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Musculoskeletal manifestations in patients with thyroid disease

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Summary

OBJECTIVE Thyroid dysfunction may cause musculoskeletal symptoms. We have evaluated the prevalence of adhesive capsulitis, Dupuytren's contracture, trigger finger, limited joint mobility and carpal tunnel syndrome in a series of patients with various thyroid diseases and differing levels of function.

DESIGN AND PATIENTS Patients with euthyroid (diffuse and/or nodular) goitre, Hashimoto's thyroiditis, Graves' disease, toxic nodular goitre, toxic diffuse goitre and patients with goitre who had partial thyroidectomy were included in the study (n = 137). Neurological and musculoskeletal examinations were performed after a standardized symptom questionnaire. The prevalence of musculoskeletal problems was analysed with respect to thyroid function and thyroid autoantibody status.

MEASUREMENTS Serum concentrations of free T3, free T4, TSH and thyroglobulin and thyroperoxidase antibodies were determined. Serum levels of creatine kinase, lactate dehydrogenase, calcium and phosphate along with erythrocyte sedimentation rate were measured to exclude other causes of musculoskeletal complaints.

RESULTS When the study group (n = 137) was divided according to thyroid status, 30·6% (n = 42) were thyrotoxic, 16·8% (n = 23) had subclinical thyrotoxicosis, 28·5% (n = 39) were euthyroid, 7·3% (n = 10) had subclinical hypothyroidism and 16·8% (n = 23) were hypothyroid. Overall, adhesive capsulitis was found in 10·9% (n = 15), Dupuytren's contracture in 8·8% (n = 12), limited joint mobility in 4·4% (n = 6), trigger finger in 2·9% (n = 4) and carpal tunnel syndrome in 9·5% (n = 13) of the patients. The prevalence of adhesive capsulitis was highest in patients with subclinical thyrotoxicosis (17·4%); Dupuytren's contracture, limited joint mobility and carpal tunnel syndrome were commonest in hypothyroid patients (21·7%, 8·7% and 30·4%, respectively). Trigger finger occurred in 10% of patients with subclinical hypothyroidism. When these prevalences were analysed with respect to thyroid status, carpal tunnel syndrome was significantly more prevalent in the hypothyroid group (P = 0·004). When thyroperoxidase antibody-positive and -negative patients were compared, adhesive capsulitis negatively (P = 0·03, r = −0·18) and trigger finger positively correlated with (P = 0·03, r = 0·21) thyroperoxidase antibody existence.

CONCLUSIONS These results demonstrate that musculoskeletal disorders often accompany thyroid dysfunction. In addition to the well-known observation that these disorders are common in patients with hypothyroidism, they are also observed in patients with thyrotoxicosis. Patients with thyroid dysfunction should be questioned for musculoskeletal complaints and referred to a specialist if necessary.

Hypothyroidism and thyrotoxicosis may cause signs and symptoms of musculoskeletal dysfunction (Cronin, 1997; Baran, 2000). Muscle weakness and wasting are common clinical manifestations of thyrotoxicosis. Carpal tunnel syndrome, mononeuropathy and symmetric peripheral neuropathy have also been described, albeit rarely (Boyages, 2000). Hypothyroid patients, on the other hand, often complain of articular and muscular pains and even may present with joint effusions involving knees or small joints. Myopathy suggesting polymyalgia rheumatica, nerve entrapment and tenosynovitis are diagnoses that should be considered in these patients. A variety of musculoskeletal symptoms and signs have been reported in patients with thyroid diseases (Rossner *et al*., 1977; Duyf *et al*., 2000). From the perspective of rheumatology, the prevalance of thyroid function test abnormalities in connective tissue diseases has also been investigated (Arnaout *et al*., 1994). In patients without a known diagnosis of rheumatological disease, the skeletal and muscular

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complaints may be underestimated as these patients are seen primarily by endocrinologists. This study investigates the prevalance of musculoskeletal manifestations in patients with different levels of thyroid function and autoantibody status. These musculoskeletal disorders include adhesive capsulitis (AC), Dupuytren's contracture (DC), trigger finger (TF), limited joint mobility (LJM) and carpal tunnel syndrome (CTS).

Patients and methods

One hundred and thirty-seven patients (111 female, 26 male) who visited the endocrinology outpatient clinic and had diffuse and/or nodular goitre with normal or abnormal thyroid function tests on their first visit were recruited to the study. Based on their clinical diagnosis, the study group included patients with euthyroid diffuse or nodular goitre, Hashimoto's thyroiditis, Graves' disease, toxic nodular goitre, toxic diffuse goitre and patients with goitre who had partial thyroidectomy. According to thyroid hormone levels patients were allocated into five categories: thyrotoxicosis, subclinical thyrotoxicosis, euthyroid, subclinical hypothyroidism and hypothyroidism. Hypothyroidism was defined as low free T3 (fT3) and/or free T4 (fT4) with elevated TSH levels; subclinical hypothyroidism was defined as elevated TSH with normal thyroid hormone levels; euthyroidism was defined as normal fT3, fT4 and TSH levels; subclinical thyrotoxicosis was defined as suppressed TSH with normal thyroid hormone levels; and thyrotoxicosis was defined as high fT3 and/or fT4 levels accompanying suppressed TSH. Hypothyroid and thyrotoxic patients also had signs and symptoms of thyroid dysfunction, while subclinical hypothyroid, subclinical thyrotoxic and euthyroid groups were clinically symptom-free. Toxic nodular goitre was defined as one or more hot nodules on scan with subclinical or overt thyrotoxicosis. Graves' disease was diagnosed when the patient had positive thyroperoxidase antibodies (TPO Ab) and/or thyroglobulin antibodies (Tg Ab) with subclinical thyrotoxicosis or thyrotoxicosis. Some patients, whose Graves' disease had been diagnosed previously, were in remission and their hormone levels were within normal limits. Hashimoto's thyroiditis was defined as positive TPO Ab and/or Tg Ab, a heterogenous parenchyma on thyroid ultrasound and hormone levels consistent with hypothyroidism or subclinical hypothyroidism or euthyroidism. When thyrotoxicosis and diffuse goitre with undetectable thyroid autoantibodies were noted, toxic diffuse goitre was diagnosed. Patients with euthyroid diffuse and/or nodular goitre had no history of hypo-/hyperthyroidism and had normal hormone levels. The last group of patients had goitre with a past history of partial thyroidectomy for benign nodular thyroid disease and were euthyroid, subclinical hypothyroid or hypothyroid.

As local trauma, myocardial infarction, hemiplegia, Pancoast tumour, cerebral tumour and epilepsy have been described in association with the development of AC, patients with these diseases were excluded (Balci *et al*., 1999). Patients with chronic diseases (e.g. diabetes mellitus, alcoholism, liver, kidney disease, connective tissue diseases) and drug use liable to cause musculoskeletal disease or neuropathy and other serious illnesses were also excluded.

After their diagnosis of thyroid disease, patients were directed to the Department of Physical Medicine and Rehabilitation for examination. Before neurological and musculoskeletal examinations, a standardized symptom questionnaire was completed including questions about sensory symptoms (paraesthesias and dysaesthesia in the hand and feet, painful tingling in the wrists and hands, mainly in the thumb, index, middle finger), muscle weakness (difficulty in daily activities), restricted joint mobility (difficulty in shoulder movements, raising the arms), musculoskeletal pain (shoulder and muscle pain, widespread pain, morning stiffness, fatigue). On neurological examination, deep tendon reflexes, sensory modalities (touch, pin-prick), muscle strength and pathological reflexes were evaluated. Range of movement of joints, effusion or swelling of joints were assessed. For CTS, Tinnel and Phalen tests were performed and nerve conduction studies were undertaken for patients with positive tests. The diagnostic criteria used for shoulder AC were as follows: shoulder pain for at least 1 month, inability to lie on the affected shoulder and restricted active and passive shoulder joint movements in at least three planes for maximal passive abduction, internal rotation and external rotation movements of one or both shoulder joints (Pal *et al*., 1986). To confirm LJM, patients were asked to approximate the palmar surfaces of fingers in a praying position with fingers fanned and wrists maximally dorsi-flexed. If the patient failed to approximate the palmar surfaces completely, the examiner attempted to extend the fingers passively. Equivocal or unilateral findings or simply a sense of unlimited resistance was accepted as normal joint mobility. Failure of any joint to make contact was classified as LJM (Rosenbloom *et al*., 1981). The diagnosis of DC was made by one of the authors (PETA) observing one or more of the four features: palmar or digital nodule, tethering of palmar or digital skin, a pretendinous band and digital contracture (Noble *et al*., 1984). Although not planned as a parameter of the study fibromyalgia syndrome (FMS) was also assessed in our patients. The diagnosis of FMS was made according to criteria of American College of Rheumatology (Hazleman, 1998).

Chemiluminescence assays were used for measurements of fT3, fT4, TSH, Tg Ab and TPO Ab levels, as follows: serum concentrations of fT4 (Immulite, 2000; Diagnostic Products Corporation, Los Angeles, CA, USA); fT3 (Immulite, 2000; Diagnostic Products Corporation, LA, USA); TSH (Third-Generation TSH & Immulite, 2000; Diagnostic Products Corporation); Tg Ab (Immulite, Diagnostic Products Corporation); TPO Ab (Immulite, Diagnostic Products Corporation). Reference values

were 0·35–5·5 μIU/l for TSH, 11·5–23·2 pmol/l for fT4 and 3·5–6·5 pmol/l for fT3. Creatine kinase (CK total), lactate dehydrogenase (LDH), erythrocyte sedimentation rate, calcium and phosphate were measured in order to exclude other possible factors causing musculoskeletal problems.

Statistical analysis

The distribution of musculoskeletal problems was calculated as percentages according to thyroid status. The prevalances were compared with Chi-square test. Correlations were done with Spearman's test. A *P*-value below 0·05 was considered statistically significant.

Results

The mean age of the study group was 46 ± 12 (20–76) years, while 81% were female and 19% male. When divided according to thyroid status, 30·6% ($n = 42$) had thyrotoxicosis, 16·8% ($n = 23$) had subclinical thyrotoxicosis, 28·5% ($n = 39$) were euthyroid, 7·3% ($n = 10$) had subclinical hypothyroidism and 16·8% ($n = 23$) were hypothyroid (Fig. 1). The distribution of thyroid diseases was: 27·7% ($n = 38$) toxic nodular goitre, 19% ($n = 26$) euthyroid diffuse and/or nodular goitre, 19·7% ($n = 27$) Hashimoto's thyroiditis, 19·7% ($n = 27$) Graves' disease, 10·2% ($n = 14$) patients with goitre who had thyroidectomy and 3·7% ($n = 5$) toxic diffuse goitre. Thyroid diseases and status are shown in Table 1. As expected, hypothyroidism was generally seen in patients with Hashimoto's thyroiditis and most of the thyrotoxic patients had toxic nodular goitre. Mean values of thyroid hormone levels are seen in Table 2. Table 3 shows total number and prevalences of musculoskeletal problems in the whole group. Adhesive capsulitis was the most common problem, affecting 10·9% of patients. The distribution of musculoskeletal problems according to thyroid status is shown in Fig. 2. Although the prevalences were quite different between the groups, a statistically significant difference was noted only for CTS, with a prevalence of 30·4% in the hypothyroid group ($P = 0·004$). When TPO Ab-positive and -negative patients were compared, TF was significantly more prevalent in the TPO Ab-positive group ($P = 0·03$, $r = 0·21$), and a significant negative correlation between AC and TPO Ab positivity was noted ($P = 0·03$, $r = -0·18$; data not shown).

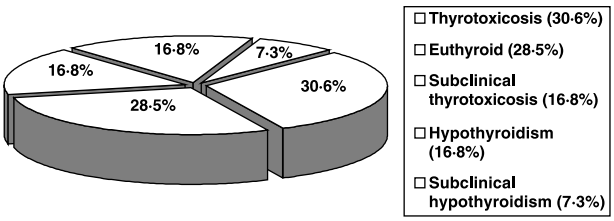

Fig. 1 Distribution of the study group according to thyroid status.

Table 1 Distribution of thyroid diseases according to hormone status

Status	Euthyroid goitre* % (*n*)	Hashimoto's thyroiditis % (*n*)	Graves' disease % (*n*)	Toxic nodular goitre	Toxic diffuse goitre % (*n*)	Patents with goitre who had thyroidectomy % (*n*)	Total % (*n*)
Thyrotoxic	–	–	47·6 (20)	47·6 (20)	4·8 (2)	–	100 (42)
Subclinical thyrotoxic	–	–	21·7 (5)	69·6 (16)	8·7 (2)	–	100 (23)
Euthyroid	66·6 (26)	15·4 (6)	5·1 (2)	2·6 (1)	–	10·3 (4)	100 (39)
Subclinical Hypothyroid	–	70 (7)	–	–	–	30 (3)	100 (10)
Hypothyroid	–	61 (14)	–	4·3 (1)†	4·3 (1)†	30·4 (7)	100 (23)

*Euthyroid diffuse and/or nodular goitre.
†Although original diagnosis was TNG and TDG, patient was hypothyroid at the time of study because of past radioactive iodine therapy.

Table 2 Median (range) of hormone levels in all categories of hormone status

Status	Free T3 (pmol/l)	Free T4 (pmol/l)	TSH (μU/ml)
Thyrotoxicosis	10·2 (4·2–30·8)	28·4 (12·9–112·2)	0·01 (0–0·01)
Subclinical thyrotoxicosis	4·5 (2·6–6·5)	16·8 (11·6–23·2)	0·05 (0·01–0·26)
Euthyroid	4·3 (1·8–5·7)	14·2 (11·6–22·4)	0·97 (0·4–5·3)
Subclinical hypothyroidism	4 (3·5–4·9)	12·9 (11·6–15·5)	7·4 (5·8–23·6)
Hypothyroidism	3·2 (1·1–6·3)	7·7 (1·29–11·6)	29 (6–339)

Table 3 Prevalences of musculoskeletal problems in the study group

Diagnosis	*n* (%)
Adhesive capsulitis	15 (10·9)
Dupuytren's contracture	12 (8·8)
Limited joint mobility	6 (4·4)
Trigger finger	4 (2·9)
Carpal tunnel syndrome	13 (9·5)
Fibromyalgia syndrome	10 (7·3)

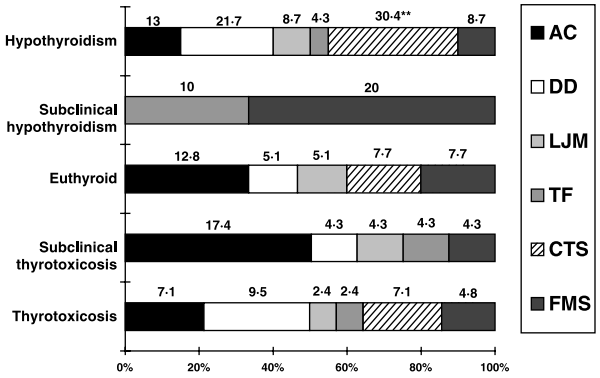

Fig. 2 Prevalence of musculoskeletal problems according to thyroid status (S, subclinical; AD, adhesive capsulitis; DC, Dupuytren's contracture; LJM, limited joint mobility; TF, trigger finger; CTS, carpal tunnel syndrome; FMS, fibromyalgia syndrome). $^{**}P = 0{\cdot}004$ (when prevalence of CTS in hypothyroid group is compared with other groups).

Discussion

Musculoskeletal disorders are rarely the presenting symptoms in patients with thyroid dysfunction. Variable prevalences of these disorders have been reported previously, and are generally based on neuropathy- and myopathy-complicating thyroid diseases. The current study was designed primarily to determine the prevalence of musculoskeletal system disorders in hypothyroid and thyrotoxic patients.

Adhesive capsulitis, also known as frozen shoulder, is a regional skeletal problem reported in association with thyroid disorders, in addition to other diseases such as diabetes mellitus, coronary artery disease, cerebrovascular events, pulmonary disorders and epilepsy (Lee & Khunadorn, 1986; Deal, 1998; Balci *et al*., 1999). The prevalence of primary idiopathic AC in the general population has been reported as 2–3% (Siegel, 1999). Case reports relating AC with hypothyroidism (McGrory & Endrizzi, 2000), hyperthyroidism (Wohlgethan, 1987; Molinier *et al*., 1998), and two controlled studies from the 1970s proposing a link between AC and altered thyroid function (Wright & Haq, 1976; Rossner *et al*., 1977), exist in the literature. The association of AC with thyrotoxicosis was attributed to the close resemblance of hyperthyroidism to activation of the sympathetic nervous system. Prevalence studies from the 1950s reported AC as between 1·7% and 27% in thyrotoxicosis (Baran, 2000). As TSH could not be measured at that time, subclinical thyrotoxic patients would have been missed. Nevertheless, the prevalence of AC (10·8%) in our study was in the range previously noted, when subclinical thyrotoxic and thyrotoxic patients were evaluated as a whole (data not shown).

Patients with hypothyroidism often complain of muscular pain and stiffness of extremities (Klein & Ojamaa, 2000). Pain and paraesthesiae in the fingers, sometimes secondary to tenosynovitis, but mostly to CTS, is a frequently observed complaint in hypothyroidism. It has been suggested that a combination of mild compression within the carpal tunnel and neuropathy due to hypothyroidism-induced demyelinization may occur in the affected nerve. It also appears that many hypothyroid patients continue to experience CTS symptoms even after achieving the euthyroid state (Kloppenburg *et al*., 1993; Palumbo *et al*., 2000).

Widely differing prevalences of CTS have been reported in different countries. In a population-based study from the USA, self-reported CTS had a prevalence of 1·5% among adults (Tanaka *et al*., 1994), whereas in Sweden, self-reported prevalence rates reached 14·4%. Based on electrophysiological studies, however, the prevalence was only 3·8% in another study (Atroshi *et al*., 1999). However, much higher rates are observed in hypothyroidism. Median nerve compression has been found in 5–80% of cases (Cruz *et al*., 1996; Cronin, 1997; Duyf *et al*., 2000). Conversely, several series have observed hypothyroidism in 6·7–10% of patients with CTS (Cronin, 1997). In our hypothyroid group, 30·4% of patients were diagnosed to have CTS and the difference was statistically significant ($P = 0{\cdot}004$).

Several hypotheses have been proposed to explain the aetiology of nerve entrapment in hyperthyroid patients. Infiltration of tendon sheaths with mucopolysaccharides, and the influence of thyroid hormone on axonal function demonstrated by neurophysiological analysis, are two of these. Based on our literature research, other than case reports, there is only one prospective study regarding the association between CTS and thyrotoxicosis (Roquer & Cano, 1993). In this particular study, the prevalence of CTS in 60 thyrotoxic patients followed for a 2-year period was reported as 5%, which is comparable to the 7·1% reported in our study.

Although not found to be directly related to thyroid dysfunction, patients with FMS were shown to have a blunted response of TSH and thyroid hormones to TRH stimulation (Neeck & Riedel, 1992; Riedel *et al*., 1998; Boyages, 2000). This blunted response and some other hormonal changes (suppression of gonadal function, an augmented response to ACTH) in patients with FMS were interpreted as an adjustment of the CNS to chronic pain and stress. This is primarily evoked by activated corticotropin-releasing hormone (CRH) neurones. CRH

stimulates somatostatin secretion at the hypothalamic level and this, in turn, causes inhibition of GH and TSH secretion at the level of the pituitary (Neeck & Crofford, 2000). In a survey of 554 individuals with FMS, thyroid problems were noted more frequently than in the control group (Waylonis & Heck, 1992). On the other hand, in a prevalance study in 100 patients with subclinical or clinical hypothyroidism, a diagnosis of fibrositis was made in 5% of the patients and it was concluded that fibrositis itself is not common in hypothyroid patients, although symptoms suggesting this disorder were common (Carette & Lefrancois, 1988). In our study, when subclinical and clinical hypothyroid patients were evaluated as a whole, the prevalence of FMS was 8·8%, but this rate did not reach a statistical significance when compared to euthyroid patients (data not shown). Unfortunately, there is no population-based prevalence study for FMS in Turkey. Nevertheless, in the previous studies, the prevalence of FMS has been reported at 2–3·3% in the general population (Wolfe *et al*., 1995; White *et al*., 1999).

As connective tissue diseases are well-known to have a strong autoimmune basis, a relationship between these disorders and autoimmune thyroid diseases may be expected. Studies suggesting an association between autoimmune thyroiditis and connective tissue diseases such as rheumatoid arthritis and systemic lupus erythematosus (SLE) have been reported (Shiroky *et al*., 1993; Arnaout *et al*., 1994). Anti-microsomal antibodies were found, with the highest incidence in patients with SLE in a large group of patients with connective tissue disorders (Arnaout *et al*., 1994). In an investigation of the mechanisms of arthritis associated with chronic lymphocytic thyroiditis, mild polyarthritis and oligoarthritis were observed in the absence of thyroid dysfunction (Punzi *et al*., 1997). The arthritis probably has an autoimmune basis in these patients. In the follow-up period, however, some patients developed severe rheumatoid arthritis, whereas other patients did not. In a very interesting study by Blake *et al*. (1979), microsomal and thyroglobulin autoantibody activity was detected in the synovial fluid of patients with various forms of arthritis, including rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and gout. Although only four of the serum samples were positive for thyroid autoantibodies, 34 of the 50 patients' synovial fluid samples were positive for autoantibody activity. A survey performed in Norway showed a significantly higher prevalence of detectable antimicrosomal antibodies in persons with than without musculoskeletal complaints (Aarflot & Bruusgaard, 1996). In our study, a significant negative association was noted between AC and TPO Ab positivity, while TF was significantly more common in TPO Ab-positive patients. These results are not surprising as primary or idiopathic AC is not common and no autoimmune disturbances or association with histocompatibility antigens have been shown previously in this disorder (Fam, 1998). However, in another study, 40 patients with AC showed a pretreatment increase in circulating immune-complex levels and C-reactive protein compared to control group. Repeated measurements after 8 months showed a decline in these values towards control levels (Bulgen *et al*., 1982). The prevalence of TF has been investigated primarily in studies of occupational- and sports-related musculoskeletal disorders. An association between TF and autoimmunity is a novel finding of this study.

To the best of our knowledge, DC and LJM have not been studied previously in patients with thyroid disease. In population-based studies, LJM affects up to 5% (Renard *et al*., 1994), whereas DC had an estimated prevalence of 19·2% in men and 4·4% in women (Gudmundsson *et al*., 2000). Our study is the first prevalence study for these musculoskeletal disorders in patients with thyroid diseases. However, no significant relationship was observed with thyroid function or autoantibody positivity, for either DC or LJM.

Our study is the very first prevalence study carried out to determine the above described musculoskeletal disorders in patients with thyroid diseases. With a large number of patients assessed, this study provides important and novel information on the musculoskeletal problems which commonly accompany thyroid diseases.

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