Which neuromusculoskeletal pain syndromes are associated with hyper-and hypothyroidism?
The purpose of this study was to investigate which neuromusculoskeletal pain syndromes could be associated with hyper- and hypothyroidism, both before diagnosis of the thyroid disorder and during treatment. From a clinical and osteopathic perspective, these associations are important to be aware of in order to provide the best possible care. This literature review was a quantitative study, based on searches performed on six databases, which focused on the neuromusculoskeletal complaints and diagnoses in patients before or in connection with their thyroid disorder diagnosis, or as a residual symptom during their treatment.

The results showed that neurological, muscular or skeletal symptoms could be the only manifestations of a thyroid disorder, that the majority of patients with hyper- and hypothyroidism have neuromuscular complaints, and many suffer from clinical weakness and neuropathies. The most commonly associated diagnoses were carpal tunnel syndrome, adhesive capsulitis and Dupuytren’s contracture. For hyperthyroidism, osteopenia and osteoporosis, tremor and hyperreflexia could be relevant, for hypothyroidism the separate diagnoses of hypothyroid myopathy and hypothyroid arthropathy along with several different skeletal and joint manifestations were noteworthy. The findings also showed that a large group of these patients suffer from residual symptoms related to neuromusculoskeletal issues.

The identification and recognition of neuromusculoskeletal signs and symptoms which could be either the initial manifestation of a thyroid disorder or an associated issue are of importance to provide fast and correct treatment. Further research into optimal treatment methods would be warranted to decrease the residual symptoms experienced by far too many patients, especially those with hypothyroidism.
Declaration of conformity

I hereby assure on oath to have created this present work independently and to have used exclusively the sources and aids indicated. I have not submitted this thesis anywhere else. This work is not in any conflict of interest with any persons or institutions.

Charlotte Nelin, Göteborg, 20200305
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# List of Abbreviations

<table>
<thead>
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<th>Ab</th>
<th>Antibody</th>
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<tbody>
<tr>
<td>CK</td>
<td>Creatine kinase</td>
</tr>
<tr>
<td>CTS</td>
<td>Carpal tunnel syndrome</td>
</tr>
<tr>
<td>RCTs</td>
<td>Randomized controlled trials</td>
</tr>
<tr>
<td>T3</td>
<td>Triiodothyronine</td>
</tr>
<tr>
<td>T4</td>
<td>Tetraiodothyronine, also known as thyroxine</td>
</tr>
<tr>
<td>TPO</td>
<td>Thyroperoxidase</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid stimulating hormone</td>
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</table>
1 Introduction

1.1 Background

Thyroid disorders are dysfunctions of the thyroid gland of which there are three main types; thyroid cancer, hyper- and hyposecretion of thyroid hormones.

Thyroid cancers are rare, affecting approximately 600 people per year in Sweden (Sköldkörtelförbundet, n.db), yet it is the most common type of endocrine cancers, representing 4% of all new cancer cases worldwide (Rodriguez-Torres et al., 2019, p. 1). As a consequence of treatment, thyroid hormones dissipate, resulting in a hypothyroidism state (hyposecretion) for these patients.

Hyper- and hyposecretion of thyroid hormones involve several diseases, some of which are considered to be caused by autoimmunity, others by radiation, iodine deficiency, surgery, tumours, virus, stress, infections or by unknown causes (VanPutte et al. 2017, p. 616). The functionality of the hypothalamo-pituitary-thyroid axis and the secretions of the thyroid are measured by blood levels of thyroid stimulating hormone (TSH), free tetraiodothyronine/thyroxine (T4) and free triiodothyronine (T3), but T3 is rarely measured for diagnosis since its’ half-life is shorter and as such, more difficult to measure in a reliable way (Olivius, 20190409b).

In hyperthyroidism (hypersecretion), the TSH blood level is below the normal range whereas the blood level of T4 is above. Hyperthyroidism affect 2-3% of all women, being 5-10 times more common in women than in men (Olivius, 20190409a). Yearly, around 3500 people in Sweden are diagnosed with hyperthyroidism of which, the most common form is Graves’ disease, also known as diffuse autoimmune hyperthyroidism (Sköldkörtelförbundet, n. da).

In hypothyroidism, the TSH blood level is above the normal range while the T4 blood level is below. There is a prevalence of hypothyroidism of up to 5% among the general population, with another 5% estimated to be undiagnosed. 99% of the affected patients suffer from primary hypothyroidism, where the disorder is in the thyroid (Chiovato et al., 2019), in contrast to the considerably less common secondary hypothyroidism, where the disorder is in the pituitary gland or the hypothalamus.
According to statistics from 2018, approximately 4.5% of Swedes were diagnosed with and treated for thyroid disorders, whereof 82% were female (Socialstyrelsens statistikdatabas, 2019, Appendix 1, Socialstyrelsen, 2018, p. 7). The yearly increase of new patients with hypothyroidism, i.e. without prior thyroid treatment was 8% (Socialstyrelsen 2018, p. 14). From 2006 to 2017, the prescription of levothyroxine (synthetic T4), which is currently the only commonly prescribed drug for hypothyroidism, grew by 32%, possibly due to increased treatment of what is called subclinical hypothyroidism, which is indicated by high TSH blood levels, but normal T4 (Socialstyrelsen, 2018, p. 9). Patients aged 20-40 on levothyroxine medication have doubled from 2006 to 2017, partly based on new screening introduced in relation to pregnancy (Socialstyrelsen, 2018, p. 7).

People with thyroid disorders can display a wide range of symptoms, partly related to whether there is hyper-or hyposecretion of thyroid hormones. For hyperthyroidism the symptoms are nervousness, intolerance to heat, palpitations of the heart, sweating, muscle weakness, tremor, higher blood pressure, losing weight, psychomotor agitation and goiter (Olivius, 2019a, VanPutte et al., 2017, p. 614). For hypothyroidism, the early symptoms are vague (tiredness, depression, sense of something being wrong), becoming more noticeable later on, with fatigue, myalgia, cold intolerance, cold and dry skin, hair falling off, bradycardia, lower blood pressure, apathy, swelling and gaining weight (Olivius, 2019b, VanPutte et al., 2017, p. 614).

In the patient and medical community related to thyroid disorders and endocrinology, there are currently two topics being widely discussed; firstly, the practice to use the TSH and T4 blood levels to measure the functionality of the thyroid gland, and secondly, the recommended monotherapy of levothyroxine (Olivius, 20190409b, Socialstyrelsen, 2018, pp. 9-11). In light of 5-20% of patients reporting residual symptoms, even though on medication and with what is considered to be normal thyroid hormone levels (biochemical normalization or euthyroidism), the diagnosis and treatment guidelines are being questioned (Chaker et al., 2017, p. 1557, Sköldkörtelförbundet De VårdLösa, n.d).

Most patients receiving thyroid medication gradually return to normal TSH and T4 blood levels (within 2-6 months (McKeran et al., 1975, p. 659)) and the signs and symptoms are transient. But for some, diverse symptoms remain (Chaker et al., 2017, p. 1550, Moncayo & Moncayo, 2017, p. 130) and in one survey made by Svenska Institutet För Opinionsundersökningar (SIFO) on assignment from Sköldkörtelförbundet, 19% of patients stated they were dissatisfied with the care they receive (Sköldkörtelförbundet,
Musculoskeletal complaints, as well as neurosensory and gastrointestinal signs and symptom are associated with thyroid disorders (Chaker et al., 2017, p. 1553), before receiving the diagnosis and afterwards.

This literature review investigated the association of different neuromusculoskeletal pain syndromes with hyper-and hypothyroidism, before and during treatment. The purpose was to provide an overview of which pain syndromes could be related to the patient’s hyper-or hypothyroidism, including the pain syndromes which could be indicating a thyroid disorder and those associated with a confirmed diagnosis. Both the patient and the practitioner could benefit from being able to connect the patient’s neurological, muscular or skeletal complaints and symptoms with the endocrinological disorder, when relevant. The knowledge of the association could increase the patient’s understanding of their disorder and their situation and also help to motivate the patient’s adherence to treatment. For the practitioner, by the integrating the knowledge of these associations into clinical practice and decision-making, it could provide an opportunity to quicker make the correct diagnosis and ultimately provide better total care.

1.2 Hypothyroid myopathy

In the context of this study, the symptoms and signs of hypothyroid myopathy are particularly relevant, since it can develop as a complication in cases of untreated or uncontrolled hypothyroidism. Proximal muscle weakness in the upper and lower limbs are one of the main symptoms, but also nonspecific myalgia, cramps, and delayed relaxation of deep tendon reflexes. More rarely seen are acute compartment syndrome and rhabdomyolysis. Myoedema is typical clinical sign, used to differentiate hypothyroid myopathy from other types of myopathy. There are four subtypes of hypothyroid myopathy; myasthenic syndrome, atrophic form, Kocher-Debré-Semelaigne syndrome, and Hoffman’s syndrome. The atrophic form and Hoffman’s syndrome can affect adults. The atrophic causes selective atrophy of type 2 muscle fibers (fast twitch), Hoffman’s presents as pseudohypertrophy, stiffness and spasms, where the tongue is commonly involved, along with the muscles of the upper and lower limbs. Besides the prerequisite confirmation of the hypothyroidism diagnosis through tests of TSH and T4 blood levels, the elevated blood level of creatine kinase (CK) is the most common laboratory findings of hypothyroid myopathy. With quick discovery and treatment (thyroid hormone replacement),
most symptoms are usually resolved within a year, but could also take several years (Fariduddin & Bansal, 20191113).

1.3 Hypothyroid arthropathy

Hypothyroid arthropathy is described as joint tenderness, sometimes with synovial thickening and joint effusions, but without redness or heat indicative of inflammation. It most commonly affects the knees, wrists, metacarpal- and metatarsophalangeal joints and the proximal interphalangeal joints (Pincus, 20200120). The symptoms will improve during hormone replacement therapy, and radiographic improvement was also noticed (McLean & Podell, 1995).

1.4 Concepts used

The choice to use certain concepts related to the topic of this review, which could be used differently, are commented on below.

- **Thyroid disorder** was used to denote disturbed functionality of the thyroid. It included, but was not limited to, hypo-and hyperthyroidism, which were also indications of thyroid hormone level statuses.

- **Thyroid diseases** were used for the diseases associated with specific dysfunctions of the thyroid; for example, Hashimoto’s thyroiditis which is a form of hypothyroidism.

- **Hyperthyroidism** was used as a collective term to indicate the hormone status related to the excessive production of T4 and T3 hormones from the thyroid. Hyperthyroidism was also used in the cases where the original text might have chosen the term thyrotoxicosis.

- **Adhesive capsulitis** was used as a synonym to frozen shoulder, and it was the chosen term used in this text, even in cases where the original text might have used frozen shoulder. (Titles of articles have not been changed.)
2 Problem statement

Hyper- and hypothyroidism are common disorders, affecting women in particular, and treatment methods are relatively concordant worldwide, especially considering the monotherapy of levothyroxine for hypothyroidism. There are many patients with neurological, muscular and/or skeletal symptoms and signs which could be related to their thyroid dysfunction, either before receiving their diagnosis or during treatment (residual symptoms). Hence, this literature review aimed to investigate the current state of knowledge with regards to which pain syndromes were relevant to be aware of in association to hyper- and hypothyroidism and to summarize these into an overview.

2.1 Research question

Which neuromusculoskeletal pain syndromes are associated with hyper- and hypothyroidism?
3 Methodology and results

3.1 Methodology

This study was designed as a literature review using several databases:

- Cochrane,
- MEDLINE/Ovid,
- CINAHL,
- ScienceDirect,
- Socialstyrelsens statistikdatabas.

The choice to use multiple databases was made with the purpose to broaden the search results and extend the possibility to find relevant information. A couple of websites were also used, which provided some of the background information and statistics specific to Sweden.

The study was mostly quantitative, since the study was investigating the potential association between neuromusculoskeletal issues and thyroid disorders and their respective prevalence. However, some articles contained qualitative information related to the patients’ complaints and descriptions of symptoms.

3.1.1 Research method

In order to answer the research question, searches in the selected databases were performed, based on selected key words. The Cochrane database searches provided few hits, and none were fitting the inclusion criteria for this study. The other searches rendered a large selection of articles related to thyroid disorders and neuromusculoskeletal issues (n=284). When the exclusion criteria were applied and duplications were removed (n=256), the availability of articles was manually checked, and the remaining were reviewed in detail (n=12). Three articles were not considered fitting the scope and purpose.
of this study and nine were included. The included articles consisted of two case-control studies, two cases, three cohorts and two reviews. No randomized controlled trials (RCTs) were included.

The key words and selection criteria used per database search are detailed below. Several searches were made using the specific terms “hypothyroid” or “hypothyroidism”, without including the corresponding “hyperthyroid” and “hyperthyroidism”, this biased use was made based on the assumption that more research has been performed on this specific disorder since there is a much higher prevalence of patients suffering from hypothyroidism than hyperthyroidism, and also to catch studies made on the musculoskeletal diagnosis called “hypothyroid myopathy”.

**Figure 1 Study selection flow**
MEDLINE

1. Hypothyroidism OR hypothyroid OR thyroid disorder AND myopathy, from 2000 to 2019, in English, studies on humans (46 results, whereof 11 fits; 4 available and 2 used)

2. Hypothyroid myopathy, in English (38 results, whereof 3 fits; 1 available and used)

3. Musculoskeletal manifestations AND thyroid OR hypothyroidism OR hyperthyroidism, studies on humans, full text available (34 results whereof 10 fits; 3 available and used)

CINAHL

1. Hypothyroid OR thyroid disorder OR thyroid AND myopathy, in English (26 results, whereof 5 fits; 3 doubles and 2 available, 1 used)

ScienceDirect

1. Thyroid disorder AND musculoskeletal diagnosis, from 2010 to 2019, in English (102 results, whereof 3 fits; 2 doubles, 1 available and used)

2. Hypothyroidism AND frozen shoulder, from 2010 to 2019, in English (38 results, whereof 1 fit, available and used)

The search performed on Socialstyrelsens statistikdatabas included the anatomical therapeutic chemical (ATC) code: H03 indicative of Tyreoideabehandling, and the criteria for Sweden, all ages and both sexes (Appendix 1).
### 3.1.1.1 Inclusion and exclusion criteria

**Table 1 Inclusion and exclusion criteria**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Articles written in English</td>
<td>- Studies performed on animals</td>
</tr>
<tr>
<td>- Studies performed on human adults</td>
<td>- Studies concerning pathologies related to, associated with, or independently associated with thyroid disorders</td>
</tr>
<tr>
<td>- Studies related to thyroid disorders, hyperthyroidism and hypothyroidism</td>
<td>- Studies on thyroid disorders related to pregnancy, congenital disorders and children</td>
</tr>
<tr>
<td>- Studies investigating the association with, relation to and prevalence of neuromusculoskeletal disorders to thyroid disorders</td>
<td>- Studies related to subclinical thyroid conditions, subclinical hyper- and hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>- Studies related to the choice or the evaluation of treatment options of thyroid disorders or the respective neuromusculoskeletal disorders</td>
</tr>
</tbody>
</table>
3.1.1.2 Data analysis method

The checklists from the Critical Appraisal Skills Programme (CASP) were used to analyse the chosen articles. The checklist for qualitative studies was used to evaluate case studies, in default of one designated for that purpose by CASP. Two studies mentioned their evidence level grade with reference to evidence-based medicine, but without naming which grading standard was used (Burns et al., 2011, tables 1-4).

3.1.1.3 Randomization and blinding strategies

None of the chosen articles included studies with randomization of treatment methods, which was not a concern since the evaluation of treatment methods was not included in this study. There was also no randomization of participants. In most of the included studies and for the majority of the participants, their respective thyroid disorder diagnosis was known and constituted the foundation for the patient’s participation in the study. When the perspective was reversed, the neuromusculoskeletal diagnosis was known and used as inclusion criteria, and the thyroid functionality was being investigated. There was almost no blinding in any included study, except for some parts of examinations and some of the participant’s results during evaluations.

3.1.1.4 Ethical considerations

Four of the articles had received written consent from the participants (Qianrui et al., 2017, Duyff et al., 2000, Özek et al., 2018, Schiefer et al., 2017). Four articles did not include any details concerning ethics, the Helsinki declaration or the participant’s consent (McKeran et al., 1975, Cakir et al., 2003, Boswell et al., 2014, McLean & Podell 1995). One article removed all patient data and confirmed to follow workplace protocol with regards to the information included in the publication of the article (Berlanga-de-Mingo et al., 2019) and one article had received approval from an ethics committee (Duyff et al., 2000).
3.1.1.5 Validity and reliability, possible weaknesses and sources of bias

The information from the website belonging to Sköldkörtelförbundet was a mix of facts and statistics, patient interviews, a political program and links to research and media coverage about thyroid disorders. The site Internetmedicin was describing itself as a support for clinical decision making for doctors and nursing staff with the right to prescribe medications. There was a scientific council reviewing and approving the information before publication. Revenues from advertisements financed the site, but the advertisers were without any influence with regards to the site content. The website RheumatologyAdvisor.com, by Decision Support in Medicine and a part of Haymarket Media, declares to not having any sponsor or advertiser pay for, participate in or approve any of the sites content. The National Center for Biotechnology Information (NCBI) site is a part of the National Library of Medicine at the National Institute of Health in the USA. The views and opinions expressed by the authors published on the NCBI website are their own, NCBI does not support or recommend any commercial products or services.

Four articles declared the authors had no competing or conflicting interests (Qianrui et al., 2017, Özek et al., 2018, Berlanga-de-Mingo et al., 2019, Boswell et al., 2014) and the remaining five did not mention anything about it (McKeran et al., 1975, Duyff et al., 2000, Cakir et al., 2003, Schiefer et al., 2017, McLean & Podell 1995). Five articles stated the authors had not received any funding or grants (Qianrui et al., 2017, Özek et al., 2018, Schiefer et al., 2017, Berlanga-de-Mingo et al., 2019, Boswell et al., 2014) in association with performing the respective study, and four did not include any information about potential financial support (McKeran et al., 1975, Duyff et al., 2000, Cakir et al., 2003, McLean & Podell, 1995).
3.2 Results

The respective included studies are presented below, first with general information and results and then with comments related to this study.

3.2.1 Article summary 1

**Title:** Muscle fibre type changes in hypothyroid myopathy

**Authors:** McKeran, R. O., Slavin, G., Andrews, T. M., Ward, P., & Mair, W. P. G.

**Publication date and forum:** August 1975 in the Journal of Clinical Pathology

**Main area of research:** This cohort study on six patients investigated changes in muscle fiber type in hypothyroid myopathy, through muscle biopsy before and during hormone replacement therapy by synthetic T4 hormone. There was clinical evidence of myopathy in 30-80% of patients being diagnosed with hypothyroidism, where the main presentation included weakness, cramps, aching or painful proximal muscles, myoedema and occasionally pseudohypertrophy. Atrophy (smaller fiber diameter) and loss (fewer fibers) of type 2 muscle fiber was found, directly related to the severity degree of hypothyroidism and to the serum level of CK. The loss was occurring in all six patients, but the atrophy only in less severely hypothyroid patients, which suggested a development from atrophy to loss with the progressing severity of the hypothyroidism and the myopathy. For some participants the changes were corrected by the medication, within two to six months, but in severely myopathic patients the loss remained for up to two years after the medication had started, indicating a delayed or incomplete recovery.

3.2.1.1 Results of relevance for the study at hand

All the results were of relevance to this study. The connections of atrophy and loss of type 2 muscle fiber to the severity of the hypothyroidism and the CK levels were interesting from a clinical perspective, and the long recovery was important to become aware of, especially in cases where it might be only partial.
3.2.2 Article summary 2

**Title:** Myopathy in hyperthyroidism as a consequence of rapid reduction of thyroid hormone

**Authors:** Qianrui, L., Yuping, L., Qianjing, Z., Haoming, T., Jianwei, L., & Sheyu, L.

**Publication date and forum:** July 2017 in Medicine

**Main area of research:** A case study where a patient with Graves’ disease (hyperthyroidism) developed severe myalgia and elevated levels of CK during medication to correct thyroid hormone levels. A relative hypothyroidism state due to the quick reduction in thyroid hormone was suggested as the possible cause of the myopathy, which gradually worsened as the symptoms from the hyperthyroidism disappeared over a period of three months. Once the patient was stable in the new euthyroid state the myalgia was resolved, and the increased levels of CK were normalized. The authors proposed that a controlled, slower reduction of T4 levels than in this case would be desirable, to reduce the risk of myopathy. They also discussed previously reported cases of myopathy in relation to hyperthyroidism and speculated that there could be genetic components, since the majority of reported cases were Asians.

3.2.2.1 Results of relevance for the study at hand

Hypothyroid myopathy could be considered a feasible cause of myalgia and weakness when a patient was suffering from hypothyroidism, however this case reported that the patient was treated for hyperthyroidism, showing that hypothyroid myopathy could also occur in patients with hyperthyroidism during treatment. This possible connection could be important from the perspective of clinical practice and the procedure of differential diagnosis.
3.2.3 Article summary 3

Title: A Treatable Reason of Myopathy: Hypothyroidism


Publication date and forum: June 2018 in the Turkish Journal of Neurology

Main area of research: This was a case study, where the patient’s main reason for visiting the doctor was leg pain, weakness and fatigue. The neurological examination showed mild paresis of the proximal muscles, hypoactive deep tendon reflexes, and bilateral positive test results for Babinski’s sign. The biochemical tests showed high levels of CK and TSH. The patient was diagnosed with hypothyroid myopathy, where the main symptoms are weakness, cramp, muscle pain, decreased reflexes and myxedema, and often myalgia with activity. With synthetic T4 hormone replacement therapy, euthyroid status was achieved within a couple of months, along with normalized levels of CK and TSH. The weakness as a consequence from the hypothyroid myopathy could remain from one to six years. The case exemplified that the first signs of thyroid disorder could be neurological and stressed the importance of early discovery of thyroid disorders in order to achieve quick clinical improvement.

3.2.3.1 Results of relevance for the study at hand

This article was an example of an atypical representation of hypothyroidism, if compared to textbook symptoms, where the only presenting symptoms were neuromuscular. From an osteopathic context, the case described important factors to consider in clinical practice, including the awareness of the long timeframe of the potentially persisting weakness from the hypothyroid myopathy.
3.2.4 Article summary 4

Title: Neuromuscular findings in thyroid dysfunction: a prospective clinical & electrodiagnostic study

Authors: Duyff, R. F., Van den Bosch, J., Laman, D. M., Potter van Loon, B-J., & Linssen, W. H. J. P.

Publication date and forum: June 2000 in the Journal of Neurology, Neurosurgery and Psychiatry

Main area of research: A prospective cohort study was performed on 45 newly diagnosed adult patients with thyroid dysfunction, in order to evaluate neuromuscular signs and symptoms, by using handheld dynamometry and electrodiagnosis. Weakness, sensory signs and biochemical data were collected and evaluated during treatment. The aim was also to monitor the effect of the treatment, with follow-up after 3-4 months and 1 year of medication. 79% of patients with hypothyroidism had neuromuscular complaints, 38% had clinical weakness of one or more muscle groups, 42% had signs of sensorimotor axonal neuropathy and 29% had carpal tunnel syndrome (CTS). The serum level of CK was found not to correlate with weakness. At follow-up 12 months after the start of medication, 13% of patients had persisting weakness. 67% of patients with hyperthyroidism had neuromuscular symptoms, 62% had clinical weakness in at least one muscle group, 19% had sensorimotor axonal neuropathy and none had CTS, as shown in figure 2. The weakness was correlated with T4 levels, but not with serum levels of CK.
For patients with hyperthyroidism and weakness, the weakness developed quickly, early on and fully resolved during treatment (average 3.6 months). For patients with hypothyroidism and weakness, the weakness proved more difficult to treat, and was indicative of myopathy. Another difference was the larger number of weak muscles in patients with hyperthyroidism, and the finding that the mean T4 concentrations in patients with paresis and hyperthyroidism were significantly higher than in patients without paresis. For patients with hypothyroidism, there were no significant differences in T3, T4 and TSH levels between patients with or without weakness. The mean duration of the symptoms was much longer for the patients with hypothyroidism than the patients with hyperthyroidism, 19.9 months compared to 4.4. 16% of patients with hypothyroidism had muscular complaints as their main reason for visiting the doctor, compared to 36% of patients with hyperthyroidism. Tremor was present in 76% of patients with hyperthyroidism and generalized hyperreflexia in 38%, but not at all in patients with hypothyroidism.

The findings suggest that neuropathy, weakness and neuromuscular complaints like cramps should be investigated in both groups of patients, at the time of diagnosis but also afterwards, since 1/3 of patients with hypothyroidism would have residual symptoms after one year of treatment, and that those could be related to pathological changes in muscles; muscle fiber type 2 atrophy, increased number of internal nuclei and structural changes in type I fibers. For patients with hyperthyroidism, no pathological changes in muscles were found.
3.2.4.1 Results of relevance for the study at hand

All the results of the study were relevant. The study results accentuate the high prevalence of neuromuscular complaints in patients recently diagnosed with hyper- and hypothyroidism. It clearly presents the difference in symptoms and signs between the two diagnoses, as well as the differences in expected recovery. The relatively high percentage of patients with hyperthyroidism for whom the muscular complaint was the reason for visiting the doctor was notable from a clinical perspective. For patients with hypothyroidism, the same figure was also quite high.
Title: Musculoskeletal manifestations in patients with thyroid disease

Authors: Cakir, M., Samanci, N., Balci, N., & Balci, M. K.

Publication date and forum: August 2003 in the Journal of Clinical Endocrinology and Metabolism

Main area of research: Thyroid dysfunction could cause musculoskeletal symptoms, and the study analysed the prevalence of adhesive capsulitis, Dupuytren’s contracture, trigger finger, limited joint mobility and CTS in patients with different thyroid disorders and status (euthyroid with diffuse or nodular goiter, Hashimoto’s thyroiditis, Graves’ disease, toxic nodular goiter, toxic diffuse goiter and patients with goiter who had partial thyroidectomy). After being diagnosed with their respective thyroid disorder, the patients filled in a symptom questionnaire before being examined neurologically and orthopedically. The prevalence of the respective musculoskeletal disorders was analysed with regards to thyroid disorder and thyroid antibody (Ab) status - thyroglobulin (Tg) and thyroperoxidase (TPO). The group of 137 patients were classified; 42 with hyperthyroidism, 23 with subclinical hyperthyroidism, 39 with euthyroidism, 10 with subclinical hypothyroidism and 23 with hypothyroidism and their respective thyroid diseases (table 2).
Table 2 Division of patients per thyroid disorder

<table>
<thead>
<tr>
<th>Thyroid disorder (hormone status)</th>
<th>Number of patients</th>
<th>Patients in % of total</th>
<th>Thyroid disease</th>
</tr>
</thead>
</table>
| Hyperthyroidism                   | 42                 | 30,6%                  | 20 Graves’ disease  
20 toxic nodular goiter  
2 toxic diffuse goiter |
| Subclinical hyperthyroidism       | 23                 | 16,8%                  | 5 Graves’ disease  
16 toxic nodular goiter  
2 toxic diffuse goiter |
| Euthyroidism                      | 39                 | 28,5%                  | 26 euthyroid goiter  
6 Hashimoto’s thyroiditis  
2 Graves’ disease  
1 toxic nodular goiter  
4 goiter & partial thyroidectomy |
| Subclinical hypothyroidism        | 10                 | 7,3%                   | 7 Hashimoto’s thyroiditis  
3 goiter & partial thyroidectomy |
| Hypothyroidism                    | 23                 | 16,8%                  | 14 Hashimoto’s thyroiditis  
1 toxic nodular goiter*  
1 toxic diffuse goiter*  
7 goiter & partial thyroidectomy |

* The original diagnosis was toxic nodular goiter and toxic diffuse goiter, but the patients were hypothyroid at the time of the study, as a consequence of radioactive iodine therapy.

One musculoskeletal diagnosis was added during the course of the study; fibromyalgia syndrome. Each included diagnosis was described with regards to tests, diagnosis criteria or standard and methods of examination. Adhesive capsulitis was diagnosed in 15 patients (10,9%), Dupuytren’s contracture in 12 (8,8%), limited joint mobility in 6 (4,4%),
trigger finger in 4 (2,9%), CTS in 13 (7,3%) and fibromyalgia syndrome in 10 (7,3%), as viewed in figure 3.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adhesive capsulitis</td>
<td>10,9%</td>
</tr>
<tr>
<td>Dupuytren's contracture</td>
<td>8,8%</td>
</tr>
<tr>
<td>Limited joint mobility</td>
<td>4,4%</td>
</tr>
<tr>
<td>Trigger finger</td>
<td>2,9%</td>
</tr>
<tr>
<td>Carpal tunnel syndrome</td>
<td>9,5%</td>
</tr>
<tr>
<td>Fibromyalgia syndrome</td>
<td>7,3%</td>
</tr>
</tbody>
</table>

**Figure 3 Prevalence of musculoskeletal diagnosis in the study group**

The prevalence of the musculoskeletal diagnoses varied between the different groups of patients, but there was only one significant difference documented, for CTS in patients with hypothyroidism (P=0,004), where many of these patients had residual symptoms from it even after becoming euthyroid. Dupuytren’s contracture (21,7%) and limited joint mobility (8,7%) were also most common in the patients with hypothyroidism. Adhesive capsulitis (17,4%) was most common in patients with subclinical hyperthyroidism, fibromyalgia syndrome (20%) and trigger finger (10%) in patients with subclinical hypothyroidism. Trigger finger was significantly more prevalent in patients who were TPO Ab positive (P=0,03) and there was a significant negative correlation between adhesive capsulitis and TPO Ab positivity (P=0,03). The detailed prevalence of each musculoskeletal diagnosis in percent per thyroid disorder was included in figure 4. Only limited joint mobility, Dupuytren’s contracture and CTS are included when the authors discuss and compare their findings with the prevalence in the general population.
Figure 4 Prevalence of musculoskeletal diagnosis per thyroid status

The findings in this study show that musculoskeletal disorders often coexist with thyroid dysfunction, and that routine examinations of patients with thyroid disorders should include questions related to musculoskeletal complaints.

3.2.5.1 Results of relevance for the study at hand

The musculoskeletal diagnoses found in patients with hyper- and hypothyroidism, and their respective prevalence, are relevant in the scope of this study.
3.2.6 Article summary 6

**Title:** Prevalence of hypothyroidism in patients with frozen shoulder

**Authors:** Schiefer, M., Santos Teixeira, P. F., Fontenelle, C., Carminatti, T., Santos, D. A., Righi, L. D., & Conceicao, F. L.

**Publication date and forum:** January 2017 in the Journal of Shoulder and Elbow Surgery

**Main area of research:** This case-control study investigated 401 shoulders on 93 patients with adhesive capsulitis and on 151 controls, which were patients visiting an orthopedic clinic for other reasons, to determine the prevalence of hypothyroidism in patients with adhesive capsulitis. The diagnosis criteria used for adhesive capsulitis were described. Measurements of serum levels of TSH and T4 were performed in all participants. 16.3% of patients had previously been diagnosed with hypothyroidism, compared to 0.7% of controls. In total, including those with prior diagnosis and those who were diagnosed during the study, 27.2% of patients and 10.7% of controls suffered from hypothyroidism. 62% of the confirmed adhesive capsulitis diagnoses were on the nondominant side of the patient. The study found that the prevalence of hypothyroidism was significantly higher in the patient group with adhesive capsulitis (P=0.001), but neither the hypothyroidism nor the TSH levels affected the duration of symptoms. There was a trend towards higher prevalence of bilateral adhesive capsulitis in patients with elevated TSH levels (P=0.09) and the mean TSH serum level was higher in patients with severe adhesive capsulitis than those with mild and moderate put together (P=0.03). For those with hypothyroidism diagnosis bilateral adhesive capsulitis was as common as unilateral.
Table 3 shows uni- and bilateral examination and diagnosis of patients and controls and also diagnosis of hypothyroidism prior to and during the study

<table>
<thead>
<tr>
<th></th>
<th>93 patients (cases) with confirmed adhesive capsulitis</th>
<th>151 controls without adhesive capsulitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral shoulder examination &amp; diagnosis</td>
<td>87 patients</td>
<td></td>
</tr>
<tr>
<td>Bilateral examination (patients &amp; controls), bilateral diagnosis (patients)</td>
<td>6 patients (12 shoulders)</td>
<td>151 controls (302 shoulders)</td>
</tr>
<tr>
<td>Hypothyroidism diagnosis prior to study</td>
<td>16,2%</td>
<td>0,7%</td>
</tr>
<tr>
<td>Hypothyroidism diagnosis in total (prior to &amp; during study)</td>
<td>27,2%</td>
<td>10,7%</td>
</tr>
</tbody>
</table>

The study results showed an association between adhesive capsulitis and hypothyroidism (P=0,002), and the age range 40-60 years (P<0,001), due to the significant difference in prevalence, and that the association was independent of other variables in a multivariate analysis. For bilateral adhesive capsulitis, there was an independent association to the male sex (5 men out of 6 patients), whereas generally adhesive capsulitis mainly affected female patients (70% female patients).

3.2.6.1 Results of relevance for the study at hand

Results related to hypothyroidism were applicable in this study (not elevated blood levels of TSH). The association between adhesive capsulitis and hypothyroidism, and a specific age range, were established, and the gender aspect shown with the general distribution as well as the specific for bilateral manifestation.
3.2.7 Article summary 7

Title: Association between multiple trigger fingers, systemic diseases and carpal tunnel syndrome: A multivariate analysis

Authors: Berlanga-de-Mingo, D., Lobo-Escolar, L., Lopez-Moreno, I., & Bosch-Aguila, M.

Publication date and forum: February 2019 in the Revista Espagnola de Cirugia Ortopedica y Traumatologia

Main area of research: The aim of the study was to evaluate the relationship between multiple trigger fingers, different systemic diseases, musculoskeletal diagnosis and potential precipitating factors. It was a retrospective study based on surgery performed on 279 patients with trigger finger diagnosis, aged 22-62, where the dominant hand was affected in 77,8% of cases and 59 patients had multiple trigger fingers, resulting in surgery performed on 368 trigger fingers. The multiple trigger fingers mostly affected the dominant hand (93% of cases). 91% of patients had demanding manual professions and 29% had suffered prior trauma. The collected data were included in a multivariate analysis, where no statistically significant difference was found with regards to age, sex, thyroid disorder, epicondylalgia or morbus de DeQuervain in the group with multiple trigger fingers compared to single trigger finger. The prevalence of CTS was 19,7%, which was significantly higher than in the general population (2-4%). Bivariate analysis detected that the prevalence of patients with diabetes mellitus and CTS was significantly higher in the group with multiple trigger fingers (P=0,007). The conclusion of the study was that diabetes mellitus, CTS and the dominant hand were significantly and independently related to the occurrence of multiple trigger fingers.

3.2.7.1 Results of relevance for the study at hand

5% of the patients with trigger fingers were diagnosed with hypothyroidism, and 0,3% with hyperthyroidism. There was a slight difference in prevalence of hypothyroidism between patients with multiple and single trigger fingers (8,5% compared to 4,1%, P=0,17). The patient group with thyroid diagnosis (15) might have been too small to draw conclusions regarding a potential connection between thyroid disorders and single or multiple trigger fingers.
Title: Musculoskeletal manifestations of endocrine disorders


Publication date and forum: March 2014 in Clinical Imaging

Main area of research: Endocrine disorders result in hormonal disturbances, involving almost all bodily systems and as such negatively affect homeostasis. The study was focused on endocrine disorders with musculoskeletal effects presenting on radiography ultrasound, computed tomography, magnetic resonance imaging and nuclear imaging.

The following endocrine disorders were included:

- Acromegaly
- Hypercortisolism
- Hyperthyroidism
- Hypothyroidism
- Hyperparathyroidism
- Pseudo-and pseudopseudohypoparathyroidism
- Diabetes mellitus.

The radiological manifestations of each disorder and their clinical implications and pathophysiology were described in the study. The recognition of findings of endocrine disorders in the musculoskeletal system by radiologists could assist the clinician to diagnose the patient quicker and more accurately.
3.2.8.1 Results of relevance for the study at hand

The results related to hyper- and hypothyroidism were relevant. Thyroid hormone regulates protein, carbohydrate, fat and mineral use in the body, which makes it one of the body’s main regulators of metabolism and makes dysregulation of it very impactful. For patients with hyperthyroidism, bone mineral density could decrease due to increased osteoclast-mediated bone resorption, resulting in insufficiency fractures. The vertebrae, femoral neck and distal radius were most commonly affected. Myopathy was a common manifestation of hyperthyroidism, especially in the proximal muscles of the extremities. In Graves’ disease (hyperthyroidism), acropachy could manifest, but it was uncommon, occurring in the healing phase, when the patient would be euthyroid or hypothyroid and it was almost always connected to ophthalmopathy, and sometimes also to pretibial myxedema. Acropachy mostly affect the metacarpal bones (hands), sometimes the metatarsals (feet) and less commonly the phalanges (fingers). The prevalence of adhesive capsulitis was referring to the article “Musculoskeletal manifestations in patients with thyroid disease” by Cakir et al., where it was stated as 7,1% for patients with hyperthyroidism. See details in table 4.

Table 4 Musculoskeletal findings in hyperthyroidism

<table>
<thead>
<tr>
<th>Musculoskeletal findings in hyperthyroidism</th>
<th>Affected patients, in % of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteopenia and osteoporosis with insufficiency fractures</td>
<td>3,5-50%</td>
</tr>
<tr>
<td>Myopathy with atrophy and fatty infiltration (primarily proximal muscles of extremities)</td>
<td>Up to 67%</td>
</tr>
<tr>
<td>Acropachy, ophthalmopathy and pretibial myxedema</td>
<td>0,5-1%</td>
</tr>
<tr>
<td>Adhesive capsulitis</td>
<td>7,1%</td>
</tr>
</tbody>
</table>
For young patients with hypothyroidism, epiphyseal ossification was delayed and occurred from multiple ossifications center, making it irregular in appearance. It was the femoral and humeral heads which were most commonly affected, and with hormone replacement therapy the changes were reversed. For adults, the most common findings were proximal muscle myopathy in between 25% to 79% of patients, Dupuytren’s contracture in 21.7% and CTS 30.4% (the last two referring to figures from Cakir et al.).

Table 5 Musculoskeletal findings in hypothyroidism

<table>
<thead>
<tr>
<th>Musculoskeletal findings in hypothyroidism</th>
<th>Affected patients, in % of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed skeletal maturation &amp; fontanelle closure (children), irregular or stippled epiphyses (young)</td>
<td>No figure given</td>
</tr>
<tr>
<td>Proximal muscle myopathy</td>
<td>25-79%</td>
</tr>
<tr>
<td>Dupuytren’s contracture</td>
<td>21.7%</td>
</tr>
<tr>
<td>Carpal tunnel syndrome</td>
<td>30.4%</td>
</tr>
</tbody>
</table>
3.2.9 Article summary

Title: Bone and Joint Manifestations of Hypothyroidism

Authors: McLean, R. M., & Podell, D. N.

Publication date and forum: February 1995 in Seminars in Arthritis and Rheumatism

Main area of research: Thyroid hormones have known effects on cell proliferation and differentiation of bone and cartilage, and as a consequence of dysregulation of thyroid hormones the following could appear: epiphyseal dysgenesis, aseptic necrosis, crystal-induced arthritis and arthropathy with highly viscous non-inflammatory joint effusions most commonly affecting knees, wrists and hands. Neuropathic and myopathic symptoms associated with hypothyroidism, such as CTS or muscle weakness and pain, could also manifest as joint region complaints, without actual arthropathy. The overall focus of the article was bone and joint abnormalities as the primary manifestation of hypothyroidism, and the authors suggested that thyroid dysfunction should be considered in the differential diagnosis of various musculoskeletal symptoms. The authors presented an unusual case where first knee pain, then hip pain were the isolated symptoms in a severely hypothyroid young man. The patient was first diagnosed with tenosynovitis in his right knee, but the pain remained, the patient was re-evaluated, and plain radiograph was normal. The second diagnosis was knee sprain, the treatment was 10 days in an immobilizer orthosis. During the follow-up visit, the knee was considered normal, but the hip was painful. A radiograph of pelvis and hips was normal, but a magnetic resonance imaging scan showed an effusion at the hip. More tests and images were performed which showed demineralization of the femoral head, and cartilage and bone destruction in the acetabulum. The patient had no other joint pains, no symptoms of systemic disease, did not take any medications or have any history of trauma. The physical examination displayed full, painless range of motion, no joint tenderness and the musculoskeletal examination was normal. The neurological examination showed normal strength, except for a possible delay in deep tendon reflex relaxation. Among several other laboratory tests, thyroid hormone levels were included and clearly indicated a hypothyroid state. After being treated with thyroid hormone replacement the hip pain went away within 2-3 months, and by that time the patient was euthyroid. One year later a radiograph showed a normal hip and the patient was well. The article raises two similar cases previously
reported and points out that since other signs and symptoms are more prevalent in hypo-
thyroidism, skeletal and arthritic complaints are often either misinterpreted or over-
looked. Several other studies are referred to, which include joint issues in hypothyroid-
ism, like abnormal epiphyses (in children or young adults) and patients referred for ar-
thritis evaluation who had normal rheumatological test results but were found to be hy-
pothyroid. The authors listed five bone and joint conditions which might be associated
with hypothyroidism;

- epiphyseal dysgenesis,
- slipped capital femoral epiphysis,
- aseptic necrosis,
- pseudogout/gout and
- erosive osteoarthritis.

The characteristics of hypothyroid arthropathy were noninflammatory effusions, elevated
synovial fluid viscosity and knee, hand and wrist involvement. Other musculoskeletal
manifestations from Graves’ disease (hyperthyroidism) were acropachy and myxedema,
from hypothyroidism adhesive capsulitis, proximal myopathy and Hoffman’s syndrome.
The authors concluded that symptoms of hypothyroidism often are diffuse and wide-
ranging, making the process of diagnosis more difficult and they suggested that thyroid
hormone testing would be considered in case of unusual or unexplained skeletal abnor-
malities.

3.2.9.1 Results of relevance for the study at hand

All results from the study are relevant. Hypothyroid arthropathy is well described. The
study stressed the importance of being open to abnormal displays of thyroid disorders,
in order to increase the chances of a quick diagnosis and recovery. From an osteopathic
perspective, recognizing the diffuseness and width of the skeletal and joint symptoms
from thyroid disorders and understanding when to include them in differential diagnosis
could help the patient a lot.
3.2.10 Overview of the results of the included studies

Figures 5 and 6 below are overviews of the results of the articles included this study, with the neuromusculoskeletal complaints and diagnoses listed. For patients with hyperthyroidism a vast majority of patients reported neuromuscular symptoms, most of which was confirmed to be clinical weakness and neuropathies. Myopathy, muscle weakness and stiffness together with atrophy were very common. 76% suffered from tremor and 38% had hyperreflexia. The soft tissues diagnoses were generally located in the upper extremities, with Dupuytren’s contracture, CTS and adhesive capsulitis being the most prevalent. The skeletal issues related to osteopenia and osteoporosis had a very wide prevalence range (3.5-50%).

![Figure 5 Neuromusculoskeletal pain syndromes for patients with hyperthyroidism](image)

For patients with hypothyroidism, the neuromuscular complaints were even more common than in patients with hyperthyroidism, the confirmed weakness was less, and the neuropathies were twice as prevalent. The diagnoses of hypothyroid myopathy and hypothyroid arthropathy were described and linked to clinical representation. The prevalence of soft tissues diagnoses was higher, sometimes 2-3 times higher, than in patients with hyperthyroidism. The most common were CTS, followed by Dupuytren’s contracture and adhesive capsulitis. The joint and skeletal issues besides hypothyroid arthropathy, were more varied than in patients with hyperthyroidism, with irregular epiphyses, aseptic necrosis and erosive osteoarthritis.

From a clinical perspective, it was important to note that both hyper- and hypothyroidism could be manifested only by neurological, muscular or skeletal symptoms and signs. The
relatively high prevalence of patients with residual symptoms was both highly relevant and essential to understand, in order for a more complete recovery to be achieved.

Figure 6 Neuromusculoskeletal pain syndromes for patients with hypothyroidism
4 Discussion and Conclusion

4.1 Discussion of methods in included studies

There were no RCTs included in this study, since there were no such hits in either of the searches performed. The lack of RCTs might have negatively influenced the level of evidence and grade of recommendations, but reflected the study topic, where either the thyroid or the neuromusculoskeletal disorder needed to be known (by the patient and the practitioner/medical staff) in order for a potential association to be investigated, and also the conscious exclusion by the author of any evaluation of treatment methods or techniques for either condition.

Only one study used blinding (Duyff et al., 2000); in general, the case-control and cohort studies could have benefitted from the use of blinding, of both subject and practitioner, when it came to tests and evaluations, in order to increase the credibility of the findings.

Since only four studies out of nine contained follow-up periods (McKeran et al., 1975, Qianrui et al., 2017, Duyff et al., 2000, McLean & Podell, 1995), there was a lack of descriptions of development over time – both of disorders and recovery – which potentially negatively affected both the internal and external validity. The perspective of time as to the diagnosis of the thyroid disorder was dissimilar; the subjects were recently diagnosed in six studies (McKeran et al., 1975, Qianrui et al., 2017, Duyff et al., 2000, Özek et al., 2018, Cakir et al., 2003, McLean & Podell, 1995), previously diagnosed subjects were mixed with those diagnosed during one study (Schiefer et al., 2017) and two studies included only previously diagnosed subjects (Berlanga-de-Mingo et al., 2019, Boswell et al., 2014). None of the nine studies mention this aspect but considering the difference in the presenting symptoms of thyroid disorders, transient symptoms after start of treatment and the potential residual symptoms, the author considers this dimension should have been covered, in at least some of the studies, to improve the validity of the results.

The documentation of the studies’ respective ethics, declaration of competing or conflicting interests as well as financial support was insufficient. The quality of the included articles varied; the authors’ presentations of their objectives and methods, the level of detail and the results differed quite a lot.
4.2 Discussion of results

Thyroid disorders are common worldwide and patients suffering from them frequently have neuromusculoskeletal complaints, before diagnosis but also during treatment. This study focused on investigating which pain syndromes were associated with the diagnoses of hyper- and hypothyroidism and to present these in an overview.

The results from the studies related to the diagnosis of hypothyroid myopathy demonstrated atrophy, type 2 muscle fiber loss and confirmed the patient’s experience of persisting weakness (McKeran et al., 1975), for up to six years after euthyroidism was achieved (Özek et al., 2017). The persisting weakness could be included in the residual symptoms reported by up to a third of euthyroid patients (Duyff et al., 2000, Chiovato et al., 2019). A study by Moncayo and Moncayo (2014) explored the topic of residual symptoms in patients with hypothyroidism and the effect thereof on their quality of life. They listed fatigue, instability and weakness among the main complaints from patients. In a review by McAninch and Bianco (2016), 10-15% of patients with hypothyroidism reported residual symptoms, and another 15% of patients did not achieve normal T3 levels with the monotherapy of levothyroxine, which could also produce residual symptoms. Both Chiovato et al. (2019) and McAninch and Bianco (2016) raised the possibility of an insufficient ratio of T4:T3 as a potential cause of residual symptoms. Midgley et al. (2019) instead pointed to the low-dose medication policy which had been adopted in recent years to explain the current and ongoing rise in patient complaints for residual symptoms.

In a systematic review of 29 studies by Cheng (2018), the cost-effectiveness and safety of using acupuncture alone or in combination with relevant medication for treatment of thyroid disorders and residual symptoms was investigated. The combined results indicated that the patients’ symptoms were reduced, and their biomarkers improved.

Qianrui et al. (2017) linked hypothyroid myopathy to the treatment of hyperthyroidism, which seems to be an exception worth noting for differential diagnosis in clinical practice. Another rare event related to hypothyroid myopathy was reported in the study by Sansone et al. (2000), which raised the possibility that hypothyroidism could increase the symptoms of proximal myotonic myopathy (PROMM), a genetic condition, in which the symptoms might be incorrectly interpreted as derived from hypothyroid myopathy.

Özek et al. (2018) accentuated that neuromuscular complaints could be the only presenting symptom of hypothyroidism, and this view was supported by Duyff et al. (2000),
where 36% of the patients with hyperthyroidism, and 16% of the patients with hypothyroidism, had listed muscular complaints as the reason for the doctor’s visit. The neuromuscular complaints experienced by 67% and 79% of patients with newly diagnosed hyper- and hypothyroidism, were linked to clinical weakness, CTS and neuropathy (Duyff et al., 2000). A study by Yerdelen et al. (2010) also reported neuropathy findings, describing axonal injury and/or demyelination which gave rise to peripheral mononeuropathy, polyneuropathy and entrapment neuropathies in patients with hypothyroidism. The authors also added that in absence of neuropathy, they found increased threshold values and thereby decreased axonal excitability in patients with hypothyroidism, which normalized during hormone replacement therapy.

Cakir et al. (2003) explored the prevalence of certain musculoskeletal diagnoses in patients with thyroid disorders and supported the findings of CTS in patients with hypothyroidism by Duyff et al. (2000). Schiefer et al. (2017) found a significant difference in the prevalence of hypothyroidism among patients with adhesive capsulitis, and also in the age range of 40-60 years, in contrast to Cakir et al. (2003) who found no occurrences of adhesive capsulitis among patients with hypothyroidism, but instead quite a few with subclinical hyperthyroidism. Berlanga-de-Mingo et al. (2019) investigated the association between thyroid disorders and multiple trigger fingers and found no significant differences, but the prevalence trigger finger was similar to figures from Cakir et al. (2003).

The studies related to joint complaints indicated several types of joint issues could be related to thyroid disorders and raised especially hypothyroid arthropathy (Boswell et al., 2014, McLean & Podell, 1995). However, detailed prevalence was missing, and this is an area where further research would be desirable. McLean and Podell (1995) emphasize that thyroid disorders should be a differential diagnosis in cases of skeletal and joint complaints, since this could be the presenting symptoms.

The combined data in this study suggested that thyroid disorders exhibit a wide range of signs and symptoms, often in several of the systems of the body. This high variability complicated the diagnosis of the thyroid disorder and of any comorbidities. Several neuromusculoskeletal disorders could accompany a thyroid diagnosis or be the initial manifestation of it. As exhibited by Boswell et al. (2014) thyroid disorders could be indicated by specific radiological findings, or by neuromuscular symptoms and signs such as weakness, neuropathy, hypo- or hyperactive deep tendon reflexes or tremor (Duyff et al., 2000) or by skeletal and joint complaints (McLean & Podell, 1995). The results of this
study fit with current research and knowledge, where thyroid disorders are often associated with neuromusculoskeletal complaints and diagnosis, both before diagnosis and during treatment.

4.3 Discussion of clinical relevance and connection to osteopathy

The results of this study were relevant from a clinical perspective, since the included studies provided a background and context to some of the neuromusculoskeletal issues which were associated to patients with thyroid disorders and indicated that thyroid disorders should be included in the process of differential diagnoses for various neuromusculoskeletal complaints. A skeletal, muscular or neurological symptom could be the only manifestation of a thyroid disorder, and if caught early and investigated by medical staff, recovery was usually quick and more complete. If the patient was biochemically compensated and stable, it was however also of clinical relevance to note and act on any residual skeletal, muscular or neurological issues that might be related to the patient’s thyroid disorder.

From a specific osteopathic clinical perspective, a study by Sonberg et al. (2010) focused on osteopathic treatment of residual symptoms of musculoskeletal pain, where the same general treatment protocol was given to all 18 participants on three occasions. The results were statistically significant improvements in pain intensity score and in pain interference with daily life.

Considering the holistic aspect of osteopathy, the results from this study suggest that patients with thyroid disorders could greatly benefit from osteopathic treatment as a complement to medication and as part of a multimodal approach with person-centered care. The osteopath could be treating the neurological, muscular and skeletal associated symptoms and residual complaints of confirmed thyroid disorders but could also be identifying early warnings of thyroid disorders, when the presentation is partly or mainly neuromusculoskeletal.
4.4 Future direction

A lot of research has been performed on thyroid disorders and a lot of progress has been made with regards to medication, reduction of symptoms and the prevention of long-term complications. But there is still a need for more knowledge and further advancements in order to secure better quality of care and of life for patients with thyroid disorders. Since the global prevalence is relatively high, the costs for treatments are also relatively high, especially considering the increased number of sick days and increased mortality for these patients, but also the associated comorbidities (including neuromusculoskeletal issues). In addition, the societal and individual costs for patients who are undiagnosed, untreated or undertreated should be able to be decreased (Chiovato et al., 2019). Any research related to how to minimize residual symptoms while achieving complete recovery from thyroid disorders and their associated neuromusculoskeletal issues would be desirable.

In light of the recent increase in residual symptoms, research into the optimisation of treatment would be desired. Ideally, the treatment should be taking into consideration the recent findings of the T4:T3 ratio, the interrelationship between TSH, T4 and T3 and the need to establish more individualized reference ranges for TSH to meet the current patient demands of a multi-modal approach and person-centered care. Brown et al. (2005) advocated the use of a biopsychosocial model in the treatment of hypothyroidism, to better cover the wide variety of patient’s symptoms and signs, and refer to an upcoming RCT, which the author of this study has been unable to find. Research into this treatment model would be of interest.

Further research into hypothyroid arthropathy with prevalence and more details about the condition would be beneficial for both clinicians and patients.
4.5 Conclusion

Thyroid disorders are to be considered as relatively common worldwide, especially among women. The identification and recognition of the various neuromusculoskeletal symptoms and signs which could be associated with a diagnosed or an undiagnosed thyroid disorder were important in order to provide correct and fast treatment. Several neuromusculoskeletal disorders could accompany either a thyroid diagnosis or be the initial manifestation of it. Untreated or undiagnosed thyroid disorders and their associated skeletal, muscular and neurological issues cause unnecessary suffering and might have serious and long-term health consequences.

The findings in this study show that various neuromusculoskeletal disorders often coexist with thyroid dysfunction and that about 30% of patients suffer from residual symptoms. Further research into optimal treatment methods and how to minimize residual symptoms to achieve complete recovery would be desirable and beneficial, from the perspective of both society and patients.

4.6 Limitations

The author’s limited experience with data base searches, analysis and evaluation of the search results as well as of the results of studies might have influenced the choice of included articles, the understanding of the selected articles and their respective results. This could imply limitations to the presentation and the results of this study.
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