Indications for Requesting Laboratory Tests for Concurrent Diseases in Patients with Carpal Tunnel Syndrome: A Systematic Review

MARISKA A.J. VAN DIJK,1 JOHANNES B. REITSMA,2 JOHAN C. FISCHER,1 and GERARD T.B. SANDERS1*

Background: Carpal tunnel syndrome (CTS) is known as a repetitive motion disorder, but the role of other diseases in the development or prognosis of CTS is uncertain. We reviewed the literature to determine whether there is evidence for an increased prevalence of specific conditions in CTS patients and whether this evidence would support laboratory screening for these conditions.

Methods: Medline, Embase, and Cochrane Controlled Trial Register were searched for key words related to CTS and associated diseases. Relevant articles were selected according to specific criteria. Sources of bias and heterogeneity attributable to differences in study design and in patient selection were investigated by subgroup analysis.

Results: After an initial search, we limited ourselves to three potentially important conditions: diabetes mellitus (DM), hypothyroidism (HT), and rheumatoid arthritis (RA). We identified nine articles with a total of 4908 CTS patients and 7671 controls that met our selection criteria. The nine studies were heterogeneous with respect to clinical and methodologic factors. In general, the prevalence of concurrent diseases was higher in CTS patients than in controls: the pooled odds ratios were 2.2 (95% confidence interval, 1.5–3.1) for DM, 1.4 (1.0–2.0) for HT, and 2.2 (1.4–3.4) for RA. Studies of lower methodologic quality reported, on average, higher odds ratios. Only one study provided information about whether the diagnosis of the concurrent condition was already made at the time of the CTS diagnosis.

Conclusions: We found evidence that the prevalences of DM, HT, and RA are higher in CTS patients, but only one study specifically addressed the issue of the prevalence of nonmanifest cases of the concurrent condition. At present, there is insufficient evidence for routine laboratory screening for concurrent conditions in all newly diagnosed CTS patients.

Carpal tunnel syndrome (CTS) arises as a result of increased pressure in the carpal tunnel, leading to entrapment of the median nerve of the hand in the carpal tunnel. CTS is characterized clinically by pain, numbness, and tingling in the hands. Prolonged episodes of this increased pressure in the carpal tunnel may eventually lead to irreversible nerve dysfunction. Reports on prevalence rates of CTS, as measured by the presence of several clinical symptoms combined with electrodiagnostic nerve conduction delay, estimate the prevalence of CTS in general western European populations at 3.0% (3) to 5.8% (4) for women and 0.6% (4) to 2.1% (3) for men. Peak incidence is at age 50–59.

CTS has long been known as a repetitive motion disorder, whereby repeated movements of the hand cause increased pressure in the carpal tunnel, but during the last decade it became more and more recognized that CTS may have a more complicated etiology, involving other diseases that cause or predispose to CTS.

Conditions that have recurrently been associated with an increased prevalence in CTS patients are diabetes mellitus, thyroid disorders, rheumatoid arthritis, pregnancy, and obesity. Knowing that the prevalence of certain conditions is higher in CTS patients than in the general population could be clinically relevant for two reasons: (a) this knowledge could lead to earlier diagnosis...
of these conditions in CTS patients through specific testing or increased attention to minor symptoms, thereby improving the clinical outcome of that condition (e.g., diabetes mellitus); and (b) confirming the link between a specific concurrent condition and CTS would provide more insight into the pathogenesis of CTS. In return, this could lead to specific recommendations or treatment of the concurrent condition that would help to resolve the increased pressure in the carpal tunnel, thereby leading to decreased CTS symptoms.

Existing guidelines on CTS have focused on the diagnosis and treatment of CTS and paid little attention to the existence of concurrent conditions in CTS patients. For example, the guideline of the American Society of Plastic Surgeons, available via the National Guideline Clearinghouse, has only one paragraph on this subject, which states that “laboratory tests should be performed when systemic disease is suspected”, without providing any evidence (7).

We therefore reviewed the literature to determine whether there is evidence for an increased prevalence of certain conditions in CTS patients and whether this evidence would support laboratory screening for these conditions.

**Materials and Methods**

**SEARCH FOR CANDIDATE CONDITIONS TO BE INCLUDED IN THE REVIEW**

We used the following process to include potential relevant conditions. We asked clinical experts (neurologists) about concurrent conditions they considered in CTS patients and searched for such conditions in clinical guidelines. We also did a search of the literature (including Medline, Embase, and the Cochrane Controlled Trial Register) to find potential relevant conditions that have been associated with CTS. We included a condition in our review if the diagnosis of the condition is made through laboratory testing and if we found two or more articles examining its prevalence in CTS patients.

**SYSTEMATIC SEARCH OF THE LITERATURE**

We did a systematic literature search to identify relevant publications examining the relationship between a particular condition and CTS. We searched the Medline, Embase, and Cochrane Controlled Trial Register databases, using four different queries: (a) carpal tunnel syndrome [mesh] AND prevalence [mesh]; (b) carpal tunnel syndrome [mesh] AND general population [text word]; (c) carpal tunnel syndrome [mesh] AND associated [text word] AND (condition [text word] OR conditions [text word]); (d) carpal tunnel syndrome [mesh] AND risk factors [mesh]. Searches were limited to articles published after 1984 and to studies involving humans. No language selection was made. Searches were performed in May and June 2002.

**SELECTION OF RELEVANT STUDIES AND DATA EXTRACTION**

Abstracts of articles identified by the systematic literature search were screened for eligibility by one reviewer (M.v.D.). Articles were included if they provided data on the prevalence of one of the conditions of interest in a
well-defined group of CTS patients. We did not exclude studies if there was no control group, but we did exclude studies that reported on the prevalence of CTS in a population with a potential concurrent condition (e.g., studies on the prevalence of CTS in diabetic patients). Nine relevant articles could be included based on these criteria. Cross-checking the references of the included articles led to one more article. Subsequently, data from the 10 included articles were extracted independently by two reviewers (M.v.D. and J.R.). One article was excluded at that stage because the selection of CTS patients was unclear (8). We extracted data on the following characteristics of each study: the selection of CTS patients and controls (if present), definition of the concurrent disease(s), whether the study adjusted for confounding by either design or in the analysis, and whether the data collection was prospective or retrospective. Disagreements in data extraction were resolved by consensus.

**Calculation of Odds Ratios**

The majority of the nine included studies (3, 6, 9–15) reported separate prevalence rates for concurrent diseases in CTS patients and in the control group but calculated no measure of association. Because most studies used a case-control design, we calculated odds ratios with 95% confidence intervals (CIs), using the reported prevalence in CTS patients and in the control group. If a study had no control group, we calculated an odds ratio based on the prevalence estimate (upper limit) in the general population: for diabetes mellitus this was 6.5% (16, 17), for hypothyroidism it was 3.0% (18–20), and for rheumatoid arthritis it was 1.0% (21, 22). We used the random effects model of DerSimonian and Laird to pool odds ratios (23). Statistical heterogeneity in the odds ratios of included studies was assessed using the Q-test based on a $\chi^2$ distribution with $k - 1$ degrees of freedom.

We performed subgroup analyses to investigate the effect of potential confounding factors by comparing the odds ratios in studies with and without a particular feature. The following potential sources of bias were investigated: spectrum of CTS patients included, selection of controls, manner of data collection, and whether the study applied measures to control for confounding.

**Results**

**DISEASES CONCURRENT WITH CTS**

Our broad search identified more than 28 conditions that have been reported in association with CTS, including acromegaly, diabetes mellitus, Down syndrome, obesity, arthritis, hypothyroidism, pregnancy, gout, Lyme disease, and leprosy (a full list is available from the authors on request). For many conditions, there were only case reports in which no attempt was made to determine the prevalence in a larger group of CTS patients. After discussing the results with neurologists, we decided to limit ourselves to the following three conditions: diabetes mellitus, hypothyroidism, and rheumatoid arthritis.

**Results of Systematic Literature Search**

The systematic search of the literature gave 297 articles. Of these, we identified nine studies that reported on the prevalence of these concurrent diseases in CTS patients.
The relationship between CTS and diabetes mellitus was examined in all nine studies, hypothyroidism in eight studies, and rheumatoid arthritis in seven studies. A total of 4908 CTS patients and 7671 controls were included in these primary studies.

Five studies used a case-control design, whereas four studies had only a cohort of CTS patients without a control group. The spectrum of patients and the case definition of CTS varied from studies involving only operated CTS patients to studies based on self-reporting. We found no randomized studies. Further details on the primary studies are presented in Table 1.

PEAK OCCURRENCE OF CONCURRENT CONDITIONS AND POOLED RATES

The individual odds ratios showing whether the prevalence of concurrent conditions was higher among CTS patients than in the control group (odds ratios >1) are shown in Fig. 1. We also calculated a summary estimate of the odds ratios, using a random effects model.

Nine studies determined the prevalence of diabetes mellitus in CTS patients (Fig. 1A). These prevalence rates ranged from 0.9% to 26.0%. Pooling of the individual odds ratios produced a summary estimate of 2.2 (95% CI, 1.5–3.1).

Eight studies examined whether the prevalence of hypothyroidism or the use of thyroid medication was higher in CTS patients (Fig. 1B). The prevalence rates of hypothyroidism in CTS patients varied from 1.3% to 10.3%. The pooled odds ratio was 1.4 (95% CI, 1.0–2.0).

Seven studies determined the prevalence of rheumatoid arthritis in CTS patients; the reported prevalence varied between 1.6% and 14.1% (Fig. 1C). There was significant variation in individual odds ratios, leading to a pooled odds ratio of 2.2 (95% CI, 1.4–3.4).

One study provided details about whether the diagnosis of the concurrent condition was already known to the patient at the time of the CTS diagnosis (9). From the total of 17 CTS patients with diabetes mellitus in that study, there was only 1 new diagnosis. For hypothyroidism, there were 13 new diagnoses of a total of 18 diagnoses, and for rheumatoid arthritis all 5 diagnoses were new.

POTENTIAL SOURCES OF BIAS

In general, studies with a less than optimal design tended to overestimate the prevalence of concurrent conditions in CTS patients, leading to higher odds ratios (Table 2). Higher odds ratios for all three concurrent conditions were found for studies that included operated CTS patients, studies that relied on chart review for their data collection, and studies that did not adjust for differences in gender and age distribution between CTS patients and controls.

Discussion

Our search identified many conditions that have been linked to CTS. We found no previous overview of diseases that appear to be concurrent with CTS. For three potentially relevant conditions, we identified nine studies examining their prevalence in CTS patients compared with the general population. The majority of these nine studies showed an increased prevalence of diabetes mellitus (summary odds ratio, 2.2), hypothyroidism (summary odds ratio, 1.4), and rheumatoid arthritis (summary odds ratio, 2.2).

We will first discuss the possible factors that could explain the relationship between concurrent conditions and CTS. Thereafter, we will pay specific attention to the effect of potential sources of bias and variation as a result of the many differences in design and conduct of these observational studies. We end the discussion with a section discussing the key issue of whether to screen for these specific conditions in CTS patients.

POSSIBLE INTERACTIONS BETWEEN CTS AND CONCURRENT DISEASES

Because of the relatively high prevalence of CTS in the population, many other conditions will occur in CTS patients just by chance. The long list of studies in which one or more conditions was reported in association with CTS is probably a reflection of that. The majority of these studies were case reports that did not formally examine the relationship between CTS and the condition of interest. Some mechanisms that have been suggested to link certain conditions to CTS are alterations in body fluid balance and peripheral tissue edema leading to increased pressure in the carpal tunnel, and inflammation or damage to the median nerve that renders it more sensitive to changes in the contour or content of the carpal tunnel (24).

In our review we found a relationship between CTS and diabetes mellitus, hypothyroidism, and rheumatoid arthritis. For all three conditions, there are arguments that they are not simply concurrent with CTS but interact with the process of CTS development itself. Diabetes mellitus predisposes to development of peripheral neuropathy, which can make the median nerve more sensitive to alterations of the carpal tunnel and thus predisposes to CTS development. Hypothyroidism produces alterations of fluid balance and peripheral tissue edema, which may lead to CTS development. The inflammatory process of rheumatoid arthritis can increase the pressure in the carpal tunnel, which may also lead to CTS. Consequently, treatment of diabetes mellitus, hypothyroidism, and rheumatoid arthritis may help to reduce or cure CTS complaints.

SOURCES OF BIAS AND HETEROGENEITY IN RESULTS

All nine studies in our systematic review were observational studies. We therefore paid specific attention to the potential of confounding within each study. In addition, there were substantial clinical differences among the studies. We attempted to investigate the potential effects of clinical and methodologic differences by performing subgroup analyses (25). However, because of the limited...
number of primary studies, these analyses should be interpreted with care. These subgroup analyses revealed that the association between concurrent diseases and CTS was influenced by the spectrum of CTS patients included, the type of data collection, the choice of controls, and the measures taken to control for confounding.

We examined the impact of spectrum of disease by comparing the odds ratios in studies that included only surgery patients with the odds ratios in the remaining studies (mostly patients included at first diagnosis of CTS). This analysis revealed that studies with surgery patients reported, on average, higher prevalences of concurrent diseases than studies with nonsurgical patients. This can be explained by the fact that only those patients who do not respond to the initial treatment (steroid injections, splinting) are referred for surgery. The presence of a concurrent disease may negatively influence the response to the initial treatment, leading to more surgery. Because our final aim was to make recommendations for laboratory screening in patients with newly diagnosed CTS, the results in surgery patients clearly overestimate the importance of concurrent diseases.

The effect of data collection was measured by comparing studies with retrospective data collection to studies with prospective data collection. Studies with retrospective data collection rely on routinely collected data, which are of lesser quality than dedicated collection driven by a specific research question. In this review we also found evidence that retrospective data collection overestimated the role of concurrent diseases in CTS (Table 2).

### Table 2

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Prevalence (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atcheson et al. (9), strict</td>
<td>9.4 / 4.0</td>
<td>2.5 (0.9 to 6.7)</td>
</tr>
<tr>
<td>Atcheson et al. (9), less strict</td>
<td>7.3 / 2.9</td>
<td>2.6 (0.7 to 9.4)</td>
</tr>
<tr>
<td>Atroshi et al. (3)</td>
<td>3.0 / 3.2</td>
<td>0.9 (0.2 to 3.9)</td>
</tr>
<tr>
<td>Bahou (6)</td>
<td>16.8 / 6.5</td>
<td>2.9 (1.8 to 4.6)</td>
</tr>
<tr>
<td>De Krom et al. (4)</td>
<td>2.5 / 3.6</td>
<td>0.7 (0.2 to 2.1)</td>
</tr>
<tr>
<td>Ferry et al. (11)</td>
<td>0.9 / 0.5</td>
<td>1.8 (0.7 to 5.0)</td>
</tr>
<tr>
<td>Hurst et al. (12)</td>
<td>7.3 / 1.7</td>
<td>4.8 (2.7 to 7.9)</td>
</tr>
<tr>
<td>Karpitskaya et al. (13)</td>
<td>11.3 / 4.0</td>
<td>3.1 (1.1 to 8.6)</td>
</tr>
<tr>
<td>Solomon et al. (14)</td>
<td>26.6 / 19.0</td>
<td>1.5 (1.2 to 1.8)</td>
</tr>
<tr>
<td>Stevens* et al. (15)</td>
<td>6.1 / NA</td>
<td>2.4 (1.6 to 3.4)</td>
</tr>
</tbody>
</table>

Fig. 1. Prevalence rates and odds ratios for diabetes mellitus (A), hypothyroidism (B), and rheumatoid arthritis (C) in CTS patients compared with controls. * indicates odds ratios (OR); horizontal lines indicate 95% CIs. The study of Atcheson et al. (9) uses two definitions for CTS: strict, results of 96 patients with a strict definition of CTS; less strict, results of 193 patients with a less strict definition of CTS. Only the data based on the strict definition have been used in the random-effects pooling of odds ratios; **, prevalence rate and odds ratio for all inflammatory arthritis, including rheumatoid arthritis.
Selection of controls is a crucial factor in case-control studies (26). Ideally, controls should be selected from the same population that gives rise to the cases. We found that if studies used patients with different conditions or general population figures as their control group, the role of concurrent diseases in CTS was overestimated.

SCREENING FOR CONCURRENT DISEASES IN CTS PATIENTS

Our final goal was to review the literature on the role of concurrent diseases in CTS and whether that evidence would support laboratory screening for these conditions. Many factors come into play in the decision whether to screen for certain conditions in CTS patients. We will discuss two general ones and one factor that is specifically relevant to our situation. The first factor is that conditions suitable for screening should pose a significant health risk to patients and that early treatment should offer advantage above late treatment. This is certainly true for diabetes mellitus and hypothyroidism, but less obvious for rheumatoid arthritis. The second factor is that the diagnostic test(s) used in the screening program should have excellent properties to avoid negative consequences from false-positive and -negative test results. The tests and their properties that are used in the diagnosis of diabetes mellitus, hypothyroidism, and rheumatoid arthritis are discussed below.

A specific issue in our situation is that screening for concurrent conditions is relevant only if the condition is undiagnosed at the time of the CTS diagnosis and also not suspected based on findings from history and physical examination. Unfortunately, only one study paid specific attention to the sequence of diagnoses in their patients, both for the CTS group and for the control group (9). This study found that of the total of 17 CTS patients with diabetes mellitus, there was only 1 new diagnosis. For hypothyroidism, there were 13 new diagnoses in a total of 18, and for rheumatoid arthritis all 5 diagnoses were new.

The absence of this information in the other studies greatly limits their value in answering the question of whether to screen for concurrent diseases in CTS patients.

DIAGNOSING DIABETES MELLITUS, HYPOTHYROIDISM, AND RHEUMATOID ARTHRITIS

According to Sacks et al. (27), diabetes mellitus should be diagnosed through glucose measurement in plasma by an accredited laboratory (not on a portable meter). Plasma glucose testing is suitable for screening and inexpensive.

To diagnose hypothyroidism, the thyroid-stimulating hormone (TSH) concentration should be measured in serum. If TSH is increased, free thyroxine (FT4) should subsequently be measured. If FT4 concentrations are decreased, this establishes the diagnosis of hypothyroidism, whereas thyroxine concentrations within reference values indicate subclinical hypothyroidism (28, 29) (sensitivity and specificity not reported). TSH and FT4 measurements are suitable for screening but not inexpensive.

There is currently no laboratory test that is suitable for screening for rheumatoid arthritis. Rheumatoid factor should not be used because its predictive value is low in patients with a relatively low previous change of the disease, e.g., CTS patients. The performance of the relatively new anti-cyclic citrullinated peptide antibody test (30) is not known well enough to give an indication of its performance in screening. Clinical symptoms, however, can be used for diagnosing rheumatoid arthritis. The guidelines of the American Rheumatism Association state that four clinical features should be present for at least 6 weeks to diagnose rheumatoid arthritis: morning stiffness in and around joints; soft tissue swelling of three or more joint areas; swelling of proximal interphalangeal, metacarpophalangeal, or wrist joints; and symmetrical swelling (31). A clinician not specialized in rheumatology should confine to a clinical examination to find swelling of joint areas. If three or more swollen joint areas are found, a patient should be referred to a rheumatologist.

References

To diagnose rheumatoid arthritis, e.g., CTS patients. The performance of the relatively new anti-cyclic citrullinated peptide antibody test (sensitivity and specificity not reported). TSH and FT4 measurements are suitable for screening but not inexpensive.

Table 2. Stratified analysis to examine the influence of several study features on the odds ratios for the prevalence of concurrent diseases in CTS patients compared with controls. a

<table>
<thead>
<tr>
<th>Study feature</th>
<th>References to studies</th>
<th>Diabetes mellitus Odds ratios (95% CI)</th>
<th>Hypothyroidism Odds ratios (95% CI)</th>
<th>Rheumatoid arthritis Odds ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spectrum of CTS</td>
<td>Nonsurgical patients</td>
<td>(3, 6, 9–11, 15)</td>
<td>2.1 (1.5–3.0)</td>
<td>1.1 (0.8–1.5)</td>
</tr>
<tr>
<td></td>
<td>Surgical patients</td>
<td>(12–14)</td>
<td>2.6 (1.1–6.2)</td>
<td>2.2 (1.4–3.4)</td>
</tr>
<tr>
<td>Control group</td>
<td>Within study population</td>
<td>(3, 10, 11, 14)</td>
<td>1.5 (1.2–1.8)</td>
<td>1.8 (1.2–2.5)</td>
</tr>
<tr>
<td></td>
<td>Other controls</td>
<td>(6, 9, 12, 13, 15)</td>
<td>2.9 (2.3–3.7)</td>
<td>1.2 (0.7–2.3)</td>
</tr>
<tr>
<td>Control of confounding</td>
<td>Yes</td>
<td>(9–11, 13, 15)</td>
<td>2.1 (1.4–3.0)</td>
<td>1.4 (0.8–2.3)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>(3, 6, 12, 14)</td>
<td>2.3 (1.2–4.3)</td>
<td>1.7 (1.1–2.6)</td>
</tr>
<tr>
<td>Data collection</td>
<td>Prospective</td>
<td>(3, 9–11)</td>
<td>1.4 (0.8–2.6)</td>
<td>1.4 (0.8–2.3)</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>(6, 12–15)</td>
<td>2.6 (1.7–3.9)</td>
<td>1.5 (0.8–2.8)</td>
</tr>
</tbody>
</table>

a For specific details on studies, see legend of Fig. 1.
DEVELOPMENT OF EVIDENCE-BASED INDICATIONS FOR LABORATORY TESTS

This systematic review shows that it is feasible to formulate evidence-based indications for requesting laboratory tests. This process consists of the following steps: identification of a specific diagnostic dilemma; comprehensive search of the literature; appropriate use of selection criteria; and thorough assessment of the included studies and their results.

The crucial step in this process is an explicit description of the diagnostic problem at hand. Key elements in this description are the clinical use of the test (addition of a test to other tests, substitution of one test with another, or triage, e.g., using a test to select patients for further testing) and the intended population. Explicit search queries can be formulated on the basis of this information. When all relevant studies are identified, there should be an assessment of the quality of the included studies. If possible, the results of the primary studies should be combined in a metaanalysis, paying specific attention to differences in study design and conduct.

Recommendations and Conclusions

We found a limited number of studies that specifically examined the prevalence of concurrent conditions in CTS patients. These studies suggest that CTS patients have a higher prevalence of diabetes mellitus, hypothyroidism, and rheumatoid arthritis than the general population, but this relationship was less clear in high-quality studies. Moreover, only one of the studies provided insight into whether these concurrent conditions were undetected at the time of the CTS diagnosis. This information is critical when addressing the issue of screening. We conclude that the current evidence on the association between CTS and other conditions is incomplete and of less than optimal quality. High-quality studies providing detailed information on the timing of the different diagnoses are still needed. At present, we recommend that physicians pay specific attention to signs and symptoms of these concurrent conditions in CTS patients. The evidence is insufficient to recommend routine laboratory screening for concurrent diseases in all newly diagnosed CTS patients.

We are grateful to Prof. Dr. Patrick Bossuyt, Dr. Ivo van Schaik, and Dr. Maarten Kraan for their comments during the preparation of this manuscript.

References


