inject [Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany] contains a total of 500 µg LT4 or 100 µg LT4 per mL). In this regard, there is also data suggesting that in cases of poor compliance and lack of opportunity for daily LT4 therapy, it would also be conceivable to administer the LT4 dose as a sevenfold daily dose once a week in such exceptional cases. For patients who are chronically taking LT4 therapy for unclear reasons and for whom it is suspected that this is not indicated, a discontinuation trial can be carried out with normal or low TSH, in which the LT4 dose is halved and then a TSH check is carried out after approximately 6 to 8 weeks, with possible complete discontinuation of LT4 with normal TSH and again a laboratory check after another 6 to 8 weeks.

Regarding selenium supplementation, it is not currently recommended by guidelines in the treatment of hypothyroidism and Hashimoto thyroiditis because of insufficient evidence, although it should be noted that selenium reduces thyroid autoantibodies and is a cofactor of type 1 deiodinase, which catalyzes the conversion of T4 to T3 [169]. Despite this insufficient evidence, many endocrinologists prescribe selenium supplementation in hypothyroidism and Hashimoto thyroiditis, but this should be viewed critically in view of the costs and insufficient data on clinical effects as well as side effects. We do not currently recommend selenium supplementation for these indications [170].

4.6 Myxedema coma

Myxedema coma is a life-threatening condition with a high mortality rate (about 30%) that can occur as a complication of severe hypothyroidism. Despite the name "myxedema coma", a coma is rarely present [171, 172, 173]. Myxedema coma is primarily diagnosed clinically and is characterized by hypothermia, neuropsychiatric symptoms (including disorientation, lethargy, etc.), generalized edema, cardiovascular pathology (e.g. prolonged QT time, AV block, bradycardia, low voltage, heart failure), generalized hypothyroid symptoms associated with laboratory changes such as hyponatremia, hypoglycemia, hypercapnia (in hypoventilation with risk of CO2 narcosis), hypoxemia, and often also elevated CK and lactate dehydrogenase (LDH). Although there are scoring systems for myxedema coma, the condition is not precisely defined. However, it typically develops on the basis of a usually already known pronounced hypothyroidism and occurs more frequently in women and in winter, whereby infections or stress situations or certain medications (e.g. sedatives) can act as triggering factors. Myxedema coma should be treated appropriately as soon as it is clinically suspected, and the patient should then also receive intensive medical care. Due to the lack of RCTs, therapy should follow expert recommendations. Yet there is no consensus on whether LT4 therapy alone is sufficient for hormone replacement or whether additional LT3 should be used in cases of suspected reduced conversion and due to more effective passage of the blood-brain barrier. Regarding LT4, a starting dose of 200 µg to 400 µg (according to some authors up to 500 µg or even 600 µg) of LT4 i.v. is often recommended followed by 1.6 µg kg d^{-1} (p.o. or i.v.) on the following days plus — if necessary — LT3 with a starting dose of 5 µg to 20 µg i.v. with a maintenance therapy 2.5 µg to 10 µg every 8 h 1 to 2 days (caution with LT3 in patients with coronary artery disease). Since an adrenal insufficiency can also be present, additional hydrocortisone is often recommended, e.g. 200 mg in the first 24 hours. Accompanying supportive intensive medical measures are absolutely indicated with especially appropriate respiratory management, due to the frequently occurring hypoventilation with hypercapnia. With regard to hyponatremia and edema, water restriction is preferable. In cases of pronounced hypothermia passive warming, e.g., using warming blankets, must be carried out.

4.7 Discussion

Hypothyroidism and thyroid hormone replacement are one of the most commonly diagnosed conditions or therapies in clinical practice. In recent years, the indication for treatment of subclinical hypothyroidism has been increasingly questioned, thus excessive diagnosis and therapy in this regard should also be avoided. Especially in elderly patients, subclinical hypothyroidism with TSH $< 10\,\mathrm{mU\,L^{-1}}$ should not (!) be treated. However, new insights into thyroid homeostasis and allostasis could potentially modify or optimize the diagnostic and therapeutic approach to hypothyroidism in the future. In the treatment of hypothyroidism, LT4 is still the first choice, although even LT4 is not an optimal hormone replacement from a pathophysiological point of view. Future research in hypothyroidism will likely focus on identifying specific populations with a treatment effect in the presence of only mild hypothyroidism. Alternatively, studies may try to exclude such effects or will further evaluate whether LT4/LT3-combination therapies (or similar preparations) have advantages over LT4 monotherapy. However, it will be crucial to prove by means of randomized studies whether and to what extent screening or extensive testing for thyroid dysfunction is useful or effective.

Chapter 5

Thyroid: fertility, pregnancy and lactation

Contents

5.1 Introduction

Thyroid hormones have various functions in pregnancy, fertility and lactation, which is why practical inquiries regarding diagnostics and therapy of thyroid diseases are very frequent in this context [174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185]. In this article, we would like to address the clinical relevant topics and recent findings in this context, subdividing them into the areas of fertility/preconceptional

phase, pregnancy and postpartum period/lactation. Each of these chapters is based on a literature search in PubMed, which is primarily based on systematic reviews and meta-analyses (these were the search terms supplemented by the respective chapter headings) and relevant individual studies with a focus on randomized controlled trials (RCTs). The American Thyroid Association (ATA) guideline from 2017 on this topic should be particularly mentioned here, although various recent studies question some of the recommendations of this guideline, which we will also specifically address in this article [181]. The heterogeneity and complexity of recommendations regarding the diagnosis and treatment of thyroid disorders in pregnancy and for women who desire to conceive often causes uncertainty. Therefore, we would like to focus on common questions in clinical practice and point out that new studies in some areas have resulted in a partly changed evidence situation, which could not yet be considered at the time of publication of various guidelines in this field, but has a practical relevance [183].

Regarding the numerous physiological changes of the thyroid gland and thyroid hormones during pregnancy, we refer to the relevant specialized literature. However, for practical understanding, we would like to note that in early pregnancy there is a physiological increase in free thyroid hormones with a parallel decrease in TSH, mainly due to the effect of hCG, which also stimulates the receptor of TSH. Therefore, the normal values of thyroid hormones during pregnancy must also be considered differentiated from the values outside pregnancy [174, 175, 176, 177, 178]. Also the TBG increases during pregnancy, stimulated also by estrogens, although this is less relevant for routine diagnostics, since the free thyroid hormones (and not those bound to TBG) are normally determined.

5.2 Fertility and preconceptional phase

Due to insufficient evidence, various professional societies do not make a general recommendation for or against screening for thyroid dysfunction in otherwise healthy women seeking natural conception, although thyroid hormone determination is often performed in common practice [181, 184]. In view of the detection of possible previously undetected overt thyroid dysfunction, which is present in approximately 1%, we, as authors of this current article, prefer a general screening for thyroid dysfunction (determination of TSH plus, if necessary, fT4) in every woman with pregnancy intention and also at first presentation in pregnancy (not only in risk groups), despite the still open discussion in this regard [186, 187]. However, due to the increased iodine requirement

during pregnancy (because of increased renal clearance, increased thyroid hormone production and diaplacental iodine transfer), attention should be paid to an adequate iodine supply even preconceptually. In addition to iodine-containing foods, this should also be achieved by iodine supplements with e.g. 150 µg iodine per day, but there are partly regionally different recommendations regarding the iodine dose [181, 182, 184].

5.2.1 Fertility

Fertility and thyroid is a frequently discussed topic, and observational studies have shown an association between TPO-Ab (thyroid autoimmunity) and subclinical hypothyroidism, as well as an increased risk of infertility, abortions and preterm births, although the underlying mechanisms and the question of causality are currently still unclear. There are three common hypotheses concerning a possible causal relationship between TPO-Ab and reduced fertility: 1) TPO-Ab are an epiphenomenon of a general autoimmunity, but not the pathogenic factor; 2) thyroid autoantibodies are also directly harmful (pathogenic) for the ovaries (it has been shown that granulosa cells of the ovaries express TPO); 3) hypothyroidism caused by thyroid autoimmune diseases leads to infertility [175]. However, a recent RCT has clarified whether LT4 therapy increases the live birth rate in TPO-Ab-positive euthyroid women with infertility or who have had an abortion [188, 189, 190]. In this study (TABLET trial), 952 women were randomized to receive either LT4 50 µg daily or placebo before and throughout pregnancy. The live birth rate was 37.4% in the LT4 group and 37.9% in the placebo group and thus showed no statistically significant difference, as did various subgroup analyses, although it should be mentioned here in particular that even in the approximately 31% of women who had a TSH $> 2.5\,\mathrm{mU\,L^{-1}}$, there was no difference in live birth rate between the LT4 group versus the placebo group (55 versus 58 live births) [188]. Also in women with assisted reproduction/in vitro fertilization (IVF), the association between thyroid function as well as TPO-Ab and miscarriages as well as live births has been intensively studied [191, 192, 193, 194, 195]. In this context, an RCT of 600 euthyroid, TPO-Ab-positive women undergoing IVF with embryo transfer showed no significant difference in live birth and miscarriage rates between an LT4 group with 25 µg to 50 µg daily and a placebo group [191]. The recommendation of the ATA guideline 2017, according to which one can consider in euthyroid TPO-Ab-positive women with previous miscarriage a low-dose LT4-therapy starting with e.g. 25 µg to 50 µg daily, is thus highly questioned by the above-mentioned later published studies and thus not recommended by us [181, 183]. However, it should be kept in mind that the studies on this topic had various

limitations, such as a fixed rather low LT4 dose, and that therefore various gaps in knowledge still exist, which could possibly change the recommendations in this regard again in the future.

5.2.2 Hypothyroidism

Women with overt hypothyroidism should be advised against pregnancy until they have achieved euthyroidism, as overt hypothyroidism in early pregnancy increases the risk for miscarriage, premature birth or neurointellectual disorders in the child [184]. Preconceptional TSH measurement should be performed in women on LT4 therapy and seeking pregnancy, with the ATA guideline 2017 recommending a TSH target range between the lower limit of the reference range and 2.5 mU L^{-1} [181]. It should be emphasized that this target range refers only to women who are already receiving LT4 therapy with the appropriate indication, as they are assumed to have only a limited (including hCG-mediated) increase in free thyroid hormones in early pregnancy, in contrast to healthy women. Women who are already having a thyroid hormone therapy with pregnancy desire should also be informed that during pregnancy the need for thyroid hormones is increased by approximately 20 to 30%, meaning they usually require a higher dose when pregnancy occurs [181, 184]. Empirically, in addition to the determination of the thyroid hormones at the onset of pregnancy, it is often recommended to immediately increase the LT4 dose even before the thyroid hormone values are available (note: T3 is more inactivated than T4 or is not sufficiently transferred to the fetal central nervous system, which is why pure T4 preparations are to be used for substitution in pregnancy according to guidelines) [181]. In this regard, it is empirically recommended to take e.g. 2 × per week twice the LT4 dose or to increase the LT4 dose by 25 µg per day if one has taken LT4 doses of up to 100 µg per day so far or to increase the LT4 dose by 50 µg per day if one has taken LT4 doses of > 100 µg per day [181, 184].

A clinically common question is whether women with a wish to conceive and subclinical hypothyroidism with TSH levels < 10 mU L^{-1} should receive LT4 therapy (with higher TSH, therapy is generally recommended). In this regard, an association between subclinical hypothyroidism and reduced fertility is not entirely consistent in observational studies, although a recent meta-analysis of RCTs and cohort studies suggests that LT4 therapy in subclinical hypothyroidism reduces the risk of miscarriage [175, 196, 197]. The ATA guideline 2017 recommends that low-dose LT4 therapy with 25 µg to 50 µg daily should be considered for those with a desire to conceive without

assisted reproductive technology and subclinical hypothyroidism with TSH $< 10\,\mathrm{mU\,L^{-1}}$, whereas the authors of this article would in general treat a woman of childbearing potential with subclinical hypothyroidism with TSH $< 10\,\mathrm{mU\,L^{-1}}$ with e.g. LT4 50 µg daily [175, 196, 197]. In assisted reproductive medicine, screening with thyroid hormone determination is generally recommended, and LT4 therapy should also be initiated in these women in the event of subclinical hypothyroidism, as some small RCTs have demonstrated reduced miscarriages with subclinical hypothyroidism with LT4 therapy in this context [175, 196, 197].

5.2.3 Hyperthyroidism

In women with preconceptional hyperthyroidism, which in most cases is Graves' disease, pregnancy should be discouraged until euthyroidism is achieved, as overt hyperthyroidism increases the risk of miscarriage, preterm birth and growth retardation [184]. There is no clear recommendation for the further course of action in women with Graves' disease and ongoing antithyroid therapy who wish to conceive, but a detailed explanation and a joint decision regarding the various therapy options should be made [180, 184, 185]. In principle, thyrotropin receptor antibodies (TRAbs) often decrease in the course of pregnancy, presumably in the course of induction of immune tolerance, but they may increase again significantly postpartum. For a basic understanding of the therapy of Graves' disease in pregnancy, it is also important to know that both TRAbs and antithyroid drugs pass through the placenta and thus can also affect the fetal thyroid hormone production, which becomes relevant from about the 20. gestational week (start of thyroid hormone synthesis around the 14. to 18. gestational week) [180]. Antithyroid drug-induced malformations may also occur as possible side effects, although these have been observed more frequently with thiamazole (methimazole) (approximately 17 per 1000 births) than with propylthiouracil (trade name: Prothiucil(R)) (approximately 9 per 1000 births) [198]. Therefore, propylthiouracil and not thiamazole is recommended to use as an antithyroid drug in the 1. trimenon and/or in the first 16 weeks of pregnancy. Regarding the therapeutic options in women with Graves' disease and a desire for pregnancy, thyroidectomy would have the advantage that TRAbs often decrease rapidly thereafter, whereas after radioiodine therapy TRAbs increase transiently with a peak after approximately 3 months and a persistence for approximately 1 year, which may increase the risk of fetal or neonatal hyperthyroidism (in addition, at least 6 months is recommended as the minimum interval between radioiodine therapy and pregnancy). If a woman decides to continue antithyroid drug

therapy despite an existing active desire to have children, a preconceptional switch from thiamazole to propylthiouracil should already be considered, especially in young women who have a high probability of rapid conception. It must also be kept in mind that outside of pregnancy, thiamazole is preferred over propylthiouracil because of its lower risk of acute liver failure. Alternatively, it may be considered, e.g. in women with low-dose antithyroid therapy (e.g. thiamazole of maximum 10 mg daily) who have already been treated for at least 6 months and do not have a large goiter or high TRAbs, to immediately discontinue antithyroid drugs if pregnancy is detected and strive for close monitoring regarding thyroid function (e.g. every 1 to 2 weeks) in early pregnancy [180]. This approach is based on the consideration that the recurrence of hyperthyroidism in pregnancy often takes several weeks, so that the possible need for antithyroid therapy does not arise again until after the 1. trimenon and therapy can thus be delayed until after the critical period for possible teratogenic side effects of antithyroid drugs.

Women who wish to become pregnant and suffer from hyperthyroidism due to thyroid autonomy should definitely be advised to undergo definitive therapy. This therapy could be either radioiodine therapy or surgery prior to pregnancy. This is because thyroid autonomy tends to worsen over time. Additionally, unlike Graves' disease, which usually improves during pregnancy, there are no TRAbs that could somewhat offset the effects of antithyroid drugs on fetal thyroid function if antithyroid therapy is necessary[180].

5.3 Pregnancy

5.3.1 Hypothyroidism

In pregnancy, any hypothyroidism with a TSH level of $> 10\,\mathrm{mU\,L^{-1}}$ and any overt hypothyroidism should be treated with LT4 (e.g. initially with a daily dose of $2.33\,\mu\mathrm{g\,kg^{-1}}$ or approximately 150 µg), whereby this recommendation represents a general wide-ranging consensus that, although based primarily on observational studies, is unlikely to be challenged by further RCTs because of ethical concerns and yet already convincing evidence [181, 182].

At lower TSH levels, according to ATA guideline 2017, any woman with subclinical hypothyroidism (i.e. TSH level above the trimester-specific upper reference value) and positive TPO-Ab should be treated with LT4, and such a therapy should be

considered for TPO-Ab-positive women with a TSH level $> 2.5\,\mathrm{mU\,L^{-1}}$ up to the upper TSH reference value. Regarding TPO-Ab, it is recommended to determine them in every woman in pregnancy with a TSH $> 2.5\,\mathrm{mU\,L^{-1}}$, whereas elevated TPO-Ab are detected in approximately 2 to 17% of pregnant women and indicate an increased risk of hypothyroidism in pregnancy, which is why the ATA guideline 2017 recommends that TPO-Ab-positive women (this also applies to Tg-Ab) have their TSH checked approximately every 4 weeks. However, for pathophysiological understanding it is important to know, that TPO-Ab cross the placenta but do not affect fetal thyroid function. The ATA guideline 2017 recommends for TPO-Ab-negative women and in subclinical hypothyroidism up to a TSH level of $10\,\mathrm{mU\,L^{-1}}$ to consider a therapy with LT4. However, in this regard, recent RCTs have provided additional results showing that a LT4 therapy in women with subclinical hypothyroidism and initiation of therapy from the 2. trimenon does not reduce pregnancy complications or improve neurocognitive development of the children [199, 200, 201, 202]. In a large multicenter RCT, after screening 97.228 pregnant women, 677 women (gestational week: 16+4 days) with subclinical hypothyroidism (TSH $\geq 4\,\mathrm{mU\,L^{-1}}$, fT4 within normal range) were randomized to either LT4 100 µg daily or placebo, with monthly TSH monitoring with dose titration to a TSH level of $0.1\,\mathrm{mU\,L^{-1}}$ to $2.5\,\mathrm{mU\,L^{-1}}$ [199]. There were no differences in neurocognitive development including intelligence quotient (IQ) of the children (primary study endpoint) at age 5 years, and there were no significant differences in various pregnancy complications [199]. A post-hoc analysis of this study also found no differences between women with and without elevated TPO-Ab levels [199]. In the same study, 526 pregnant women (median gestational week: 18+0) with hypothyroxinemia, i.e. reduced fT4 concentration with TSH levels in the reference range, were randomized to either LT4 50 µg daily or placebo, also showing no significant differences in neurocognitive development or various pregnancy complications [199]. In the Controlled Antenatal Thyroid Screening (CATS) study, 21.846 pregnant women were randomized to a screening group in which therapy with LT4 150 µg daily, including dose titration, was initiated in the event of elevated TSH and/or reduced fT4 levels, and to a control group in which TSH and fT4 levels were also measured but no related treatment was initiated [202]. In the screening group, 499 women and in the control group, 551 women had elevated TSH and/or reduced fT4. Comparing the 390 women in the screening group (median gestational week: 13+3) treated with LT4 and 404 women in the control group who did not receive related therapy, the IQ of children aged 3 years, with a mean IQ of 99.2 in the screening group and a mean IQ of 100.0 in the control group,

did not show a significant difference [202]. Moreover, there was no significant difference in pregnancy complications between these two groups, and another investigation of this study showed that there were no significant group differences in cognitive tests even at the age of 9.5 years [200]. However, a recent additional evaluation of this CATS study showed that children of women treated with LT4 showed significantly increased symptoms of attention deficit hyperactivity disorder (ADHD) and other behavioral problems when overtreated (characterized by increased fT4), which is why the authors of this paper also emphasize that overtreatment of subclinical hypothyroidism in pregnancy can also lead to side effects and must be monitored regularly [201]. Although subgroup analyses of the CATS study with women exclusively before the 14. gestational week showed no significant effect of therapy with LT4 and it was also concluded that pregnant women are often not routinely (i.e. in practice) diagnosed and treated for subclinical hypothyroidism much earlier in pregnancy, there remains a certain gap in our knowledge as to whether therapy of subclinical hypothyroidism with LT4 initiated very early in pregnancy does show positive effects. On this topic, there is evidence from relatively small and partly non-placebo-controlled studies that therapy started very early, i.e. still in the first trimenon, could reduce pregnancy complications [175, 202, 203, 204, 205]. The procedure for the therapy of subclinical hypothyroidism, which can be derived for practice, is also complicated by the fact that there are still no finally clear and uniform TSH threshold values in pregnancy. In this regard, the ATA guideline 2017 recommends either population-based trimester-specific TSH thresholds or lowering the lower TSH threshold by $0.4\,\mathrm{mU\,L^{-1}}$ and lowering the upper threshold by $0.5\,\mathrm{mU\,L^{-1}}$, resulting in an upper TSH threshold of approximately $4.0\,\mathrm{mU\,L^{-1}}$ in the first trimenon, and then gradually adjust them in the 2. and 3. trimenon to the limits valid outside pregnancy [181]. The previously used TSH thresholds, some of which were even lower, have thus been raised again based on new evidence [174, 181, 182, 183].

To facilitate the partial complexity of the therapy of subclinical hypothyroidism in pregnancy with reference to the current evidence for practice, we recommend the following approach: In subclinical hypothyroidism in the 1. trimenon with a TSH value of $> 4.0\,\mathrm{mU\,L^{-1}}$ to $< 10.0\,\mathrm{mU\,L^{-1}}$, therapy with e.g. LT4 50 µg daily should be initiated regardless of the TPO-Ab status (and we would not initiate LT4 therapy even in TPO-Ab-positive pregnant women and a TSH level of $2.5\,\mathrm{mU\,L^{-1}}$ to $4.0\,\mathrm{mU\,L^{-1}}$, which is also supported by a recent meta-analysis) [206]. In the 2. and 3. trimenon a subclinical hypothyroidism with a TSH value of $> 4.0\,\mathrm{mU\,L^{-1}}$ to $< 10.0\,\mathrm{mU\,L^{-1}}$ can be treated with e.g. LT4 50 µg daily, but this can also be omitted according to the current

evidence (individual decision, where the authors would rather decide against therapy in case of only minimal TSH elevations, e.g. $< 5.0\,\mathrm{mU\,L^{-1}}$).

Regarding monitoring during pregnancy, the ATA guideline 2017 recommends that all women with subclinical hypothyroidism (whether treated or not), with overt hypothyroidism and euthyroid pregnant women who are TPO-Ab and/or Tg-Ab positive, should get their TSH checked approximately every 4 weeks, and have at least one additional TSH determination at approximately 30. gestational week [181]. The TSH target value for a therapy with LT4 in pregnancy should be a TSH within the normal range, with many experts and guidelines advising a TSH $< 2.5\,\mathrm{mU\,L^{-1}}$ in pregnancy as the TSH target range.

5.3.2 Hyperthyroidism

When hyperthyroidism occurs for the first time in pregnancy, it is important to distinguish primarily between pregnancy-induced hyperthyroidism and Graves' disease, while other causes of hyperthyroidism, such as thyroid autonomy in pregnancy, are rare. Pregnancy-induced hyperthyroidism is caused primarily by hCG, which leads to stimulation of the TSH receptor, and is also frequently associated with nausea or hyperemesis gravidarum. Pregnancy-induced hyperthyroidism occurs in the first trimenon and usually normalizes spontaneously (parallel to the hCG drop) from about the 15. gestational week, whereby the fT3/fT4 ratio as well as the clinical hyperthyroidism symptoms (with the exception of tachycardia) are lower compared to Graves' disease [180]. In contrast to Graves' disease, no TRAbs are detectable in pregnancy-induced hyperthyroidism, and the sonographic pattern is unremarkable. Antithyroid drugs should not (!) be used in the therapy of pregnancy-induced hyperthyroidism (even mostly not in overt hyperthyroidism), because usually spontaneous improvement occurs [181]. However, partial supportive measures such as fluid and electrolyte substitutions and beta-blockers may be indicated. In addition to the presence of TRAbs, Graves' disease is usually characterized by an enlarged thyroid gland with increased blood flow and sonographically echo-poor pattern, although endocrine orbitopathy may of course also be diagnostic.

If antithyroid drug therapy is necessary in pregnancy for Graves' disease, initial dosages should be adjusted according to the level of thyroid hormones and symptoms, usually initially with propylthiouracil with 200 mg to 400 mg daily or thiamazole with 10 mg to 20 mg daily (less frequently, as propylthiouracil should be preferred in the first 16 gestational weeks; confer [207]). For clinical practice, it has to be considered that the

efficacy of propylthiouracil to thiamazole is approximately 1:10 to 20. If a woman has taken thiamazole until the 16. gestational week and continues to require antithyroid drug therapy, a switch to propylthiouracil would in principle be indicated in the first 16 weeks, although a recent observational study suggests that in this case a switch to propylthiouracil does not reduce teratogenicity, so it is questionable whether the switch to propylthiouracil would be appropriate in these circumstances [198]. It is important to keep the antithyroid drug dose as low as possible, whereby the target parameter should be an fT4 value at or slightly above the upper reference value, because one wants to avoid infantile hypothyroidism and antithyroid drug side effects are also partly dose-dependent. Thyroid hormone monitoring should then be performed initially every 2 to 4 weeks or, if the fT4 target range is reached, every 4 to 6 weeks, whereas due to the frequently declining TRAbs in the course of pregnancy, the antithyroid drug dosage can be reduced regularly or the antithyroid drugs can even often be discontinued (at approximately 1/3 in the 3. trimenon). Whether it is beneficial to switch back from propylthiouracil to thiamazole within pregnancy after the first 16 weeks is unclear, and there is no clear recommendation in this regard. In any case, TRAbs monitoring during pregnancy is recommended for all patients with Graves' disease (even if they have already received definitive therapy), with determination of TRAbs at the time of pregnancy detection and, if elevated, again in the 18. to 22. gestational week and if necessary again in the 30. to 34. gestational week (if elevated in the 18. to 22. gestational week or antithyroid drug therapy is present). This is recommended because TRAbs elevation above three times the upper limit indicates an increased risk of fetal hyperthyroidism and should result in intrauterine and postpartum fetal hyperthyroid monitoring.

5.4 Postpartum period and lactation

5.4.1 Thyroid hormone replacement

Women who have increased their pre-conceptional LT4 dose due to pregnancy should reduce their therapy back to the pre-conceptional dose immediately after delivery with subsequent TSH monitoring after approximately 6 weeks [181]. Women who first received LT4 therapy during pregnancy are candidates for a discontinuation attempt, especially if they are taking a low dose such as 50 µg daily, although this is an individual decision, but of course after discontinuation attempt approximately 6 weeks later a

TSH control should be done [181].

5.4.2 Postpartum thyroiditis

Postpartum thyroiditis is a new onset of autoimmunologic thyroid dysfunction within one year after delivery that cannot be attributed to Graves' disease and occurs in approximately 5% of all women [180]. Women with positive TPO-Ab in the first trimenon are at increased risk for postpartum thyroiditis. Typically, this disease is manifested by an approximately 2 to 6 months after birth occurring and about 1 to 2 months lasting transient hyperthyroidism, which then progresses to an approximately 4 to 6 month lasting hypothyroid phase, before euthyroidism sets in again [180]. However, there are also courses in which only hypo- or hyperthyroidism occurs. In approximately 80% of women with postpartum thyroiditis, thyroid dysfunction normalizes within a year, although chronic hypothyroidism may persist in some cases, and approximately 70% of patients develop thyroiditis again during a subsequent pregnancy. Differential diagnostic, postpartum thyroiditis must be distinguished from Graves' disease, whereas in postpartum new-onset hyperthyroidism, the incidence of postpartum thyroiditis is approximately 20 × greater than that of Graves' disease. Unlike Graves' disease, TRAbs are not present in postpartum thyroiditis and women with postpartum thyroiditis are usually TRAbs positive. The ratio of fT3 to fT4 is lower in postpartum thyroiditis than in Graves' disease, thus the clinical symptoms are usually milder. Thyroid scintigraphy is not necessary for differential diagnosis in the vast majority of cases, but uptake on thyroid scintigraphy would usually be low to decreased in postpartum thyroiditis, unlike Graves' disease. Therefore, antithyroid drugs are ineffective and not indicated in the treatment of postpartum thyroiditis, although treatment with beta-blockers may sometimes be indicated in cases of severe symptoms of hyperthyroidism. Hypothyroidism in the setting of postpartum thyroiditis is treated with LT4 and after approximately 12 months of therapy a gradual discontinuation should be attempted to evaluate whether thyroid function has recovered.

5.4.3 Antithyroid drugs during breastfeeding

Both thiamazole and propylthiouracil are secreted into breast milk, but the amounts are so small that, according to various studies, breastfeeding women receiving antithyroid drug therapy did not cause hypothyroidism in their infants [180]. Therefore, it can be assumed that doses of thiamazole up to 20 mg daily and of propylthiouracil up to

450 mg daily during breastfeeding are safe for infants and therefore monitoring of infant thyroid function is not necessary in this context [180].

In any case, the generally recommended newborn screening for connatal hypothyroidism must be performed in the first days after birth [208].

5.5 Discussion

Thyroid disorders are common in women preconceptually, during pregnancy and in the postpartum period and it must be accepted that there is still scientific debate about the respective hormone thresholds in this context and the practical approach in routine clinical practice is quite heterogeneous [209, 210, 211]. Various observational studies in the past have shown an association between subclinical hypothyroidism or TPO-Ab positivity and pregnancy complications, and the neurocognitive development of children associated with thyroid disease has also been intensively studied with mixed results [174, 212, 213, 214, 215, 216, 217]. In this context, we can now reassure many pregnant women that recent RCTs have shown no significant effects of LT4 therapy in women with mild TSH elevation on pregnancy outcome or neurocognitive development of children [199, 200, 201, 202, 206]. Thus, in recent years, there has been a development from a formerly very aggressive therapy of subclinical hypothyroidism to a currently significantly weakened therapy recommendation, although there are still some knowledge gaps in this area. On the other hand, we would like to emphasize the importance of diagnosis and the compulsory treatment of overt thyroid dysfunctions, with the exception of pregnancy-induced hyperthyroidism. We therefore also clearly advocate general screening for thyroid dysfunctions in all women of childbearing potential and in all with a positive pregnancy test.

Chapter 6

Discussion and Conclusion

The four main chapters of this thesis are based on four publications, all of which are focused on clinical research in the context of thyroid disorders. First, we have demonstrated that RHR is closely linked to the thyroid hormones fT3 and fT4, suggesting that monitoring heart rate could aid in detecting changes in thyroid function. Additionally, our clinical case report underscores the critical importance of fast and accurate diagnosis of thyroid inflammation. However, our critical reflection on current guidelines for hypothyroidism indicates a pressing need for further research, particularly with respect to the treatment of subclinical hypothyroidism. Furthermore, our systematic literature search on thyroid hormones in relation to fertility, pregnancy, and lactation presents a contrasting view, suggesting that current clinical practice may be overly aggressive, highlighting the complexities of thyroid dysfunction treatment. Our goal in each of these works is to improve patient care in the present and to provide new insights that could ultimately lead to innovative treatment and monitoring strategies in the future. In particular, our research on the association between heart rate and thyroid hormones may lay the foundation for future investigations to enhance the diagnosis and treatment of thyroid disorders.

The original article on the association between RHR and thyroid hormones is a cross-sectional study on this relationship. The result was a highly significant positive association between RHR and the thyroid hormones fT3 and fT4. From a formal scientific perspective it must be noted that causal inference cannot be uncritically made from such a study design as we can, for example, not rule out some sort of confounding or bias. Regarding the formal approach, it is, however, noteworthy that the statistical analyses plan was pre-specified, which is important to avoid issues such as HARKING, i.e. hypothesizing after results are known. Avoiding HARKING and other violations of accurate scientific principles was a clear aim of this thesis. The results of the association between thyroid hormones and resting heart rate is of particular importance, in our opinion, as it may provide the scientific basis for future developments in this field. Specifically, these data suggest that monitoring heart rate may be a useful

clinical tool to gain some information on thyroid function in patients. This may, for example, be useful for patients suffering from Graves' disease to detect re-emergence of hyperthyroidism or hypothyroidism in patients overdosed with methimazole. It is one of our future plans to work on studies addressing these issues. For such future studies, we aim to build a bridge between monitoring patients in terms of heart rate by using technical devices such as smartwatches and the clinical and laboratory profile of the study participants. Using smartwatches may form an inexpensive, easily accessible, and highly acceptable form to incorporate medically relevant measurements into everyday life. Those measurements must still be viewed on a population level, as the RHR changes may be subtle viewed from a per-patient perspective. However, such easily accessible, non-invasive data measurements are certainly worth investigating. In the end, this may lead to the ultimate goal to implement heart rate monitoring in the daily management of patients with thyroid dysfunctions.

In chapter 3, we discussed a case report that described a patient with an unusual case of acute suppurative thyroiditis that was very challenging in the diagnosis and management as the differential diagnosis is quite challenging. Such case reports, although they can only be viewed as anecdotal, can put rare cases into the spot light and thus ensure that unlikely cases—even though they happen rarely—are not overlooked in clinical practice. Obviously, this attention is especially important in the case of rare, but life-threatening conditions, which should always be considered due to their potential severe outcomes. With such a case report and the considerations and conclusions of this case we also hope to provide a useful guidance for clinicians facing similar challenges with such patients suffering from this rather rare but potentially life threatening thyroid disorder. In summary, we can emphasize that AST represents a rare but potentially life-threatening bacterial thyroid infection, which should be treated with immediate medical attention. Differential diagnosis between AST and other thyroid disorders, especially SAT, is often difficult, as outlined by our report. Thus, in uncertain cases, liberal additional diagnostic measures such as CT scans of the neck region and fine needle aspiration biopsy are strongly advised.

In chapter 4, we summarized and extended our review article on hypothyroidism, which is based on a systematic literature search including clinically relevant articles on the diagnosis and treatment of hypothyroidism. As hypothyroidism is extremely common and thyroid hormone replacement drugs are among the most widely prescribed drugs worldwide, this review may have a large impact on daily clinical practice. In the review, we especially focused on the indication for treatment of subclinical hypothyroidism,

which has been increasingly questioned; especially in elderly patients. In summary, LT4 is still the first choice in the treatment of hypothyroidism, although it is not an optimal hormone replacement. Future research will likely further focus on LT4/LT3-combination therapies and the treatment of mild hypothyroidism. Although there are already many articles published on this topic, the current review is a useful addition to the existing literature as it provides a comprehensive overview on this topic. The high access rate for a German article with currently already over 17 000 accesses on this article is a proof that this piece of literature appears to be very useful for the readers and clinicians.

The review article with its focus on thyroid disorders in the context of preconception/fertility, pregnancy and lactation is also a very clinically publication. It aims to fill a gap in the existing literature on an easy to understand and comprehend guidance paper that can be used by clinicians who have to take care of such women. The work was also based on a systematic literature search and it had a particular focus on frequent clinical questions that are often either not clearly addressed in other existing guidelines papers. Additionally, we focused on questions that existing guidelines may not cover with up-to-date evidence and thus require updates. The review article is especially interesting, as thyroid disorders are common in women preconceptually, during pregnancy and in the postpartum period. Underlining its importance is the fact that scientific debate about the respective hormone thresholds in this context and the practical approach in routine clinical practice is still ongoing. As recent studies have shown no significant effects of LT4 therapy in women with mild TSH elevation on pregnancy outcome or neurocognitive development of children, current clinical practice moves away from aggressive therapy. It is still important to diagnose and treat thyroid dysfunction in general and thus screening for thyroid dysfunction is still of importance in women who are wishing to conceive and in pregnant women.

In conclusion, we want to restate that thyroid disorders are among the most common diseases due to their high prevalence in the general population. Making any kind of treatment improvements on an individual or population level can thus be highly beneficial. In the course of the thesis, we discussed recent developments in the treatment of thyroid disorders to provide general guidelines, focused on a very specific, special case and provided insights that may point towards novel monitoring and treatment approaches. We specifically focused on scientific data that have a clear relation to clinical science and are therefore, hopefully, useful for clinicians taking care of patients. We hope that the thesis and the papers featured in this thesis form a go-to for many clinicians and may point towards future work. We are especially excited about carrying

out studies to determine the power and usefulness of RHR in the context of tele-medicine and ease future measurements in the clinical practice of diagnosis and monitoring of thyroid disorders.

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