Patients profiles and outcomes of care in temporomandibular disorders

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General Discussion
The main aim of the present thesis was to increase the currently available knowledge about patients profiles and outcomes of care in temporomandibular disorders (TMDs) and to help clinicians for decision-making in clinical practice. In the present thesis, we found that temporomandibular joint osteoarthritis (TMJ OA) has a negative effect on oral health related quality of life (OHRQoL) of patients. The severity of patients’ clinical symptoms and signs is negatively associated with OHRQoL in patients with TMJ OA. Arthrocentesis with hyaluronic acid (HA) injections combined with oral glucosamine hydrochloride (GH) is effective to improve OHRQoL of patients with TMJ OA. The prediction models for OHRQoL of patients with TMJ OA at 1-month and 6-month after patients had completed arthrocentesis with HA injections have good internal validity, calibration, discrimination and sufficient clinical added values. Besides, we found that somatization is the best predictor for orofacial pain intensity while depression is the best predictor for pain-related disability in TMD patients. The prediction model for types of treatments indicated for TMD patients has good internal validity, external validity, calibration and discrimination. Also, we found that ultrasonography (US) can be considered as a useful imaging tool to supplement the clinical examination in patients with suspected disc displacements (DDs).

In the paragraphs below, three specific points which are important through the entire thesis are discussed in a broader context.

**OHRQoL of patients with TMJ OA**

In the present thesis, OHRQoL was used as an outcome measure on multiple occasions: in a longitudinal study (Chapter 2) to determine the effectiveness of arthrocentesis with HA injections with oral GH as a treatment option for TMJ OA; to determine possible associations with clinical signs and symptoms of patients suffering from TMJ OA (Chapter 3); and as an outcome measure (low versus normal OHRQoL) in prediction models for patients suffering from TMJ OA 1 and 6 months after treatment with arthrocentesis (Chapter 4). In these chapters, OHRQoL of patients with TMJ OA was significantly impaired. The severity of clinical symptoms, especially the pain-related symptoms, were significantly associated with OHRQoL. Arthrocentesis with HA injections with oral GH was shown to be effective in terms of improving OHRQoL.
Finally, prediction models were developed for low OHRQoL 1-month and 6-month after the arthrocentesis with HA injections in individual patients. To our knowledge, this was the first time that OHRQoL was used as an outcome measure to assess the effectiveness of arthrocentesis with HA injections with oral GH in dentistry. This is congruent with contemporary views on patient-centered care [1] and allows oral healthcare professionals to assess the effectiveness of treatment from the patients’ perspectives [2]. The prediction models are also the first models for prediction of low OHRQoL in oral healthcare and in patients with TMJ OA in particular.

In these chapters, the 14-item Oral Health Impact Profile (OHIP-14) was used to assess OHRQoL. The OHIP-14 is the most commonly used instrument for the assessment of OHRQoL of TMD patients nowadays [3]. OHIP-14 is reported to have similar psychometric properties as the OHIP-49 for the assessment of OHRQoL in TMD patients [4]. However, compared with the OHIP-49, the OHIP-14 makes it easier to assess OHRQoL in diverse settings, reduces patients’ burden and saves patients’ time [4]. Compared with the OHIP-5, OHIP-14 showed better psychometric properties for the assessment of OHRQoL of TMD patients with better reliability and validity [4]. Therefore, among the three versions of the OHIP, the OHIP-14 is the preferred instrument to assess OHRQoL of TMD patients. However, this instrument is not specifically tailored to the unique characteristics or problems that TMD patients might experience in daily life. All the items in the OHIP-14 are focused on the problems with patients’ teeth, mouth, or dentures instead of muscles and joints specifically. Therefore, the OHIP-14 may not be very sensitive to some factors that affect TMD patients [5].

Besides, the OHIP-14 may contain a small number of redundant items which are not related to TMDs, like “sense of taste has worsened” (Fig. 1). The redundant items may dilute the responsiveness of OHIP-14 to change in TMDs to some extent [5-7]. Therefore, although the OHIP-14 is the best option for the assessment of OHRQoL of TMD patients from a pragmatic point of view, the question whether the OHIP-14 is the best available option to measure OHRQoL of TMD patients remains unanswered. A 22-item TMDs-specific version of the OHIP (OHIP-TMDs) has been developed by Durham et al. in 2011 [6]. In the 22 items of OHIP-TMDs, 20 items are from the OHIP-49 and the other two are new items derived from qualitative research based on patients with TMDs [6]. In the OHIP-TMDs, each item was modified to be more
suitable for the characteristics of TMDs [6]. So, the OHIP-TMDs is thought to be an instrument which is more sensitive and tailored to the problems that TMD patients may experience than other versions of the OHIP. In 2015, Yule et al. reported that the OHIP-TMDs had good reliability and validity in the assessment of OHRQoL in TMD patients [5]. Fig. 1 shows a comparison of the items of the OHIP-14 and those of the OHIP-TMDs. The OHIP-TMDs contains the same domains as the OHIP-14 does, including functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap. A total of 9 items is present in both the OHIP-14 and the OHIP-TMDs. Although the other items are different between the OHIP-14 and the OHIP-TMDs, most of these items in the same domain between the OHIP-14 and the OHIP-TMDs are comparable in contents. As can be seen in Fig. 1, all the items in the OHIP-14 are focused on patients’ problems caused by teeth, mouth, and dentures in the past year, while all the items in the OHIP-TMDs are specifically focused on the problems caused by muscles and joints besides teeth, mouth, and dentures in the last month. These small modifications make the OHIP-TMDs more sensitive and discriminative to assess small changes in TMD patients’ OHRQoL over time than the OHIP-14 [5]. It is reported that compared with OHIP-14, OHIP-TMDs shows somewhat better psychometric properties for the assessment of OHRQoL in TMD patients [6].

However, research so far has provided some but rather limited evidence on the psychometric properties of the OHIP-TMDs. Yule et al. tested the reliability and validity of the OHIP-TMDs only with a limited number of 20 TMD patients for test-test reliability determination, and assessed the discriminative validity and responsiveness to change in 76 TMD patients with 76 matched controls [5]. Moreover, the TMD patients in both the study of Yule et al. [5] and that of Durham et al. [6] were diagnosed with the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) instead of the more recently developed Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) [5,8]. Therefore, it is recommended that future studies on the psychometric properties of the OHIP-TMDs should include a larger number of TMD patients, diagnosed with the more recent diagnostic criteria system DC/TMD. These future studies should also assess whether the OHIP-TMDs is more sensitive to detect different levels of OHRQoL in different subtypes and severity of TMDs than the
OHIP-14. Also, whether the OHIP-TMDs is more sensitive to detect the changes in OHRQoL of TMD patients over time than the OHIP-14 should be further assessed.

<table>
<thead>
<tr>
<th>OHIP-14</th>
<th>OHIP-TMDs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Functional limitation</strong></td>
<td><strong>Difficulty in chewing any foods</strong></td>
</tr>
<tr>
<td>Trouble in pronouncing any words</td>
<td>Difficulty in opening/closing mouth</td>
</tr>
<tr>
<td>Sense of taste has worsened</td>
<td></td>
</tr>
<tr>
<td><strong>Physical pain</strong></td>
<td><strong>Painful aching in the mouth</strong></td>
</tr>
<tr>
<td>Painful aching in the mouth</td>
<td></td>
</tr>
<tr>
<td>Uncomfortable to eat any foods</td>
<td></td>
</tr>
<tr>
<td><strong>Psychological discomfort</strong></td>
<td><strong>Self conscious</strong></td>
</tr>
<tr>
<td>Self conscious</td>
<td></td>
</tr>
<tr>
<td>Feeling tense</td>
<td></td>
</tr>
<tr>
<td><strong>Physical disability</strong></td>
<td><strong>Feeling miserable</strong></td>
</tr>
<tr>
<td>Inturrupting meals</td>
<td></td>
</tr>
<tr>
<td>Diet unsatisfactoris</td>
<td></td>
</tr>
<tr>
<td>Difficult to relax</td>
<td><strong>Interrupting meals</strong></td>
</tr>
<tr>
<td>A bit embarrassed</td>
<td></td>
</tr>
<tr>
<td><strong>Psychological discomfort</strong></td>
<td><strong>Difficult to relax</strong></td>
</tr>
<tr>
<td>A bit irritable with other people</td>
<td></td>
</tr>
<tr>
<td>Difficulty doing usual jobs</td>
<td></td>
</tr>
<tr>
<td><strong>Social disability</strong></td>
<td><strong>A bit irritable with other people</strong></td>
</tr>
<tr>
<td>Feeling life in general less satisfying</td>
<td></td>
</tr>
<tr>
<td><strong>Handicap</strong></td>
<td><strong>Difficulty doing usual jobs</strong></td>
</tr>
<tr>
<td>Feeling life in general less satisfying</td>
<td></td>
</tr>
<tr>
<td>Totally unable to function</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Feeling life in general less satisfying</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Unable to work to full capacity</strong></td>
</tr>
</tbody>
</table>

Fig. 1. Items of the OHIP-14 and the OHIP-TMDs. The items in bold are shared in both the OHIP-14 and the OHIP-TMDs (Slade 1997 [9] and Durham et al. 2011 [6])

**Clinical prediction models**

In Chapter 4, prediction models for OHRQoL 1 month and 6 months after arthrocentesis with HA injections in patients with TMJ OA were developed. With these models, clinicians can predict the probability of low OHRQoL in the follow-up for individual patients with TMJ OA based on the patients’ profiles. With the help of the predicted probability of individual patients, clinicians can make decisions at patients’ first visit about whether arthrocentesis with HA injections will likely have sufficient
benefits to improve patients’ OHRQoL in the follow-up, and if not, whether other
treatments, like psychological and social support, are needed or to be preferred. In
Chapter 7, a prediction model for types of treatments indicated for TMD patients
was developed. With the model, clinicians can find out which factors in patients’ pro-
file are significantly associated with different types of treatment indicated for TMD
patients and determine which treatment option would be recommended given a spe-
cific TMD patient.

Clinical prediction models are relatively new but important in dentistry. Prediction
modelling is defined as a process by which combinations of clinical findings, that have
been statistically demonstrated to be meaningful predictors of a condition or outcome
of interest, are used to categorize a heterogeneous group of patients into subgroups
(binary or multinomial subgroups) based on an individual likelihood of the presence
of that condition or outcome [8]. Clinical prediction models can, for instance, provide
both clinicians and patients with important information about risks and benefits as-
associated with different types of treatment [10]. Clinicians can use clinical prediction
models to make more informed decisions about the diagnosis, treatment, or progno-
sis of individual patients before starting invasive examination or treatment. Individual
patients can be informed more accurately, which will result in more realistic expecta-
tions regarding diagnosis, treatment, or prognosis. Moreover, clinical prediction mod-
els are useful to make optimal use of medical resources and to optimize patients’ care,
and are therefore important to be developed and used in dentistry.

The clinical usefulness of clinical prediction models should be the most important
purpose to develop these models. For such purpose, determining a cutoff for the
predicted probability to correctly classify patients into targeted outcome categories
is an important premise for clinical usefulness. In both Chapter 4 and Chapter 7,
the cutoffs were determined solely based on statistical criteria. In Chapter 4, the
ROC curves, where the sum of sensitivity and specificity is the maximum, were used
to determine the cutoffs for the probability to dichotomize the patients with TMJ
OA into low OHRQoL or normal OHRQoL. In Chapter 7, the TMD patients were
assigned to one out of three types of treatment based on which probability was
the highest. However, when the optimal cutoff was determined, the relative weight
of false-negatives and false-positives in the decision context is recommended to be
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considered in addition to statistical criteria [11,12]. For example, if a false-positive decision is much less important than a false-negative decision, the cutoff for the positive outcome should be low. However, if a false-positive decision results in serious risks, the cutoff for the positive outcome should be high. Biesheuvel et al. developed a multinomial prediction model for the diagnoses of residual retroperitoneal mass histology in patients with nonseminomatous testicular germ cell tumor [13]. The differential diagnoses have three outcome categories, including benign tissue, mature teratoma, and viable cancer. The predicted probability of each category was weighted with 1:3:8, respectively [13]. The ratio of 1:3:8 was the relative severity of the three categories based on the evidence in the previous literature, which showed that the untoward and irreversible consequence for under-treatment is more severe than that for over-treatment in viable cancer, while the untoward and irreversible consequence for under-treatment is less severe than that for over-treatment in benign tissue [13]. However, based on the clinical experience, the severity of consequences for false-negative and that for false-positive in both Chapter 4 and Chapter 7 are not obviously different, and the consequences of both false-negatives and false-positives are not likely to cause irreversible and extremely severe loss of health in TMD patients. Therefore, we consider the cutoffs that we determined based on statistical criteria as acceptable in clinical practice. In clinical practice, when prediction models are used in patient care, the potential consequences for an individual patient resulting from false-positives and false-negatives is important to consider in advance.

The models developed in the present thesis were the first models developed in TMDs. So, the models need to be externally validated and updated in TMD patients from other populations. Also, the model in Chapter 7 can only give insight into what types of treatments are chosen for which types of patients, and not the effectiveness of treatment, due to the absence of follow-up data. However, it would be very interesting to see whether those treatments are effective in improving the health outcomes of TMD patients. That is what future research can be aimed at.

**RDC/TMD and DC/TMD**

RDC/TMD and DC/TMD are both commonly used diagnostic systems to classify TMD patients into different subcategories in clinical practice and research [14,15]. In
Chapter 2 to Chapter 4, the RDC/TMD was used to diagnose patients with TMJ OA in West China School of Stomatology, China. However, in Chapter 5 and Chapter 6, the DC/TMD was used to diagnose patients with TMDs at ACTA, the Netherlands. The DC/TMD was newly developed in 2014 in order to improve validity and clinical utility of RDC/TMD [14]. Compared to the RDC/TMD, the DC/TMD optimizes the classifications of TMD diagnoses in axis I based on findings of the literature published recently, and adds more subtypes of TMDs than RDC/TMD [14]. The reason why the new DC/TMD was not used in Chinese TMD patients in the present thesis is that there was no Chinese version of DC/TMD available at the time that the data were collected.

In the RDC/TMD, TMJ OA is defined as the presence of arthralgia, and either crepitus in the temporomandibular joints or bony changes in radiographic examinations [15]. However, in the DC/TMD, TMJ OA is no longer a subtype of TMDs. TMJ OA is dually coded as degenerative joint disease (DJD) and arthralgia in DC/TMD [14] (Fig. 2). That is, the same patient diagnosed with TMJ OA in the RDC/TMD is diagnosed with both arthralgia for the pain in the joint and DJD for the crepitus detected with palpation in the DC/TMD. However, in the DC/TMD, some modifications in the collection of patients’ history and clinical examinations were made compared to the RDC/TMD. Fig. 2 summarizes the similarities and differences in diagnostic algorithms of TMJ OA between the RDC/TMD and the DC/TMD. It shows that there were some minor modifications in the DC/TMD in history and clinical examinations, but the main structure of examinations remained the same. That is, in both RDC/TMD and DC/TMD, the clinical examinations contain pain on TMJ palpation, pain on TMJ movement, and crepitus on palpation. Actually, the main reason for the modifications in DC/TMD was to make clinical examinations discriminate better between TMD patients and non-TMD patients and to be easier to use by clinicians, but not to change the definition of TMJ OA. Therefore, we can expect that most patients who are diagnosed with both DJD and arthralgia in the DC/TMD can be diagnosed with TMJ OA in RDC/TMD. So, the findings of Chapter 2 to Chapter 4 are unlikely to be significantly changed when applied to the patients diagnosed with DC/TMD. Similarly, the findings of Chapter 5 and Chapter 6, which were based on the TMD patients diagnosed with the DC/TMD are also unlikely to be significantly changed when applied in the patients diagnosed
with the RDC/TMD. This is because all the subtypes of TMDs in the DC/TMD except subluxation have corresponding subtypes in the RDC/TMD, although the classification system was not completely the same between the RDC/TMD and the DC/TMD (Fig. 3). The prevalence of subluxation without any other subtypes of TMDs in TMD patients is rare. In Chapter 6, which included a total of 536 consecutive TMD patients at ACTA from September 2013 to January 2017, only 1 patient had a diagnosis of sole subluxation (1/536). That is, whether or not patients with sole subluxation were included is unlikely to significantly influence the outcomes. Furthermore, it is true that some modifications in history and clinical examinations were made for diagnosis of different subtypes of TMDs in the DC/TMD, so it is possible that some patients who were diagnosed with TMDs in the RDC/TMD may not be diagnosed with TMDs in the DC/TMD or vice versa. However, this may only occur in a very small number of patients. Therefore, the findings in Chapter 5 and Chapter 6 should still be valid after being updated and adjusted when applied to TMD patients diagnosed with RDC/TMD.
Fig. 2. Similarities and differences in diagnostic algorithms of TMJ OA between RDC/TMD and DC/TMD. The black boxes in RDC/TMD indicate that the diagnostic criteria of the same horizontal level in DC/TMD is not a part of the criteria in RDC/TMD. The black box in DC/TMD indicates that the diagnostic criteria of the same horizontal level in RDC/TMD is not a part of the criteria in DC/TMD (Dworkin and LeResche 1992 [15] and Schiffman et al. 2014 [14]).
In the future, researchers should develop and test a Chinese version of the DC/TMD in order to make the DC/TMD widely used in China. This is because the DC/TMD optimizes diagnostic procedures in history and clinical examinations compared to the RDC/TMD and improves the diagnostic validity. This is also because it is better to use the same diagnostic system of TMDs as other research groups in order to compare or bundle results, such as the effectiveness of different treatment options for different types of patients, from different studies conducted in different countries. Researchers can also update the findings of Chapter 2 to Chapter 4 based on the TMD patients diagnosed with the DC/TMD in the future. Besides, although the differences in diagnostic algorithms between the DC/TMD and the RDC/TMD are unlikely to significantly influence the outcomes, it is still worthy assessing the concordance rate of patients who are diagnosed with TMDs or non-TMDs between the RDC/TMD and the DC/TMD and the discordance for patients who are diagnosed with TMDs only in one diagnostic system but without TMDs in the other diagnostic system. This may make it possible to directly compare the findings of a study which used one diagnos-

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**Fig. 3.** Subtypes of TMDs in RDC/TMD and DC/TMD. The black box indicates that subluxation is not a diagnosis in RDC/TMD (Dworkin and LeResche 1992 [15] and Schiffman et al. 2014 [14]).
tic system with that which used the other diagnostic system and quantify how much extent that the findings based on TMD patients diagnosed with one diagnostic system can be applied to another TMD patients diagnosed with the other diagnostic system.

**Conclusion**

OHRQoL is an important outcome measure for patients with TMJ OA. Future research can be aimed at developing and validating OHRQoL measures which are tailored specifically to TMD related problems. Prediction models can be used for optimizing health care by aiding to clinical decision-making and informing patients about risks and benefits of different treatment options. Future research can be aimed at validating the models in the present thesis in new populations, with the DC/TMD as the recommended classification scheme for the diagnosis of TMDs.
References


