EJM

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Intracranial Pressure Monitoring in patients with Traumatic Brain Injury

A systematic review and meta-analysis

Are old donors a good alternative to expand the current donor pool?

Systematic review

Systematic review

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Review

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Colophon

The Erasmus Journal of Medicine (EJM) is a scientific magazine by and for students, especially students of Erasmus MC University Medical Center Rotterdam. It was initiated by the MFVR (the medical students' organization of Erasmus MC). We strive to release the journal twice a year. It is published on paper (1250 copies) and on the EJM website (www.erasmusjournalofmedicine.nl).

The main purpose EJM is to encourage medical and research master students to conduct research (empirical studies or systematic reviews), report on this research, and become acquainted with the professional publishing process either as authors, reviewers or editors. A secondary purpose is to make the results of excellent student-driven research known to others.
The Journal accepts articles describing original research, systematic reviews, extended abstracts (summaries of recently conducted studies), calls from research projects for students to participate, opinion papers written by students, editorial comments, case reports, clinical lessons, clinical images, and letters to the editor.
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Erasmus Journal of Medicine and Our New Erasmus MC

On September 6, king Willem-Alexander officially opened Our New Erasmus MC, which marks the beginning of a new period in the history of our center. All medical specialists are now concentrated at one location and 'under one roof' (photo). The new building meets the requirements that are imposed on a modern, forward-looking academic medical center. It facilitates a working practice that puts the patient in the core, while giving way to clinical, translational and fundamental research that focuses on innovations in care and cure. Also, importantly, our education center (photo) is now connected with the new Erasmus MC. Thus, medical students not only have access to lectures and tutorials, but also, at low threshold, to medical specialists, (clinical) researchers and to state-of-the-art research facilities.

Obviously, as an academic teaching center, we aim to teach our students in the current state of medicine. However, we consider it even so important to make them understand that it is essential to continue developing new knowledge, so that boundaries can be shifted. We make them aware of the fact that they themselves are important in this respect, as the students of today are the researchers of the future. *The Erasmus Journal of Medicine* (EJM) is one of the tools that has been developed to promote publication of scientific articles by medical students. In this way, students get the opportunity to be involved in performing medical scientific research at an early stage of their career.

We are delighted to present this 12th issue of *EJM*. Again, similar to previous issues, it is mainly the result of the effort of our students: they are the auteurs and acted as editors and reviewers. Various topics are addressed, ranging from the role of *intracranial pressure monitoring in patients with traumatic brain injury* to the question whether *old donors form a good alternative to expand the current donor pool*. We do hope that will enjoy reading as much as we enjoyed tutoring the students.

Indeed, students benefit of guidance and mentorship. In that respect, we regret that Dr. Tom Birgenhäger has decided to retreat as staff-editor. We thank him for many years of dedication to EJM.

Prof. Hans van Leeuwen, dean

Prof. Eric Boersma, chair of the editorial board

Erasmus Journal of Medicine

Are old donors a good alternative to expand the current donor pool?

David de Jong, Ruben Mijnster, Tobias Defesche , Pascal Clephas, Lina Al-Hassany
Editorial board of the Erasmus Journal of Medicine

In the current issue of the Erasmus Journal of Medicine, a systematic review by van Leeuwen and colleagues reports the outcomes of a comparison of young and older kidney transplant donors. They examined whether these older donors are a good alternative to expand the current donor pool. They showed that renal allografts from older donors might be a good alternative to expand the donor pool. However, because of the heterogeneity between the studies, a clear conclusion cannot be drawn yet. The authors chose a very clinically relevant topic to examine, as kidney transplant donors are rare.

Wolfe et al. showed in 1999 already that kidney transplantation was the superior treatment compared to dialysis, for patients with end-stage renal disease (ESRD).[1] Due to the increase in population age, the incidence of end stage renal disease ESRD is increasing and so the demand for donor kidneys. However, the gap between demand and supply is too large. This is the reason why it is important to find ways to expand the donor pool., One of these is the use of older donors. Advanced donor age increases the risk of kidney allograft failure.[2, 3] However, the effect of the donor age on transplant outcome remains uncertain.

Van Leeuwen et al. found a RR for delayed graft function comparing old and young donors of 1.55 (95%CI 1.29 - 1.87). The delayed graft function is an important parameter, because it is defined as needing dialysis within a week after transplantation and therefore represents the donor function right after transplantation. The older donor group had a significantly lower glomerular filtration rate. No differences were found between old and young donors with regard to incidence of acute rejection or graft survival.

The meta-analysis of van Leeuwen et al. found 11 suitable articles, which were comparable to a certain extent. The studies combined included 9192 patients, which is a substantial number of included patients, providing it with much power. The differences in cut-off of the age defining “old” versus “young”, weakens the strength of this meta-analysis. To actually get the true effect, the databases should be combined and one cut-off value should be used. In further research, this is an issue that should be taken into account.

Overall, the authors performed a relevant analysis by pooling all the articles about this subject in one systematic review. A future large multicenter cohort study should be carried out to investigate the difference between stratified donor ages. Also large prospective cohort study with different cut-off ages would be a next step for further research into this topic. This future research is much required in order to take further steps into expanding the current donor pool.

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The safety of the use of ketamine as sedation in paediatric Emergency Department patients

A systematic review

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Abstract

Objective: **The aim of this study is to evaluate the safety of the use of ketamine in paediatric patients in the Emergency Department (ED).**
Methods and Materials: **A literature search about this subject was performed using Pubmed.**
Results: **The search revealed 17 articles, of which five were selected for this review. The articles were selected based upon adverse events of ketamine use in children, written in English and published after the year 2000. In none of the studies that were selected, the safety of ketamine was the main objective to investigate. However, all five studies did find that no severe adverse events took place and thereby conclude that the use of ketamine in paediatric ED patients in the short term is safe. They did find that the use of ketamine as a sedative causes more episodes of emesis than other frequently used sedatives.**
Discussion: **Further investigation is needed to assure the long-term safety of the use of ketamine in paediatric patients in the ED.**

Introduction

Ketamine is becoming more and more popular as a sedative for adults in Emergency Departments (EDs).[1] This trend is recently also seen in the paediatric ED. Ketamine is the only dissociative anaesthetic agent currently approved for clinical use and has unique advantages over other sedatives. Ketamine provides a combination of amnesia, sedation, immobilization and analgesia in a painful or stressful procedure, while having little effect on respiratory and hemodynamic functions of the patient. Many sedatives, such as benzodiazepines and opioids cause hemodynamic and/ or respiratory problems or even instability, which can severely impact patients. Ketamine has not been known to cause these adverse events. The Dutch Society for Anesthesiology and the Dutch Society for Pediatrics have come up with a current standard of care in the pediatric ED when administering procedural sedation (PSA). When performing very painful, stressful and/or complex procedures it is advised to give PSA with deep sedation. First choice of recommendation is ketamine intravenous (i.v.), second and third choice include the use of propofol, fentanyl and midazolam.[2] Nonetheless, no conclusive research has been performed addressing the safety of this medication in paediatric patients.[2] Therefore, we decided to evaluate the safety of the use of ketamine in paediatric patients by assessing the frequency of adverse events after the ketamine administration in the ED. The aim of this study is to evaluate the safety of the use of ketamine in paediatric patients in the ED.

Methods

Literature search

A search strategy was created using the terms "Ketamine"[Mesh] and "Paediatrics"[Mesh]. The term "adverse"[text] was also added, together with the date limitations ("2000/01/01"[PDAT] : "2017/10/10"[PDAT]) and the command English[lang]. On October 10th 2017 a literature search was performed using PubMed.

Inclusion/exclusion criteria

Inclusion criteria were (1) articles describing ketamine use in the ED, (2) a research population consisting of paediatric patients and (3) the description of adverse events that occurred in the study population. The patients in the articles had to be (4) under the age 17 years old. All articles included had to be written in English and had to be published after the year 2000.

Quality assessment

The quality of the included articles was assessed by two independent researchers using a risk of bias scale. This scale was based on a Cochrane risk of bias assessment form modified for this study objective.[3] As can be seen in appendix B, risk of bias was based on how well-defined the patient group was (mean age and male-female ratios), how clearly defined outcome measures were, whether selection bias or allocation bias was present and if explicit criteria for inclusion were mentioned.

Results

Study characteristics

On October 10th 2017, a literature search using Pubmed was performed. As a result, 17 articles were found. Two independent reviewers excluded 8 articles based on a subject not matching the inclusion criteria. Then, two reviewers read the abstracts and titles of the articles and excluded 3 articles that did not match the study objective of this review. This process is also shown in figure 1.

Quality assessment

The quality of the articles was assessed using a modified version of the Cochrane risk of bias scale. In all studies, the inclusion criteria were explicitly described. In all studies, except from the study of Newman et al. (2003). In most of the studies allocation bias could not be ruled out, which decreases the validity of the studies. However, it must be noted that randomization is very hard to accomplish in paediatric populations. All in all, the validity of the studies described is moderate to high. An overview of the quality assessment can be found in table 1.

Heilbrunn et al.[4]

The primary goal of this retrospective study was to determine whether using i.v. ketamine at a dosage of 1 mg/kg (k1.0) compared to a dosage of 1.5 mg/kg k(1.5) required more administered doses during a single paediatric procedural sedation. The occurrence of adverse events in each group was also noted.
In the k1.0 group (n=159) 15 adverse events were observed. Hypoxia was seen in two patients (1.3%), emesis in 9 patients (5,7%), dysphoria in two (1,3% and 'other' in two (1.3%). In the k1.5 group (n= 187) 21 adverse events were observed. Hypoxia was seen in two 2 patients (1,1%), emesis in 18 patients (9.6%) and dysphoria in one (0,5%). No episodes of apnea or laryngospasm occurred in either of the groups. The article concluded that no difference was found in the rate of adverse events between the groups. No patient was hospitalized because of adverse events of the use of ketamine as sedation during their study.

Allen et al.[5]

This randomized, double-blind, placebo-controlled trial aimed to determine whether a continuous infusion of ketamine can decrease the severity of a moderately severe acute asthma exacerbation. The study included 68 patients aged two to 18 years, of whom no further descriptive statistics were given.
Although this article does not describe the rate of adverse events during the study period, the authors state that no patients were lost during the study periode because of dysphoria, laryngospasm, salivation, or intolerance of adverse effects.
Family was contacted by telephone after discharge to find out if ketamine induced any long-term adverse effects. They used a standardized questionnaire to evaluate the need for a primary care physician or ED revisit within 48 hours after discharge from the hospital. Of the 58 patients who were contacted, one patient visited the primary care physician for a scheduled re-examination, but needed no subsequent medical intervention. One patient returned to the ED, was treated and then discharged. No families reported any nightmares, dysphoria, or long-term abnormal change in behaviour.

Roback et al.[6]

The objective of this retrospective study was to compare the frequency and severity of adverse events associated with parenteral drugs commonly used for procedural sedation and analgesia (PSA) in a paediatric ED

Figure 1- Flow of patients through the study

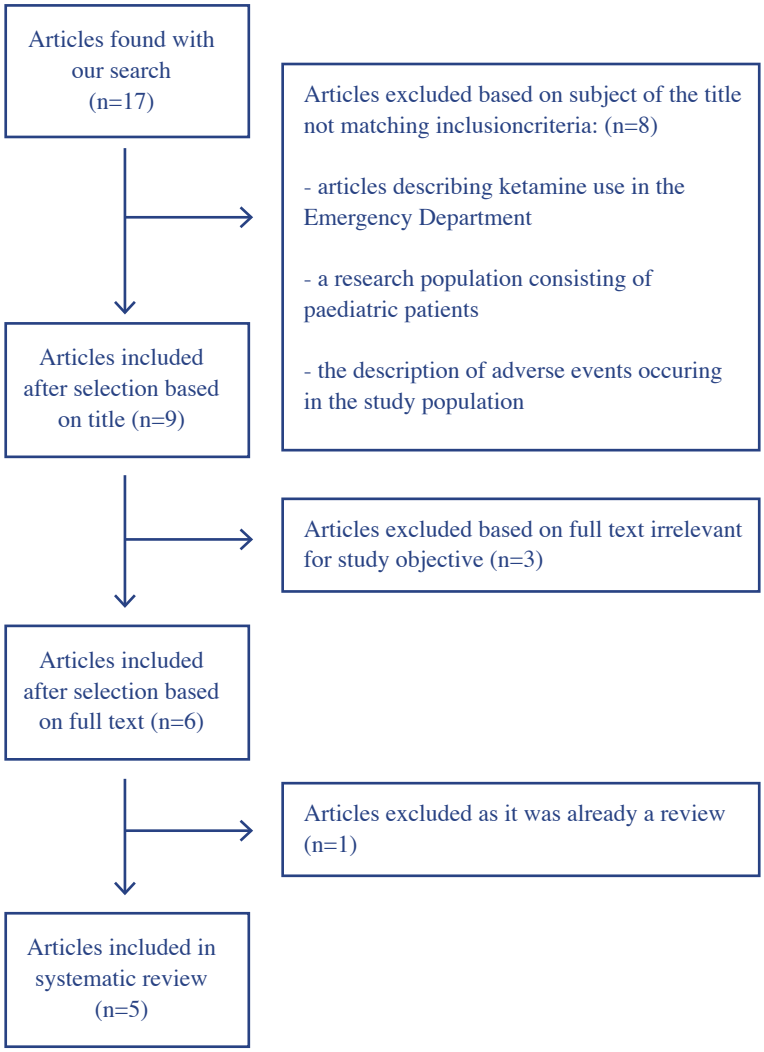

Table 1 - Quality Assessment table

Article	Score on risk of bias scale	Well-defined patient group	Clearly defined outcome measures	Absence of selection bias	Absence of allocation bias	Explicit criteria for inclusion
Heilbrunn et al. (2015)	+++	+	++	-	-	+
Allen et al. (2005)	+++++	-	++	+	+	+
Roback et al. (2004)	+++++	+	++	+	-	+
Agrawal et al. (2003)	+++++	+	++	+	-	+
Newman et al. (2003)	++++	+	+	+	-	+

The authors identified four major drug combinations: ketamine alone (n = 1,492; 59.7%), ketamine/midazolam (n = 299; 12.0%), midazolam/fentanyl (n = 336; 13.4%), and midazolam alone (n = 260; 10.4%). All patients who received ketamine alone or a ketamine/midazolam combination also received the antisialagogue glycopyrrolate. A total of 113 patients (4.5%) received various other combinations of drugs.
From the sedation sheets, a total of 458 adverse events were identified in 426 patients (17%). Simple odds ratios with 95% confidence intervals were calculated using the administration of ketamine alone as the reference group. Respiratory adverse events were experienced by 91 (6.1%; OR 1) of patients who received ketamine alone, and by 30 (10%; OR 1.72 (1.11, 2.65)) of patients receiving ketamine/midazolam. Vomiting was most common in the ketamine alone group (n=151; 10.1%; OR 1). In the ketamine/midazolam group only 16 patients experienced vomiting (5.4%; OR 1 (0.30, 0.85)). Apnea occurred in 11 (0.7%) patients receiving only ketamine and in three (1.0%) patients receiving a combination of ketamine/midazolam. Laryngospasm was only observed in the ketamine alone group. One patient (0.07%) in this group experienced laryngospasm.
Four patients receiving ketamine reported to have seizures. One patient had an underlying seizure disorder and the seizures in the three other patients resolved without intervention. No seizure episodes were noted in the other three major drug combinations. Other adverse events observed were rash (n=43), nausea (n=11), hypertonicity/muscle rigidity (n=2), and intravenous infiltration (n=1); which group these patients belonged to is not stated in the article. None of the patients were admitted to the hospital secondary to adverse events associated with PSA. Furthermore, no patients were reported to have experienced clinically apparent pulmonary aspiration.

Agrawal et al.[7]
The primary objective of this prospective observational study was to characterize the fasting status of patients receiving procedural sedation and analgesia in a paediatric ED. Secondary objectives included assessing the relationship of pre-procedural fasting state to observed adverse events.
Adverse events were defined a priori and divided into 2 types. Type I adverse events included oxygen desaturation less than 90%, apnea, stridor, airway misalignment requiring repositioning, laryngospasm, bronchospasm, cardiovascular instability, paradoxical reactions, emergency reactions, emesis, or pulmonary aspiration. Type II adverse events were defined as complications that negatively affected outcome, delayed recovery, or resulted in actual harm to the patient.
In the ketamine group (n=473), 33 AE were experienced. The authors do not state which adverse events specifically occurred. The article does give an overview of which adverse events were experienced, but does not make a distinction between administered analgesic and adverse events.
The authors do state that there was a correlation between the occurrence of emesis and older age (median age of patients with emesis was 11.1 years).
The occurrence of emesis was related to ketamine as a sedation regimen (11 of the 15 patients with emesis were sedated with ketamine). The odds ratio for emesis with ketamine compared with non-ketamine sedations was 3.2 (95% CI 1.1 to 9.6; P=.04).

Newmann et al.[8]
The aim of this prospective study was to establish the timing of adverse effects in a cohort of procedural sedations.
Ketamine was administered in 342 patients in either a combination with midazolam and atropine (n=326) or in combination with midazolam (n=16). In the ketamine/midazolam/atropine group 32 patients experienced adverse effects. The ketamine/midazolam group reported no adverse effects. Which adverse effects occurred is not stated in the article.
The article does describe the risk ratios of adverse effect events and selected sedation characteristics. Ketamine alone (n=353) has a risk ratio of adverse effects of 0.61 (95% CI, 0.44-0.85). Ketamine combined with midazolam/atropine (n=284) has a risk ratio of 0.84 (0.61-1.12).

General comment
In none of the studies that were selected, the safety of ketamine was the main objective investigated. However, all five studies found that no severe adverse events took place and thereby conclude that the use of ketamine in paediatric ED patients in the short term is safe. No research has been done to investigate the long-term (more than 24 hours after administration) adverse effects of ketamine in paediatric patients.
Moreover, all studies found that the use of ketamine as a sedative causes more episodes of emesis than other frequently used sedatives. Furthermore, none of the adverse events caused by ketamine administration resulted in hospital admissions.
The results of this data extraction can also be seen in table 2.

Discussion

Interpretation of results
In this study, we reviewed five articles about the use of ketamine in paediatric ED patients. Most articles conclude that ketamine has shown no serious adverse events. Roback et al. (2005) and Agrawal et al. (2003) do however report an increased incidence of emesis in patients administered ketamine.[6,7] There also was no difference in the occurrence of adverse events between different doses of ketamine, according to Heilbrunn et al. (2015). However, no long term studies have been performed to study the effects of ketamine on the development of children that received ketamine for a procedure in the ED. Therefore, further investigation is needed to assure the long-term safety of the use of ketamine in paediatric patients in the ED.

Limitations
A major limitation of this review is that no adequate randomized controlled trials have been performed regarding the safety of ketamine use in paediatric patients in the ED. Also, the quality of the articles that were selected was poor as can be observed in the quality assessment.
Secondly, many of the articles mention that enough research has been done on the safety of ketamine itself. However, all of this has been focused on adults and not on paediatric patients in the ED. Therefore, none of the reviewed articles studied our actual study objective.

Table 2 - Extraction table

Article	Goal of study	Adverse events for ketamine use in paediatric ER patients	Patients (number and characteristics)	Ketamine use compared to other sedatives?	Measurement methods of adverse events?	Conclusions in the article
Heilbrunn, et al. (2015)	To determine whether using i.v. ketamine at 1 mg/kg (k1.0) compared with 1.5 mg/kg k(1.5) required more administered doses during a single paediatric procedural sedation.	K(1.0) = 1.3% hypoxia 0% apnea 5.7% emesis 1.3% dysphoria 0% laryngospasm 1.3% other K(1.5) = 1.1% hypoxia 0% apnea 9.6% emesis 0% laryngospasm 0% other	Study included 346 patients. K(1.0): n=159, 64% male, median age of 6 years. K(1.5): n=187, 62% male, median age of 4 years.	-	Sedation charts completed by nurses were abstracted for adverse events.	No difference was found in the rate of adverse events between the groups. No patient was hospitalized because of adverse events.
Allen, et al. (2005)	To determine whether a continuous infusion of ketamine can decrease the severity of a moderately severe acute asthma exacerbation.	Of the 58 patients who were contacted, 1 patient visited the primary care physician for a scheduled re-examination and needed no subsequent medical intervention. One patient returned to the ED but was treated and discharged. No families reported any nightmares, dysphoria, or long-term abnormal change in behaviours.	Study included 68 patients. Ketamine cohort: n=33, 64% male. Mean age 5,7. Placebo cohort: n=35, 57% male. Mean age 6,5.	-	The attending physician noted adverse events when experienced by patients. The patient's family was contacted by telephone after discharge using a standardized questionnaire to assess long-term adverse effects caused by ketamine.	No short-term adverse effects necessitating discontinuation of the infusion or adverse behavioural impacts at 48 hours after discharge were noted.
Roback, et al. (2005)	To compare the frequency and severity of adverse events associated with parenteral drugs commonly used for procedural sedation and analgesia (PSA) in a paediatric ED.	Respiratory adverse events: ketamine alone, 91 patients (6.1%); ketamine/midazolam, 30 patients (10%). Vomiting: ketamine alone, 151 patients (10.1%); ketamine/midazolam, 16 patients (5.4%).	Study included 2500 patients Ketamine alone: n=1492 (59.7%), 63% male, median age of 6.85 years. Ketamine/midazolam: n=299 (12.0%), 57% male, median age of 6.21 years.	Four major drug combinations were identified: ketamine alone (n=1492), ketamine/midazolam (n=299), midazolam/fentanyl (n=336), midazolam alone (n=260). A total of 113 patients received various other combinations of drugs.	Patients were monitored with continuous pulse oximeter and cardiorespiratory monitors. Blood pressure measurements were recorded every five minutes by a nurse who had completed a pre-sedation assessment and was at the bedside from the time of administration of the sedation drug to the time the patient was ready for discharge.	Drug types used in paediatric PSA are associated with different adverse event profiles. Patients receiving ketamine with or without midazolam experienced fewer respiratory adverse events but more vomiting than the commonly used combination of midazolam and fentanyl.
Agrawal, et al. (2003)	To characterize the fasting status of patients receiving procedural sedation and analgesia in a paediatric ED.	In the ketamine group, 33 AE were experienced. Emesis was seen in 11 patients who received ketamine. The odds ratio for emesis with ketamine compared with non-ketamine sedation was 3.2 (95% CI 1.1-9.6).	Study included 1014 patients Ketamine: n=473	Eight medication regimens used for procedural sedation and analgesia were recognized. The three biggest groups were ketamine (n=473, 46.7%), midazolam/fentanyl (n=235, 23.2%) and chloral hydrate (n=125, 12.3%).	Adverse events were extracted from the patient's medical record.	There was no association of adverse events to medication regimens. Emesis was associated with ketamine as a sedation regimen.
Newman, et al. (2003)	To establish the timing of adverse effects in a cohort of procedural sedations.	In the ketamine- /midazolam/ atropine group 32 patients (9.8%) experienced side effects. In the ketamine- /midazolam group no adverse effects were observed. Ketamine had a risk ratio of adverse effects (95% CI) of 0.61 (0.44-0.85).	Study included 1341 patients who were divided into 2 groups: patients with adverse effects (AE) versus no AE. AE: n=184, 55% male. Median age 64.4 months. Non-AE: n=1157, 53% male. Median age 64.3 months	Seven medication regimens used for procedural sedation and analgesia were recognized. The three biggest groups were midazolam/fentanyl (n=660, 49.2%), ketamine/midazolam- /atropine (n=326, 24.3%) and midazolam (n=205, 15.3%).	Nursing staff completed a standardized procedural sedation and analgesia record for each sedation event.	No conclusion on adverse effects in patients receiving ketamine is expressed in the article.

Conclusions and recommendations

This manuscript shows that in the ED, ketamine has been proven to cause little adverse events in the short term. So, it can be concluded that the use of ketamine as a sedative in paediatric patients in the ED in the short term is safe. We would therefore recommend the use of ketamine in paediatric patients in the ED when performing very painful, stressful and/or complex procedures.

Nonetheless, further investigation is needed to determine long term outcomes, which are generally defined as occurring more than 24 hours after administration of ketamine. Thus, a randomized study has to be conducted with a follow-up time of at least one or two weeks in order to assess these long term effect and/or events. This may prove difficult as it is not ethical to randomise paediatric patients in the ED, when the effectiveness and short term safety of ketamine has already been proven. . All in all, future research needs to be focussed on the safety of ketamine after 24 hours, as the effectiveness and the safety within 24 hours has already been established.

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Intracranial Pressure Monitoring in patients with Traumatic Brain Injury:

a systematic review and meta-analysis

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Abstract

Objective: **Traumatic brain injury (TBI) can be a cause of serious health problems worldwide. Guidelines for severe TBI include monitoring of intracranial pressure (ICP). In this article we want to clarify the effect of ICP monitoring (ICPM) on in-hospital mortality as well as intensive care unit (ICU) length of stay and duration of mechanical ventilation.**
Methods: **The authors systematically searched PubMed for relevant articles. Articles were included when they compared ICPM with non-ICPM, were available free or for Erasmus MC, assessable in English and with a publication date later than October 2013.**
Results: **In total 9 studies were analysed, including 26351 patients. Three of these studies showed a significant decrease in hospital mortality when ICP was monitored. A meta-analysis presented no evidence that ICPM affects in-hospital mortality (RR 0,88 [95% CI 0,71-1,09]). ICP monitoring seems to increase hospital and ICU length of stay and duration of mechanical ventilation.**
Conclusions: **We found no evidence that ICP monitoring reduces in-hospital mortality. Further research on the effectiveness of ICPM is needed.**

Keywords
Brain injuries, Intracranial pressure, Monitoring, Mortality

Introduction

Traumatic brain injury (TBI) can be the cause of serious public health problems worldwide as well as psychological problems such as depression [1] and resolve in an economic burden for society. [2] An estimated 10 million people suffer from TBI each year. People affected by TBI have to deal with either morbidity or mortality. [3]

Intracranial pressure (ICP) can be predictive of the outcome of severe TBI. High intracranial pressure is associated with impaired neurological status and therefore is a risk factor for a poorer outcome. [4] The primary intention of ICP monitoring (ICPM) is to maintain a decent perfusion pressure to prevent secondary brain injury.[5] Therefore, the Brain Trauma Foundation (BTF) Guidelines for the Management of Severe Traumatic Brain Injury recommend intracranial pressure monitoring for all salvageable patients with a TBI (Glasgow coma score (GCS) 3-8 after resuscitation) and an abnormal computed tomography (CT) scan. An abnormal CT scan is one that reveals hematomas, contusions, swelling, herniation or compressed basal cisterns. ICPM is also indicated in patients with severe TBI with a normal CT scan if two or more of the following features are noted at admission: age over 40 years, unilateral or bilateral motor posturing, or systolic blood pressure (BP) <90 mm Hg. [6]
Nowadays, two techniques for ICPM are used: intraparenchymal monitoring and intraventricular monitoring with a ventriculostomy. Considered as the golden standard is intraventricular monitoring, although this is mainly based on tradition rather than evidence based knowledge. The device choice has to depend on the patient as well as the nursing competencies and the trauma mechanism. [7]
Despite the guidelines, there is still significant variability in mortality outcomes with the use of ICPM. [8-16] Various systematic reviews and meta-analyses have been published about this subject. Including the review of Yuan et al. [17] In this study the authors wanted to determine if differences exist between ICP and ICPM in mortality, ICU length of stay and hospital length of stay. A meta-analysis showed no evidence that ICPM decreases mortality (OR 0.93 [95% CI 0.77-1.11]). However studies conducted after 2012 were significantly associated with a greater decrease in mortality. Therefore the authors predicted a trend towards the association of ICPM with lower in-hospital mortality. We tend to elucidate if this trend has continued. Furthermore, more recent studies are published and new evaluation of research is needed.

In this systematic review the objective was to evaluate the effect of ICPM on in-hospital mortality of adult patients with TBI in comparison to non-ICPM. Furthermore, we assessed the effects of ICP monitoring on hospital length of stay, intensive care unit (ICU) length of stay and duration of mechanical ventilation.

Methods

Search strategy

A search on the PubMed electronic database was conducted from their induction to January 26th 2018 using appropriate Medical subheadings (Mesh) and keywords including Brain injuries, Intracranial pressure, Mortality, Monitoring/physiologic. See figure 1 for full query.

Figure 1 - Full query

("Brain Injuries"[tiab] OR "Brain injury"[tiab] OR "Brain Injuries"[Mesh]) AND ("Monitoring"[tiab] OR "monitored"[tiab] OR "Monitoring, Physiologic"[Mesh]) AND ("Intracranial pressure"[tiab] OR "Intracranial Pressure"[Mesh]) AND ("Mortality"[Mesh] OR "Mortality"[tiab]) AND English[lang]

Inclusion and exclusion criteria

Only observational studies were included, that compared ICPM with non-ICPM including case control cross sectional, cohort and observational studies. Articles had to be available free or for Erasmus MC, assessable in English and with a publication date later than October 2013. Articles were excluded if they didn't measure in-hospital mortality. We also excluded articles that were primarily interested in research on children (age <18).

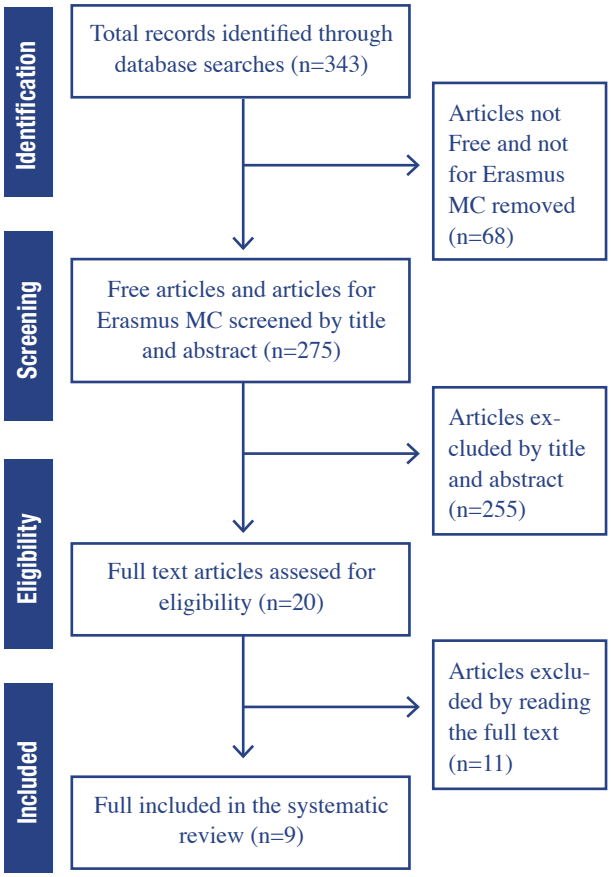
Data extraction

According to inclusion and exclusion criteria, both reviewers, independently, reviewed all articles based on title and abstract.

Figure 2 - Quality assessment

Criteria - Articles with a score ≤6 were seen as weak articles	Score
Methods	
1. Description of study population	1
2. Clear description of source of data	1
3. Explicit inclusion/exclusion criteria	1
4. Distinct description of exposure	1
5. Specifically described outcome measures	1
6. Comparability of intervention and controls:	
• Both groups have an ICPM indication according to the BTF guidelines	2
• Both groups have an ICPM indication, no description for indication parameters	1
• No ICPM indication for one of the groups, or no mention of ICPM indications	0
Statistical analysis	
7. Assessment of confounding:	
• Use of propensity score matching with the following variables: GCS, age.	2
• Use of propensity score matching without any of the following variables: GCS, age.	1
• No propensity score matching	0
Discussion	
8. Conclusions are supported by shown results	1

Figure 3 - Flow diagram study selection



Data were extracted concerning study characteristics, patient characteristics, treatment methods and results.

Quality assessment

The researchers analysed the full articles independently according to a self-modified quality score (figure 2). This questionnaire contained eight criteria suitable for the setup of this systematic review, which offered the ability to correctly address the quality of all articles. When scores didn't match the two authors discussed until consensus was reached. Articles with a score of 6 or lower were seen as weak articles. Therefore we also conducted a sub-analysis without these articles.

Endpoints

Our primary endpoint was in-hospital mortality, defined as mortality from any cause during initial submission. Secondary outcomes included ICU length of stay, hospital length of stay and duration of mechanical ventilation.

Meta-analysis

We performed a meta-analysis expressing the association between ICPM and mortality as risk ratio (RR) with 95% confidence intervals (CI). For this we used "Review Manager Software 5.3" empowered by the Cochrane Library. In this review I-squared statistics are used to describe the percentage of variance across studies that is due to study heterogeneity. If I2 was > 50% we would use a random effects model, to control for unobserved heterogeneity.

Results

Study selection

With the search strategy described above, we identified 343 articles. From these, 275 were available for free and Erasmus MC. After screening title and abstract we excluded a further 210 articles. After analysing the retaining articles based on inclusion and exclusion criteria and quality assessment we finally included 9 articles in this review (figure 3).

Study Characteristics

The included studies were published between march 2015 and July 2017 and were performed in the USA, Brazil, India, China and Japan. The studies were prospective (3 studies) as well as retrospective (5 studies). Inclusion criteria varied in age (adults, >12, >16, >55, >65), GCS (<8, <9) and use of BTF guidelines as well as which device was used for ICPM. Quality scores ranged from 4 (Suehiro et al. [13]) up to 10 (Agrawal et al. [14]). Study characteristics are presented in table 1.

Patient characteristics

The number of patients in the studies varied from 123 in the study of MacLaughlin et al. [11] up to 13.188 (Aiolfi et al. [8]). Median age differed from 32 (Agrawal et al. [14]) to 69 (Dang et al. [9]), with a percentage of women from 11% (Agrawal et al. [14]) to 34,6% (Dang et al. [9]). Ferreira et al. [16] presented a median GCS of 8, while Dawes et al. [10] and Dang et al. [9] had a median GCS of 3. The percentages ICPM fluctuated from 9,3% (Ferreira et al. [16]) to 46,0% (Dawes et al. [10]). Patient characteristics are presented in table 2.

In-hospital mortality

The RR of mortality when ICP was monitored ranged in the articles from 0,55 to 2,09 (figure 4). Three of the articles showed a significant lower in-hospital mortality when ICP was monitored. Respectively relative risks of 0,57 [95%CI 0,48-0,68], 0,67 [95%CI 0,56-0,81] and 0,66 [95%CI 0,46-0,96]. [7,11,12]. The articles were heterogenous (I2 = 92%). A meta-analysis presented no evidence that ICPM decreased in-hospital mortality (RR 0,88 [95%CI 0,71-1,09]).

Table 1 - Study characteristics

AUTHORS AND YEAR	TRAUMA CENTER, COUNTRY	STUDY DESIGN	!NCLUSION CRITERIA	INCLUDED PATIENTS	MEASUREMENT OF ICP	QUALITY ASSESSMENT
DAWES ET AL. 2015 MAR	TTEMIS, USA	Prospective registry	- Blunt head trauma - GCS < 8 on arrival - Abnormal intracranial findings on initial head CT	822	-	8
FERREIRA ET AL. 2015 OCT	Level 1 Trauma center in Sao Paulo, Brazil	Retrospective observational study	- Admitted due to TBI	299	Intracranial pressure catheter: intraparenchymal, external ventricular drainage Target ICP < 20 mmHg	7
QUEC DANG ET AL. 2015 OCT	The National Trauma Databank, USA	Retrospective observational study	- BTF criteria for ICPM - Blunt mechanism of injury - Age > 55	4437	-	8
MACLAUGHLIN ET AL. 2015 DEC	Level 1 Trauma center LA, USA	Retrospective analysis	- Adult patients admitted with sTBI (GCS </=8, intracranial hemorrage) - Blunt mechanism of trauma	123	-	8
AGRAWAL ET AL. 2016 MAY	AIIMS/JPNATC Severe TBI registry, India.	Prospective observational study	- Severe TBI (GCS < 8) - Age > 12 - BTF criteria for invasive ICPM	1345	Intraparenchymal monitoring. External ventricular drains only in case of hydrocephalus.	10
YOU ET AL. 2016 JUL	Renji Hospital affiliated with Shanghai Jiao Tong University, China	Prospective observational study	- Admitted with TBI - Age > 65 - GCS < 9 at admission - CT scan showed abnormalities consistent with head trauma	166	Target ICP < 20 mmHg Intraventricular ICP monitor. Target ICP < 20 mmHg	7
AIOLFI ET AL. 2017 FEB	American college of surgeons TQIP database, USA	Retrospective observational study	- Age >16 - Isolated blunt sTBI - BTF criteria for ICPM	13 188	-	7
PICCININI ET AL. 2017 APR	American college of surgeons TQIP database, USA	Retrospective observational study	- Age >16 - Isolated blunt sTBI - BTF criteria for ICPM	4880	Intraparenchymal and extracranial ventricular monitoring	7
SUEHIRO ET AL. 2017 JUL	JNTDB, Japan	Retrospective observational study	- GCS </=8 on admission - Or deterioration to that level within 48 hours of impact or craniotomy for traumatic hematoma	1 091	-	4

GCS = Glasgow Coma Scale, TBI = traumatic brain injury, BTF = Brain trauma foundation, ICPM = intracranial pressure monitoring, sTBI = severe traumatic brain injury

Table 2 - Patient characteristics

Authors and Year	Total patients	Age in years, median (IQR)	Sex, female (%)	GCS, median (IQR)	ICPM (%)	NON-ICPM (%)
Dawes et al.	822	42,5	24,6	3 (3-6)	378 (46,0)	444 (54,0)
2015 Mar						
Ferreira et al.	299	39 (28 – 53)	17	8 (5 – 13)	28 (9,3)	271 (90,7)
2015 Oct						
Dang et al.	4437	69 (SD 10,2)	34,6	3 (3-6)	495 (11,2)	3942 (88,8)
2015 Oct						
Maclaughlin et al.	123				40 (32,5)	83 (67,4)
2015 Dec						
Agrawal et al.	1345	32 (25-45)	11		497 (37)	848 (63)
2016 May						
You et al	166				80 (48)	86 (52)
2016 Jul						
Aiolfi et al.	13 188	52 (32-71)	28,9		1519 (11,5)	11669 (88,5)
2017 Feb						
Piccinini et al.	4880	50 (31-68)	27,3		529 (10,8)	4351 (89,2)
2017 Apr						
Suehiro et al.	1091		30,9		305 (28)	786 (72)
2017 jul						

GCS = Glasgow Coma Scale, ICPM = intracranial pressure monitoring, Non-ICPM = Non-intracranial pressure monitoring

Sub-analysis

Only one of the articles did not reach our target of 6 point in the quality assessment. Suehiro et al. [13] scored 4 points. Removing this article from the analysis had almost no effect on the heterogeneity (I2 = 93%). A meta-analysis without this study did also not show a significant reduction of in-Hospital mortality (RR 0,91 [95%CI 0,72-1,14]) (figure 5).

Hospital length of stay

Results of secondary outcomes are presented in table 3. Five of the included articles measured the hospital length of stay (LOS). Four of these showed a significant reduction in hospital LOS when there was no ICP monitoring. Respectively 17 (Aiolfi et al. [8]) up to 21 days (Maclaughlin et al. [11]) in the ICPM group and 6 (Maclaughlin et al. [11]) up to 10,15 days (Dang et al. [9]) in the non-ICPM group. Only You et al. [15] did not find a difference between both groups as to hospital.

Table 3 - Secondary outcomes

	Dang et al. 2015 Oct	Maclaughlin et al. 2015 Dec	You et al. 2016 Jul	Aiolfi et al. 2017 Feb	Piccinini et a 2017 Apr
Hospital LOS					
- ICPM	17,21 (8-29)	21 (11-30)	28,5 (SD 12,1)	17 (9-26)	20 (13-30)
- Non-ICPM	10,15 (5-20)	6 (3-17)	26,1 (SD 13,5)	6 (3-14)	9 (4-17)
	(P < 0,001)	(P<0,0001)	(P= 0,23)	(P<0,001)	(P<0,001)
ICU LOS					
- ICPM	14,52 (SD	15 (8-21)	14,3 (SD 6,4)	12 (6-17)	14 (9-21)
- Non-ICPM	11,8)	3 (2-7)	11,6 (SD 5,8)	4 (2-9)	5 (3-11)
	10,17 (SD	(P<0,0001)	(P =0,004)	(P<0,001)	(P<0,001)
	10,99)				
	(P<0,001)				
mechanical					
ventilation					
- ICPM		11 (6-18)	6,7 (SD 3,5)	8 (4-14)	11 (5-17)
- Non-ICPM		3 (1-6)	5,6 (SD 2,4)	2 (1-6)	3 (2-7)
		(P<0,0001)	(P=0,019)	(P<0,001)	(P<0,001)

Hospital LOS = hospital length of stay, ICU LOS = intensive care unit length of stay, Non-ICPM = non-intracranial pressure monitoring, ICPM = intracranial pressure monitoring
Data are presented as median (interquartile range).
Data at You et al. and the ICU LOS of Dang et al. are presented as mean (standard deviation).

ICU length of stay

All of the articles that used ICU LOS as an endpoint showed a significant lower ICU LOS in patients with ICPM. The measured ICU LOS differences between 12 (Aiolfi et al. [8]) and 14,52 days (Dang et al. [9]) when ICP was monitored and between 3 (Maclaughlin et al. [11]) and 11,6 days (You et al. [15]) when there was no ICPM.

Duration of mechanical ventilation

The four articles that reported mechanical ventilation days all showed a significant higher duration of ventilation when patients' ICP was monitored.

Ventilation days ranged from 6,7 (You et al. [15]) to 11 days (Maclaughlin et al. [11]) in the ICPM group and from 2 (Aiolfi et al. [8]) to 5,6 days (You et al. [15]) in the non-ICPM group.

Discussion

We conducted a systematic review to evaluate the association between intracranial pressure monitoring and in-Hospital mortality. Furthermore, we analysed the effect of ICPM on hospital length of stay, intensive care unit length of stay and duration of mechanical ventilation. A meta-analysis of 9 observational studies did not show a significant decrease in in-hospital mortality. Furthermore, ICPM seems to increase hospital LOS, ICU LOS and duration of mechanical ventilation.

The reason for these outcomes are not clear. This association might be the consequence of complications due to the placing of an ICP monitor, for example haemorrhagic complications [19] or to the used therapy when ICP raised. [20] Other possibilities are that ICP monitors do no harm in patients, but an effective treatment for ICP elevation is not yet available. This has no influence on whether ICPM is useful. At last, this result could be caused by the fact that sedation is stopped earlier in patients with no monitoring, logically leading to a shorter hospital stay. These last two explanations are not yet reviewed and can be a topic for further research.

Figure 4 - Forest plot of comparison: In-hospital mortality in patients with ICPM compared to no ICPM, outcome: Relative risk of ICP monitoring.

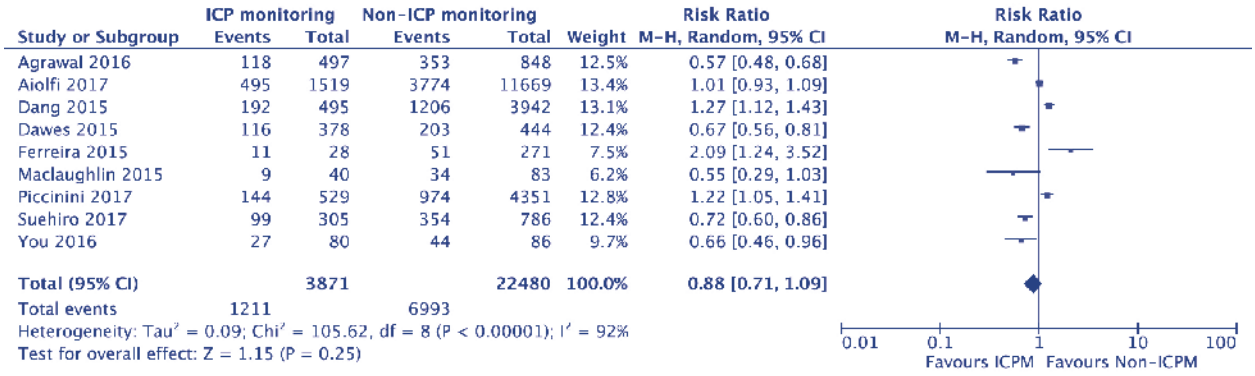
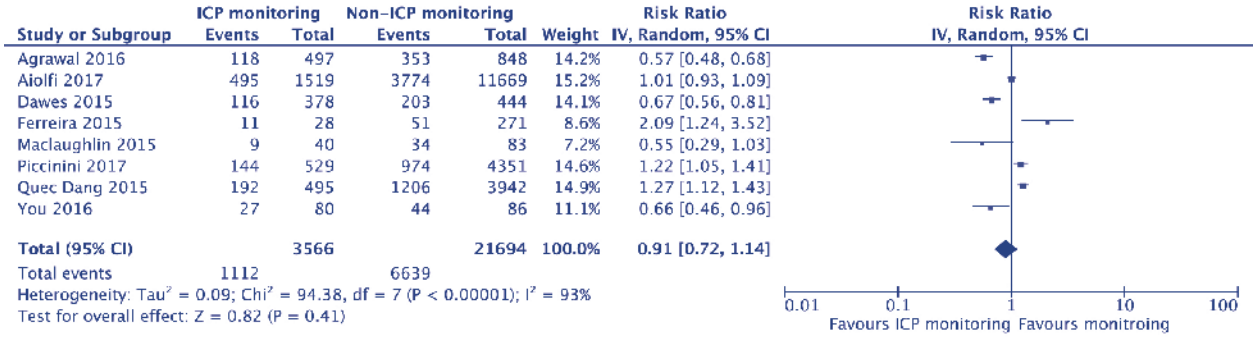


Figure 5 - Forest plot of comparison: In-hospital mortality in patients with ICPM compared to no ICPM, outcome: Relative risk of ICP monitoring sub-analysis.



The majority of the articles used a patient population were all patients had an indication for ICPM according to the current guidelines of the Brain Trauma Foundation (BTF guidelines). Yet a significant subset of the patients did not receive an ICP monitor. The most common reason presented in the articles for no monitor placement was due to clinicians' decision. No further explanation was given. Thus, this decision may have been influenced by a variety of factors. So determining an unbiased outcome in these studies is problematic.

Even more, Ferreira et al. [16] did not mention an ICPM indication for both groups at all. Due to this approach, biases may have occurred.

In addition Aiolfi et al. [8] and Piccinini et al. [12] used for their study the same database in the same time slot. Also they used the same inclusion and exclusion criteria. Yet their patient population and outcomes difference. This raises doubts about the quality of both articles.
You et al. [15] were the only ones that found that ICPM did not increase hospital LOS. The articles that described ICP measurement used all intraparenchymal monitoring as well as extracranial ventricular drains, except for You et al. However, performed research did not show a difference between both techniques. [7]
There were several limitations to this meta-analysis. First only the PubMed electronic database was searched. This means not all relevant articles are included. Still this database is a representative source for all articles existent. Therefore, we think no bias did occur on this point.

Secondly there was a considerable heterogeneity (I2=92%) for our primary endpoint in the analysed articles. A clear explanation for this wasn't found concerning age, sex or inclusion criteria. Also our review consisted partly of retrospective studies. These studies can carry biases easily, such as selection and information bias. This may negatively influence the veracity of a review.
Despite the fact that a part of the articles used a propensity score to reduce the risk of biases, these studies used propensity scores in different kinds of ways. It was not possible to combine these data in a meta-analysis. This means raw data, which are not corrected for confounders, are used.

At last, it should be noted that the presence of ICPM does not directly relate to the mortality and morbidity of patients. However, therapeutic decisions could be made based on the outcome of ICPM. Therefore ICPM could indirectly have an effect on the final mortality rates, as it could deliver better understanding of a patients status and give medical specialists the opportunity to anticipate based on this ICPM data.

Finally, although the systematic review is carried out according to the methodological standards, the results of any meta-analysis are limited by the quality of the studies included.

Yuan et al. [17] found a trend towards the association of ICPM with lower in-Hospital mortality based on studies conducted after 2012. Based on the results of this review this predicted trend cannot be confirmed. An explanation therefore is that this review contains more recent studies and these studies are not associated with a greater decrease in mortality.

Conclusion

In conclusion, in this review intracranial pressure monitoring does not seem to decrease in-hospital mortality in patients with traumatic brain injury. Future prospective studies must help to determine for who ICPM is useful, and the interpretation and treatment threshold of intracranial hypertension should be more defined.

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Serum calprotectin as a potential marker for monitoring disease activity in vasculitis

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Word count: 2998

Abstract

***Objective*: The aim of this systematic review was to investigate whether serum calprotectin could be used as a marker for monitoring the disease activity of different types of vasculitis.**
***Methods*: We conducted a systematic review by performing a search in the PubMed database in January 2018 on articles concerning the association between serum calprotectin levels and vasculitis disease activity. Our primary outcome measure was vasculitis disease activity.**
***Results*: We included eight articles, with a total of 511 participants. Seven articles observed a positive correlation between serum calprotectin levels and parameters for disease activity. Especially therapy response and relapse were significantly associated with calprotectin levels.**
***Discussion*: We observed that serum calprotectin levels could be a potential marker for monitoring the vasculitis disease activity. Further research with similar disease activity parameters is needed on the predictive value of calprotectin levels.**

Introduction

Vasculitis is characterized by inflammation of the blood vessels which eventually leads to damage of the vessels.[1] As a result, the lumen of the involved vessels can compromise causing ischaemia or the vessels could cause bleeding by rupture of the vascular wall.[1,2] Interruption of blood flow as well as bleeding can lead to organ dysfunction in the local and perfusion area of the vessel.[2] Any type and size vessel can be involved in any organ. Vasculitis can be limited to a single organ or it can be present in multiple organs.[1] The vasculitis syndromes are classified according to the size of the affected vessels which can be small, medium or large.[2] Examples of primary vasculitis syndromes are antineutrophil cytoplasmic antibodies (ANCA) associated vasculitis (AAV), microscopic polyangiitis (MPA), Behçet Disease (BD), Henoch-Schönlein purpura nephritis (HSPN), Kawasaki Disease (KD), polymyalgia rheumatica (PMR) and giant cell arteritis (GCA).[3]

Primary vasculitis can not be cured, however, the symptoms can be treated. Irreversible organ failure, caused by progression of the disease, can be prevented by use of immunosuppressant drugs.[2] Therefore, monitoring the disease activity of the vasculitis is important in order to adjust therapy on time.

Disease activity can be determined based on different parameters. There are parameters for all types of vasculitis and parameters for specific types of vasculitis. The parameters are presented in Panel 1 with the abbreviations and their link to vasculitis disease activity.

Biomarkers of systemic inflammation could help in distinguishing active from inactive vasculitis. There have been reports

Panel 1 - Parameters for all types and specific types of vasculitis and their link to vasculitis disease activity

Parameters for all types of vasculitis

- C-reactive protein (CRP): acute phase reactant and marker of systemic inflammation
- Birmingham Vasculitis Activity Score (BVAS): validated scoring system for vasculitis disease activity
- White blood cell count (WBC): acute phase reactant and marker of systemic inflammation
- Erythrocyte sedimentation rate (ESR): non-specific marker of inflammation
- Relapse: recurrence of the disease and disease acivity
- Distinction between acute disease and remission
- E-selectin: marker of vascular endothelial cell dysfunction
- Upregulated platelet aggregation, inflammatory and endothelial permeability genes
- Therapy response: marker of decrease in inflammation and disease activity.

Parameters for specific types of vasculitis

- Behçet Disease Current Activity Form (BDCAF): scoring system for Behçet Disease
- Cardiac involvement for Kawasaki disease: Kawasaki disease involves vasculitis of the coronary arteries. Therefore, cardiac involvement in the disease is linked to disease activity
- Renal changes for Henoch-Schönlein purpura nephritis occur due to disease activity:
  - Urinary protein excretion
  - Activity index (AI): a score for acute renal changes
  - Chronicity index (CI): a score for chronic renal changes
  - The degree of crescent formation

Figure 1 - Quality assessment

1. Were eligibility criteria specified?	0 / 1
2. Were point estimates, measures of variability and P-values presented for the disease activity outcome measures?	0 / 1 / 2 / 3
3. Were major outcome measures for vasculitis disease activity used?	0 / 2

on the use of myeloid-related protein 8/14 complex (MRP8/14) levels as a predictor of the disease activity of inflammatory disorders.[4] MRP8/14, also known as S100A8/A9 or calprotectin, is a heterodimer complex of the proteins MRP8 (S100A8) and MRP14 (S100A9) which are expressed by monocytes, neutrophils and early differentiated macrophages.[5,6] When calprotectin is secreted, it binds to activated endothelial cells where it causes proinflammatory effects. As a result, the endothelial monolayer integrity impairs and apoptosis as well as necrosis occurs, which eventually can lead to vasculitis.[7,8] These effects make calprotectin a potential biomarker of disease activity or tissue damage in vasculitis, in which endothelial activation and vascular damage play a central role.

Therefore, based on the current literature, we hypothesized that serum calprotectin has a positive correlation with vasculitis disease activity. The aim of this systematic review is to investigate in the existing literature whether serum calprotectin could be used as a marker for monitoring the disease activity of different types of vasculitis.

Methods

Search strategy

We conducted a systematic review by performing a search in the PubMed database on January 10, 2018 using the following MeSH Terms: "Vasculitis" [Mesh] AND "Leukocyte L1 Antigen Complex" [Mesh]. We refined our search to articles published in English. We performed our final search on January 22, 2018.

Study selection

We individually screened the titles and abstracts of the articles. We included articles concerning the association between serum calprotectin levels and vasculitis disease activity. We excluded reviews and articles based on animal subjects or fecal calprotectin (FC) levels. Subsequently, we separately assessed the eligibility of the articles which met the inclusion and exclusion criteria by reading the full-text articles. In case of disagreement, we reached consensus through discussion. We checked the references of the included articles for additional articles.

Data extraction

Our primary outcome measure was vasculitis disease activity. We determined the disease activity by collecting data on parameters for vasculitis. We screened the articles for the different parameters which were linked to vasculitis disease activity. We grouped the results based on the different parameters, beginning with parameters discussed in multiple studies and ending with parameters in single studies. The aim was to perform a meta-analysis and to subdivide the results in small, medium and large vessel vasculitis.

Quality assessment

We individually assessed the articles' quality and reached consensus through discussion in case of disagreement. We performed a quality assessment by using our own quality score system [Figure 1]. Our scoring system focused on three criteria. First, we required the eligibility criteria to have been specified by a description of the inclusion and exclusion criteria. Our second criterion focused on the point estimates, measures of variability and P-values. A maximum score was achieved when point estimates as well as measures of variability were given in the article. Our last criterion included the use of major outcome measures for vasculitis disease activity. Our own quality assessment made it possible to assess the quality of the articles based on relevant criteria specific for our research question. The possible maximum score was 6 points. A more detailed explanation is given in the appendix.

Results

Study characteristics

Our PubMed search resulted in 17 articles. After screening the titles and abstracts of the articles, we excluded 7 articles based on the exclusion criteria. After full-text review, we excluded 2 articles, which did not mention the association between serum calprotectin and vasculitis. Eventually, we included 8 articles, which met the eligibility criteria. Reference checking did not result in additional relevant articles. Figure 2 presents a flowchart illustrating the article selection process.

Table 1 presents the study characteristics of the included studies. This systematic review included trials, spin-offs and a prospective longitudinal study. The publication date of the studies varied from 2005 to 2017. The study population consisted of participants from the United Kingdom, Turkey, Japan, Germany and Norway. Four studies included adult participants, three studies were based on children and one study consisted of human micro-

Figure 2 - Flowchart of the literature selection

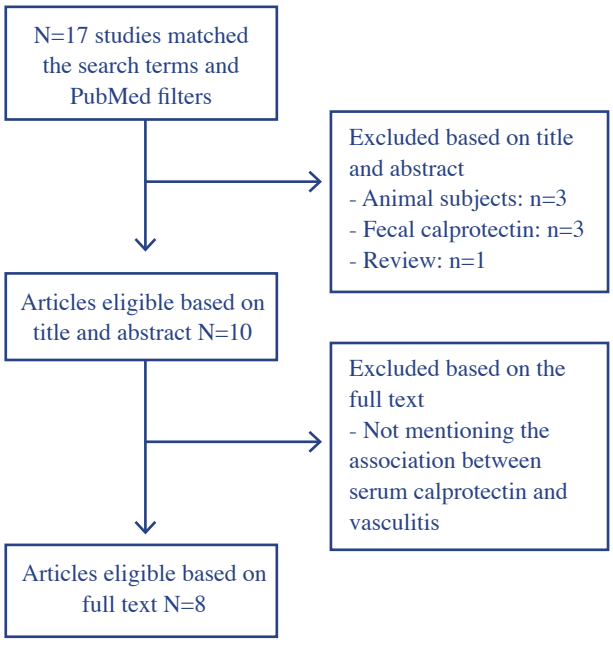

Table 1 - Study characteristics

Study	Type study	Study population/ cell line	Number of participants with vasculitis (n)	Type vasculitis	Measured disease activity parameters	Result quality assessmenters
Pepper et al. (11) UK, 2017	Spin-off multi-center RCT	Median 52.5 years (15-92)	144	AAV	- BVAS - Relapse - WBC count - CRP - Therapy response	4
Oktayoglu et al. (13) Turkey, 2015	Trial	Mean 35.5 years ± 12.2	48	BD	- BDCAF - WBC count - ESR - CRP	4
Pepper et al. (14) UK, 2013	Trial and spin-off	Median 61 years (16-85)	114	AAV	- Relapse - Acute disease and disease remission - Neutrophil and monocyte count	4
Kawasaki et al. (15) Japan, 2011	Trial	Mean 8.6 years ± 2.8	30	HSPN	- AI - CI - Urinary protein excretion - E-selectin - Degree of crescent formation	4
Hirono et al. (10) Japan, 2006	Trial	Median 2.6 years (2 months - 7.3 years)	61	KD	- Therapy response	6
Viemann et al. (7) Germany and Japan, 2005	Trial	HMEC cell line and KD patients (age not mentioned)	21	KD	- Therapy response - Gene expression	4
Abe et al. (9) Japan, 2005	Trial	Median 19.5 months (2-76)	46	KD	- Neutrophil and monocyte count - CRP - Therapy response - Cardiac involvement	5
Brun et al. (12) Norway, 2005	Prospective longitudinal study	Median 74 years (70-78)	47	PMR and GCA	- ESR - CRP - Therapy response	4

Abbreviations: AAV, ANCA-associated vasculitis; BD, Behçet Disease; HSPN, Henoch-Schönlein Purpura Nefritis; KD, Kawasaki Disease; PMR, Polymyalgia Rheumatica; GCA, Giant Cell Arteritis; BVAS, Birmingham Vasculitis Activity Score; WBC, White Blood Cell; CRP, C-Reactive Protein; BDCAF, Behçet Disease Current Activity Form; ESR, Erythrocyte Sedimentation Rate; AI, Activity Index; CI, Chronicity Index.

vascular endothelial cells (HMEC-cell line) and human serum calprotectin isolation. The number of participants included, varied from 21 to 144, with a total number of 511 participants. The articles covered different types of vasculitis. Two studies looked at AAV, three studies focused on KD and single studies included BD, HSPN, PMR and GCA. The studies used different parameters for disease activity: C-reactive protein (CRP), therapy response, Birmingham Vasculitis Activity Score (BVAS), relapse, white blood cell count (WBC count), erythrocyte sedimentation rate (ESR), Behçet Disease Current Activity Form (BDCAF), acute disease and disease remission, E-selectin, renal involvement - urinary protein excretion, Activity Index (AI), Chronicity index (CI) and the degree of crescent formation -, cardiac involvement and altered expression of platelet aggregation, inflammation and endothelial integrity genes. Some parameters were determined in multiple studies, while other parameters were measured in single studies. A difference in major and minor parameters for disease activity was made based on their specificity for vasculitis, besides their role in general inflammation. Non-specific parameters, such as CRP, could also be heightened because of the circumstances, like fever. We considered BVAS, BDCAF, therapy response, relapse, acute disease and disease remission, cardiac involvement for KD and renal involvement for HSPN as major outcome measures.

Table 2 presents an overview of the significant and non-significant results per study and the study's overall conclusion about the use of serum calprotectin levels as an indicator of vasculitis disease activity.

Study results: CRP

Pepper et al.[11] observed the correlation between serum calprotectin levels and CRP levels after the start of treatment with either a combination of cyclophosphamide and azathioprine (CYC/AZA) or rituximab (RTX). There was a significant correlation between serum calprotectin levels and CRP levels at the start (r=0.22, P=0.016) and one month after the start of treatment (r=0.24, P=0.005). By month 2, there was no significant correlation between serum calprotectin and CRP levels.

Table 2 - Results of the vasculitis disease activity parameters

Study	Significant results	Non-significant results	Study's conclusion*
Pepper et al. (11) UK, 2017	- BVAS[A] (r=0.27, P=0.002) - Relapse[C+D] ([C] month 2 RR=1.81 (95% CI 1.11-2.93) and HR=2.2 (95% CI 1.17-4.26, P=0.016); month 6 RR=1.76 (95% CI 1.1-2.83) [D] month 2 relapse 4898 ng/ml (1798-19152) and non-relapse 3900 ng/ml (1112-9413), P=0.05) - WBC count (baseline r=0.23, P=0.01; month 1 r=0.34, P=0.0001; month 2 r=0.32, P=0.0002) - CRP[E] (r=0.22, P=0.016 and r=0.24, P=0.005) - Therapy response ([A] 6509 ng/ml (1002–92267) and [B] 3141 ng/ml (346–19383), P<0.0001)	- BVAS[B] - Relapse[D] - CRPF	Useful
Oktayoglu et al. (13) Turkey, 2015		- BDCAF (p=0.230, P=0.116) - WBC count (r=0.163, P=0.268) - ESR (p=0.064, P=0.666) - CRP (r=0.098, P=0.506)	Not useful
Pepper et al. (14) UK, 2013	- Relapse (P<0.005) - Acute disease (13453 ng/ml (4769-40000)) and disease remission (8957 ng/ml (3860-25083)) (P<0.001) - Neutrophil count (r=0.29, P<0.05)	- Monocyte count	Useful
Kawasaki et al. (15) Japan, 2011	- AI (r=0.53, P<0.01) - E-selectin (r=0.58, P<0.01)	- CI (r=0.03, P=0.99) - Urinary protein excretion (r=0.42, P=0.06) - Degree of crescent formation (r=0.34, P=0.06)	Useful
Hirono et al. (10) Japan, 2006	- Therapy response[B] (non-responders 4900 ± 4519 ng/ml and responders 1265 ± 1012 ng/ml, P<0.01)	- Therapy response[A] (non-responders 4220 ± 2699 ng/ml and responders 3251 ± 1981 ng/ml)	Useful
Viemann et al. (7) Germany and Japan, 2005	- Therapy response ([A] 3630 ± 480 ng/mL and [B] 2110 ± 360 ng/mL, P=0.01) - Gene expression**		Useful
Abe et al. (9) Japan, 2005	- Neutrophil and monocyte count[B] (respectively, p=0.61; P<0.001 and p=0.52; P<0.01) - Therapy response ([A] 25.3 ± 1.5 and [B]18.4 ± 1.7 µg/ml, P=0.001) - Cardiac involvementG (P =0.02) - CRPB (r=0.76, P<0.0001)	- Neutrophil and monocyte count[A] (respectively, p=0.25 and p=0.03) - CRPA (r=0.23)	Useful
Brun et al. (12) Norway, 2005	- ESR (r=0.55, P<0.01) - CRP (r=0.60, P<0.01) - Therapy response (r=0.36, P<0.01)		Useful

Abbreviations: BVAS, Birmingham Vasculitis Activity Score; WBC, White Blood Cell; CRP, C-Reactive Protein; BDCAF, Behçet Disease Current Activity Form; ESR, Erythrocyte Sedimentation Rate; AI, Activity Index; CI, Chronicity Index.
* Study's conclusion about the use of serum calprotectin levels as an indicator of vasculitis disease activity
** Upregulated expression of platelet aggregation, inflammation and endothelial permeability genes.
A At the start of treatment
B After treatment
C Increase in serum calprotectin between baseline and different time points
D Absolute serum calprotectin at different time points
E At the start of treatment and 1 month after treatment
F By month 2 after treatment
G 4 of the 6 patients with cardiac involvement had no decrease in serum calprotectin levels

Brun et al.[12] observed a significant correlation between calprotectin and CRP levels during prednisolone use with dose reduction in patients with PMR or GCA (r=0.60, P<0.01).
On the other hand, Oktayoglu et al.[13] showed that there was no significant correlation between calprotectin and CRP levels in patients with BD (r=0.098, P=0.506).
Abe et al.[9] found no significant correlation between calprotectin and CRP levels before intravenous immune globulin (IVIG)-treatment (r=0.23), but did find a significant correlation between calprotectin and CRP levels after IVIG-treatment (r=0.76, P<0.0001).

Study results: therapy response

Firstly, Hirono et al.[10] compared the serum calprotectin concentrations in patients with KD who responded to IVIG treatment to the patients who did not respond to therapy. There was no significant difference in calprotectin levels between responders and non-responders before the start of treatment. However, after treatment calprotectin levels were significantly higher in non-responders than in responders (respectively 4900 ±4519 ng/ml and 1265 ±1012 ng/ml, P<0.01).
Secondly, Viemann et al.[7] registered serum calprotectin concentrations before and after IVIG treatment. Initially, the calprotectin levels in patients with KD were 3630 ±480 ng/mL. Within 24 hours of IVIG therapy, the calprotectin levels dropped significantly to 2110 ±360 ng/mL (P=0.01). Moreover, the reduction in calprotectin levels was associated with decreasing signs of vasculitis.
Thirdly, Abe et al.[9] measured the plasma calprotectin levels before and after IVIG therapy. Calprotectin levels were significantly higher pre-IVIG than post-IVIG (respectively, 25.3 ±1.5 and 18.4 ±1.7 µg/ml; P=0.001).
Furthermore, Pepper et al.[11] found a significant decrease in serum calprotectin levels after treatment compared to baseline (respectively, 3141 ng/ml (346-19383) and 6509 ng/ml (1002-92267), P<0.0001).
In addition, Brun et al.[12] identified a significant correlation between prednisolone dose and calprotectin levels (r=0.36, P<0.01).

Study results: relapse

Pepper et al.[11] observed no significant difference in absolute calprotectin levels and relapse, except for a significant difference at month 2 between PR3-ANCA-positive patients who did

and did not experience relapse (P=0.05). An increased calprotectin level at month 2 compared to baseline meant a relative risk for relapse of 1.81 (95% CI 1.11-2.93) and a hazard ratio of 2.2 (95% CI 1.17-4.26, P=0.016). When comparing month 6 with baseline, an increase in calprotectin levels was associated with a relative risk for relapse of 1.76 (95% CI 1.1-2.83). Furthermore, participants with an increase in serum calprotectin levels relapsed significantly earlier and more frequent than participants with a decrease in serum calprotectin levels for month 2 (P=0.004) and for month 6 (P=0.003).

The correlation between serum calprotectin and relapse was further investigated by Pepper et al.[14]. Patients who underwent relapse during the study had significantly higher levels of calprotectin than the non-relapsing patients (P<0.005) at a median of 13 months after the initiation of immunosuppressive therapy.

Study results: WBC count

Pepper et al.[11] showed a correlation of serum calprotectin with the WBC count at baseline (r=0.23, P=0.01). This correlation persisted at month 1 and 2 after treatment started (respectively r=0.34, P= 0.0001 and r=0.32, P=0.0002).

On the contrary, Oktayoglu et al.[13] found no correlation between serum calprotectin and WBC count (r=0.163, P=0.268). Two studies reported the neutrophil and monocyte counts instead of the WBC count. Pepper et al.[14] described a significant correlation between the total neutrophil count and the serum calprotectin levels (r=0.29, P<0.05). There was no correlation with the blood monocyte count. Abe et al.[9] looked at the neutrophil and monocyte counts in patient with KD before and after high-dose IVIG treatment. The calprotectin levels showed a significant correlation with the neutrophil count (ϱ=0.61, P<0.001) as well as with the monocyte count (ϱ=0.52, P<0.01) in post-IVIG patients. Before IVIG therapy there was no significant correlation between the neutrophil (ϱ=0.25) and monocyte count (ϱ=0.03) and calprotectin levels.

Study results: ESR

Two studies measured ESR. In the study of Oktayoglu et al.[13] the serum calprotectin levels did not correlate with ESR (ϱ=0.064, P=0.666). However, Brun et al.[12] showed a significant correlation between the serum calprotectin levels and ESR (r=0.55, P<0.01).

Study results: other disease activity parameters

Some parameters for disease activity were determined in single studies. At the start of treatment, Pepper et al.[11] registered a significant correlation between calprotectin levels and the BVAS for granulomatosis with polyangiitis (BVAS/GPA) (r=0.27, P=0.002). The correlation between calprotectin levels and BVAS/GPA did not remain significant at 1, 2 and 6 months after the start of treatment.

The study of Oktayoglu et al.[13] used the BDCAF score to assess the disease activity. In this study serum calprotectin levels did not correlate with BDCAF scores (ϱ=0.230, P=0.116).

Pepper et al.[14] compared the serum calprotectin levels in patients with acute disease and patients with disease remission. There was a significant difference (P<0.001) in the calprotectin levels between acute disease (median 13453 ng/ml (4769–40000)) and disease remission (median 8957 ng/ml (3860–25083)).

Kawasaki et al.[15] used several parameters for HSPN activity. The study performed correlation analyses with serum calprotectin levels for serum E-selectin levels, urinary protein excretion, AI, CI and the degree of crescent formation. Serum E-selectin levels correlated significantly with serum calprotectin levels (r=0.58, P<0.01). AI showed a significant correlation with serum calprotectin levels (r=0.53, P<0.01), whereas CI showed no correlation (r=0.03, P=0.99). Urinary protein excretion and the degree of crescent formation were also not significantly correlated with serum calprotectin levels (respectively r=0.42, P=0.06 and r=0.34, P=0.06).

The study of Abe et al.[9] included patients with KD, which preferentially affects coronary arteries.[16,17] Therefore, Abe et al.[9] monitored cardiac involvement, defined as abnormal cardiac function and coronary artery lesions. The decrease in the plasma calprotectin after IVIG treatment was absent in four of the six patients who had cardiac involvement during the acute phase of the disease (P= 0.02, by $\chi 2$ test with Yates' correction).

Viemann et al.[7] demonstrated the influence of calprotectin on endothelial cell functions. The study showed that calprotectin regulates the expression of multiple genes, which can be subdivided into three functional categories, namely platelet aggregation, inflammation and endothelial integrity. Most of the platelet aggregation and inflammation genes were upregulated, while most of the endothelial integrity genes were downregulated by calprotectin.

Discussion

The aim of this systematic review was to investigate whether serum calprotectin levels could be used as a marker for monitoring the disease activity of different types of vasculitis. Based on this systematic review, we observed that serum calprotectin levels could be a potential marker for monitoring the vasculitis disease activity.

The majority of the measured parameters, which are linked to vasculitis disease activity, showed a positive correlation with serum calprotectin levels. Major parameters, which supported the positive correlation, were relapse, acute disease and disease remission, therapy response, BVAS and cardiac involvement. Furthermore, seven out of the eight included articles concluded an association between serum calprotectin levels and vasculitis disease activity. These findings make calprotectin a potential useful indicator for vasculitis disease activity.

Oktayoglu et al.[13] did not find a significant correlation between serum calprotectin levels and the disease activity parameters BDCAF, WBC count, ESR and CRP. This was the only included study based on BD, which can affect all sizes of blood vessels, whereas AAV, HSPN, KD, PMR and GCA primarily involve only small, medium or large vessels.[2,18] It is remarkable that the vasculitis diseases, which affect one size, all show a positive correlation with calprotectin, while the vasculitis that involves all these sizes does not show this correlation. If Oktayoglu et al.[13] had focused on therapy response or relapse, the outcome might have been in favor of serum calprotectin as a marker. In five studies therapy response showed a significant result, while

WBC count - including neutrophil and monocyte count -, CRP and ESR variated more in outcome.

We performed a quality assessment with our own scale specific for this systematic review. The assessment did not result in remarkable findings which could explain the non-significant results of Oktayoglu et al.[13]

The included studies used different outcome measures to determine disease activity. This study heterogeneity formed a limitation to our systematic review, as there was no accurate way to directly compare the various parameters. In addition, only 5 parameters were observed in multiple studies, while the other 10 parameters were measured in single studies. This affected the power of evidence to draw a conclusion about the correlation between serum calprotectin and a specific disease activity parameter.

The parameters we used as primary outcomes were not in all cases the primary outcomes of the included studies. Therefore, the studies usually presented only P-values for these parameters instead of point estimates with the measures of variability. For this reason, statistical analyses were hard to perform. Moreover, we were not able to accurately determine the relevance of the significant results with nothing but the P-value.

Prior to the systematic review we aimed to subdivide the results into three categories of vasculitis: small, medium and large vessel. Because of the limited amount of studies, it was not possible to come to a conclusion about the serum calprotectin levels and the disease activity in specific types of vasculitis.

Overall, we conclude that serum calprotectin can be useful for monitoring vasculitis disease activity. Therapy response and relapse showed promising results for serum calprotectin as a clinical marker. However, because of the non-significant results in various studies, further research is needed on the predictive value of serum calprotectin levels. We recommend conducting multiple studies with similar outcome measures for vasculitis disease activity in order to perform a meta-analysis on the value of serum calprotectin levels as a marker. The most suitable disease activity parameter would be the BVAS, since this scale focuses on the vasculitis activity and can be used for all types of vasculitis. When serum calprotectin proves to be a relevant clinical marker for disease activity, it can be used to prevent relapse or exacerbations of vasculitis by adjusting therapy on time.

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Appendix

Explanation

1. Inclusion and exclusion criteria have to be described
   - 0 points: eligibility criteria are not specified.
   - 1 point: eligibility criteria are specified.
2. Point estimates are: means, medians, modes, correlation coefficient etc. Measures of variability are: ranges, standard deviations, 95% confidence intervals etc.
   - 0 points: no point estimates and no measures of variability and no P-values for significant outcomes neither for non-significant outcomes.
   - 1 point: P-values are given for the significant outcomes or for the non-significant outcomes in case there were no significant outcomes.
   - 2 points: point estimates as well as measures of variability are given for one or more significant outcomes.
     - o Deduction of 1 point if one or more outcomes are mentioned without point estimates and measures of variability and P-values.
   - 3 points: point estimates as well as measures of variability are given for all significant and non-significant outcomes
3. Major outcome measures are: BVAS, BDCAF, therapy response, relapse, acute disease and disease remission, E-selectin, cardiac involvement for KD and renal involvement for HSPN.
   - 0 points: no major outcome measure
   - 2 points: one or more major outcome measure(s)

The maximum score is 6 points.

Systematic Review

Presence of calcium in symptomatic versus asymptomatic carotid atherosclerotic plaques: *a systematic review and meta-analysis*

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Abstract

Understanding processes underlying carotid plaque stability is essential to prevent and treat cerebrovascular events. The influence of calcification on plaque stability remains uncertain. The aim of this systematic review and meta-analysis is to compare the presence of calcium between symptomatic and asymptomatic carotid atherosclerotic plaques (CAPs).
A literature search was performed on PubMed. The primary outcome was the presence of calcium in symptomatic versus asymptomatic CAPs, secondary outcomes were presence of intraplaque hemorrhages and necrosis.
The literature search was performed on January 10th 2017. Five studies were included. The presence of calcium was not significantly associated with symptomatic CAPs (OR, 0.642 [CI 0.320, 1.288]). Two studies found intraplaque hemorrhage is more common in symptomatic CAPs (OR, 5.494 [CI 1.798-16.797] and OR, 3.363 [CI 1.748-6.468]). Two studies found necrosis is significantly more present in symptomatic CAPs (OR, 2.287 [CI 1.233-4.243] and OR, 7.773 [CI 1.416-42.660]).
There is no significant difference in the presence of calcium between symptomatic versus asymptomatic CAPs. More research is needed to investigate the exact role of calcium in carotid atherosclerotic plaques.

Abbreviations: CAP, carotid atherosclerotic plaque; OM, osteoid metaplasia; OR, odds ratio

Keywords

Plaque, Atherosclerotic; Calcification; Carotid Arteries; Carotid Stenosis.

Introduction

Approximately 6.6 million Americans have experienced a stroke, while currently every 40 seconds an American gets a stroke. The American Heart Association predicts a 20% increase in stroke prevalence by 2030 compared to
2012. 5% of deaths in the USA annually are caused by strokes.[1]
Atherosclerosis of the carotid arteries can cause strokes due to plaque rupture or thromboembolism. Therefore, understanding processes underlying carotid plaque stability is essential to prevent and treat cerebrovascular events.
Plaque features determine the stability of the atherosclerotic plaque. Plaque components such as intraplaque hemorrhage and necrosis are associated with plaque instability.[2] However, the influence of calcification on plaque stability remains uncertain because of a discrepancy in results.
One study has found patients with a stroke had a significantly higher chance to have non-calcified plaques.[3] Calcification was also negatively associated with symptomatic disease.[3] Investigators of another study found that calcification is significantly associated with asymptomatic carotid atherosclerotic plaques (CAPs) and therefore tends to stabilize plaques.[4]
However, other studies found opposite results. Nandalur et al. suggest that plaque calcification is a risk marker for cerebrovascular events and is significantly associated with symptoms.[5] Menini et al. found a significant correlation between plaque calcification and plaque instability.[6]
Thus, these opposite results show there is a need to assess the relationship between plaque calcification and symptomatic CAPs. The authors' aim was to compare the presence of calcium in symptomatic versus asymptomatic CAPs and to compare the presence of several vulnerable plaque features

in symptomatic versus asymptomatic CAPs. Additionally, a meta-analysis on calcium presence was performed.

Methods

Search strategy

A literature search was performed on PubMed, using the following search stream: "Plaque, Atherosclerotic" [Mesh] AND ("symptomatic" [tiab] OR "asymptomatic" [tiab]) AND ("calcification" [tiab] OR "calcinosis" [Mesh]) AND ("carotid arteries" [Mesh] OR "Carotid Stenosis" [Mesh]).

Articles were excluded if a) their primary outcomes were the evaluation or comparison of imaging techniques or treatments b) they studied the relationship between plaque calcification and consequences other than stroke c) CAPs were compared to non-carotid atherosclerotic plaques d) the full text was not available e) there was no determination of the presence of calcium in CAPs f) there was no description of any relation between calcium and symptomatic or asymptomatic CAPs.

The authors conducted a literature search individually and in duplicate. Then the articles were screened on title and abstract and if needed on full text. After this screening a meeting was held to exclude records based on all exclusion criteria. Disagreement was resolved by consensus. Disagreements would be resolved by a third party if no consensus could be reached.

Data extraction and end points

After including studies to this systematic review, figures and tables showing primary or secondary outcomes of each article were studied. Odds ratios were extracted, representing the ratio of CAPs being symptomatic versus asymptomatic, given the plaque is calcified. When this ratio was not available, numbers of patients in each group (calcified versus non-calcified, symptomatic versus asymptomatic) were extracted and the odds ratio was calculated manually (see subheading Statistical analysis).

The primary outcome of this systematic review is the presence of calcium in symptomatic versus asymptomatic CAPs. The authors also investigated the presence of intraplaque hemorrhage and necrosis in symptomatic versus asymptomatic CAPs, as secondary outcome. Therefore no meta-analysis is performed on these data.

Statistical analysis

A statistical analysis was performed using OpenMeta[analyst] (version from 2012). The authors transformed the study outcomes to odds ratios with the following formula:

$$[1]\quad \text{Odds Ratio} = \frac{P[CalSc]/P[noCalSc]}{P[CalASc]/P[noCalASc]}$$

Equation 1/ In this formula the odds ratio of patients with symptomatic CAPs [lSc] and patients with asymptomatic CAPs [lASc], given calcified plaques [Ca] or non-calcified plaque [noCa] is calculated.

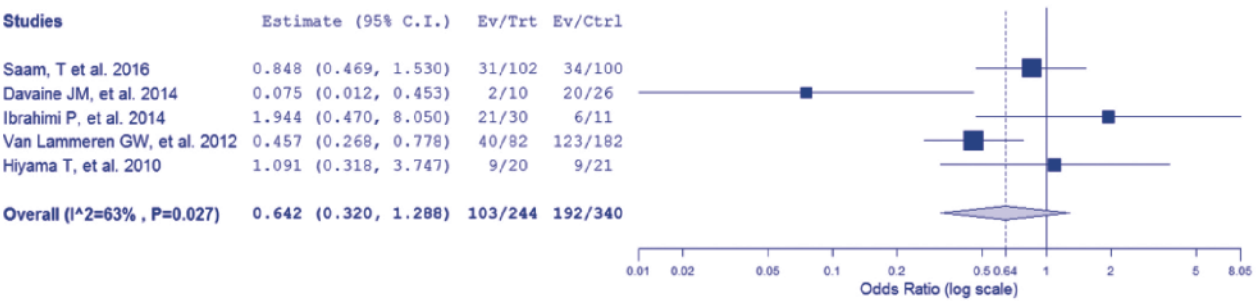
95% confidence intervals were calculated using an online confidence interval calculator. All odds ratios were made visible in a forest plot. The authors performed a binary-random effects model and defined I^2 as a way to determine heterogeneity between all included studies. Heterogeneity was considered significant if $I^2 > 30\%$. It was defined that the use of a fixed-effects model was justified if the heterogeneity was not significant.

Table 1 - Baseline characteristics of included articles

PMID:	Authors:	Year of publication:	Comparison:	Definitions:	Carotid atherosclerotic plaques (n)	Study outcome:	Calcium detected by:
26940800	Saam T, et al.	2016	Symptomatic plaques vs Asymptomatic plaques	Symptomatic= ipsilateral DWI* lesion Asymptomatic= contralateral DWI* lesion	202	% of plaques containing any calcification	MR imaging
25259713	Davaine JM, et al.	2014	Symptomatic plaques vs Asymptomatic plaques	Symptomatic= stenosis above 50-70%, associated with ipsilateral stroke	36	% of plaques containing highly or moderate calcification	Echography + Angio-MRI/Angio-CT
24953493	Ibrahimi P, et al.	2014	Symptomatic plaques vs Asymptomatic plaques	Symptomatic= ipsilateral ischemic event in last 6 months Asymptomatic= no ischemic event in last 6 months	41	% of plaques containing any calcification	Echography
22507923	Van Lammeren GW, et al.	2012	Symptomatic plaques vs Truly asymptomatic plaques	Symptomatic= ipsilateral symptoms Truly asymptomatic= never had any ipsilateral symptoms	264	% of plaques containing moderate or heavy calcifications	Histology
21206178	Hiyama T, et al.	2010	Symptomatic plaques vs Asymptomatic plaques	NA*	41	% of plaques containing any calcification	Histology

*NA = not available DWI = diffusion-weighted imaging

Figure 1 - Meta-analysis with binary-random effects model.



The studies are each represented with one line, using the calculated ORs. The black box shows the OR and the black lines show the matching confidence intervals. The blue diamond shows the overall confidence interval. A lower OR indicates calcium presence is associated with asymptomatic CAPs, while a higher OR indicates calcium presence is associated with symptomatic CAPs.

To compose this systematic review and meta-analysis, the authors used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.

Results

Literature search

The literature search was performed on January 10th 2017. The initial search resulted in thirty articles, without any duplicates. Thirteen records were excluded based on its title and abstract. The authors agreed that ten studies had their main focus on comparing imaging techniques or treatments. One study investigated the relation between CAPs and left ventricular dyssynchrony. [7] This article was excluded based on exclusion criterion b. Finally, two studies compared a carotid artery with a non-carotid artery, like a coronary artery and a femoral artery.[8-9] Twelve more articles were excluded based on its full text; one study was not available, eight studies did not determine the prevalence of calcium in CAPs and three studies did not study any relation between calcium and symptomatic or asymptomatic CAPs. General information about the included studies can be found in table 1.

Presence of calcium in symptomatic and asymptomatic CAPs

Table 2 shows the presence of calcium in symptomatic versus asymptomatic CAPs for each study. The odds ratio including 95% confidence interval is given. Two out of five studies showed that the prevalence of calcium was significantly associated with asymptomatic plaques (OR, 0.075 [CI 0.012, 0.453] and OR, 0.457 [CI 0.268, 0.778]).[12-13]

Van Lammeren et al.[12] detected more calcifications in asymptomatic plaques rather than symptomatic plaques, implying potential plaque stability.

Table 2 - Presence of calcium in symptomatic and asymptomatic CAPs

Authors	Calcium (n/total plaques) Symptomatic plaques	Asymptomatic plaques	Odds ratio (95% CI)
Saam T, et al	31/102	34/100	0.848 (0.469-1.530)
Davaine JM, et al	2/10	20/26	0.075 (0.012-0.453)
Ibrahimi P, et al	21/30	6/11	1.944 (0.470-8.050)
Van Lammeren GW, et al	40/82	123/182	0.457 (0.268-0.778)
Hiyama T, et al	9/20	9/21	1.091 (0.318-3.748)

The other three studies did not show a significant difference in presence of calcium between symptomatic versus asymptomatic CAPs (OR 0.848 [CI 0.469-1.530], OR 1.944 [CI 0.470-8.050] and OR 1.091 [CI 0.318-3.748]. These studies did not draw a conclusion about the relation between calcified CAPs and plaque stability.

Figure 1 shows the forest plot of the odds ratios calculated with the presence of calcium in symptomatic versus asymptomatic CAPs. After using binary random-effects, I^2 was 63% (p=0.027) showing heterogeneity between the studies. There was no significant difference in calcium presence between both groups (OR, 0.642 [CI 0.320, 1.288], fig. 1, blue diamond).

Difference in stability of symptomatic and asymptomatic CAPs based on other plaque features

Some of the articles suggest a difference in plaque stability between symptomatic and asymptomatic CAPs. Ibrahimi et al. implied symptomatic arteries are more vulnerable than asymptomatic arteries, based on plaque features such as grey scale median (GSM), texture and plaque irregularity.[11] Symptomatic CAPs had more surface irregularities than asymptomatic plaques and asymptomatic CAPs showed less vulnerable features, such as irregularities and lower GSM. In addition, van Lammeren et al. indicate symptomatic plaques are more vulnerable, based on decreased collagen presence. Van Lammeren et al. also noticed that intraplaque hemorrhages were more present in symptomatic CAPs and they indicated intraplaque hemorrhages are causing plaques to be more vulnerable.[12] Hiyama et al. did research to angiogenesis in atherosclerotic plaques and found that microvessels were more present in hemorrhagic CAPs.[14] Assuming that angiogenesis leads to formation of microvessels, Hiyama et al. concluded that angiogenesis causes more intraplaque hemorrhages, therefore changing into symptomatic CAPs. It was their belief that angiogenesis is a destabilizing factor in CAPs.

Three out of five studies determined intraplaque hemorrhage. [10,12,14].

Two studies showed that the presence of intraplaque hemorrhage was significantly associated with symptomatic CAPs (OR, 5.494 [CI 1.798-16.797] and OR, 3.363 [CI 1.748-6.468]).[10,12] The other study did not detect a significant difference in intraplaque hemorrhage between symptomatic and asymptomatic CAPs (OR, 3.056 [CI 0.838-11.136].[14]

Two out of five studies determined necrosis.[10,14] Saam et al. described this plaque feature as lipidrich necrotic core.[10] Both results show that necrosis is significantly more common in symptomatic CAPs rather than asymptomatic CAPs (OR, 2.287 [CI 1.233-4.243] and OR, 7.773 [CI 1.416-42.660]).

Discussion

In this systematic review and meta-analysis, the difference in calcium presence between symptomatic and asymptomatic CAPs was investigated. The authors also investigated differences in stability of symptomatic and asymptomatic CAPs based on other plaque features. The current meta-analysis showed no significant difference in the presence of calcium between symptomatic versus asymptomatic carotid atherosclerotic plaques. More research is needed to investigate the exact role of calcium in carotid atherosclerotic plaques.

Based on the secondary results, there is an indication that intraplaque hemorrhages might be associated with symptomatic CAPs, but the results are inconclusive for this plaque feature. However, necrosis does seem to be significantly associated with symptomatic CAPs. Considering that these plaque components are destabilizing factors, symptomatic CAPs seem to be more vulnerable than asymptomatic CAPs. Because the authors did not perform a meta-analysis on these secondary results, no solid conclusions can be drawn.

One study suggested that calcification leads to plaque stability. The authors believe this study's findings were misinterpreted. [13] For example, Davaine et al. presumed that symptomatic plaques are more instable and asymptomatic plaques are more stable. The authors of this study found that calcification was associated with asymptomatic CAPs. Thus, they concluded that calcium stabilizes plaques. However, they cannot conclude that calcium is a stabilizing factor within plaques, because the cause-effect relationship between calcium and the stability of those CAPs is not assessed in these studies. Besides that, the actual standings regarding the link between plaque stability and the plaque being symptomatic or asymptomatic seem to be more complicated.

Some of the studies included in this review showed the role of other plaque components in plaque stability. One could question whether the presumptions can be linked in the way the authors did. For example, Hiyama et al. found that microvessels were more present in hemorrhagic plaques.[14] They used the presumption that angiogenesis leads to formation of microvessels and the presumption that intraplaque hemorrhage is a destabilizing factor to conclude that angiogenesis is a destabilizing factor in CAPs. Both presumptions are proven to be right before, but the link between angiogenesis and whether the plaques are stable or unstable must be investigated in another research.

Limitations

In this systematic review, the authors did not research the pathophysiology behind calcification of CAPs and whether it influences plaque stability or not. However, as the included studies show associations both ways, pathophysiological evidence or explanations may help to solve this inconsistency. Therefore, the authors suggest future pathophysiological research.

This systematic review consisted of five studies. The outcome measurements of these studies were not fully the same. In three studies any calcification within the CAPs was measured, while the plaques in the remaining studies were divided into "heavy calcification", "highly calcified" or "moderate calcification". [10,11,14], [12,13] Lastly, several studies did not have the same definition of "symptomatic" and "asymptomatic". Therefore, it is harder to draw a valid conclusion.

Clinical relevance and further research

Interestingly, the three studies measuring any calcification showed no significant association between calcium presence and plaque stability, whereas the two studies measuring several degrees of calcification did find a significant association between the presence of calcium and plaque stability.[10,11,14], [12,13] This indicates that the degree of plaque calcification should be the main focus of future studies investigating the relationship between calcium and plaque stability, rather than presence itself. Therefore, the authors think it would be clinically relevant to perform a regression-analysis on the degree of plaque calcification and plaque stability. In this way, a possible crucial value of plaque calcification might be identified and used to select and treat patients with higher chance of having symptomatic disease. Moreover, to understand the pathological processes of plaque stability, it might also be valuable to investigate other plaque features such as intraplaque hemorrhages or necrosis in addition to calcium presence.

Conclusion

There is no significant difference in the presence of calcium between symptomatic versus asymptomatic carotid atherosclerotic plaques. More research is needed to investigate the exact role of calcium in carotid atherosclerotic plaque.

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Are old donors a good alternative to expand the current donor pool?

A systematic review

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Abstract

Introduction: **For patients with end-stage renal disease, kidney transplantation is the best option in terms of long-term survival and quality of life. However, the increase in population age has resulted in an increase in people needing a kidney transplantation. This has caused an organ shortage. To meet the increased demand, the age limits of donor organs accepted for transplantation are being extended.**

Objective: **The aim of this systematic review is to compare outcome after kidney transplantation using young donors and older donors and determine if older donors, i.e. donors older than 55 years, should be considered as a good alternative to expand the current donor pool.**

Methods: **We conducted a PubMed literature search to gather articles describing relevant studies. The outcomes were collected and analysed.**

Results: **Out of all the studies, 11 studies met our criteria for inclusion, giving us a total of 9192 participants. Based on a meta-analysis, the pooled overall relative risk of delayed graft function for old donors versus young donors was 1.55 (95%CI 1,29 - 1.870). There was a significantly lower eGFR in the older donor group. We found no significant difference in incidence of acute rejection or graft survival.**

Conclusions: **Renal allografts from older donors are a good alternative to expand the donor pool, but it may require a different approach.**

Keywords:

"Kidney transplantation", "graft survival", "donor age", "delayed graft function".

Introduction

The therapy of choice for most patients with end-stage renal disease (ESRD) would be kidney transplantation as it is superior to dialysis in terms of quality of life and long-term risk of mortality.[1] Due to the increase in population age, the incidence of ESRD is increasing, and concomitantly also the demand for donor kidneys. This has led to an increase in the gap between demand and supply of donor kidneys which has resulted in an extended time on the waiting list.[2] In addition to this, the age of donors who's organs get accepted for transplantation are rising.[3] In the United States of America 110 kidneys from deceased donors aged 60 years or older were transplanted in 1988, whereas in 2017, 996 kidneys over the age of 60 years were transplanted.[4] One of the reasons for the increasing donor age is that less young people die in road accidents.[5]Another reason is that we all live to grow older.[5] The third reason may be because of the improvement of immunosuppressive drugs.[6] However, advanced donor age is a well-known risk for kidney allograft failure [7,8] due to a higher serum creatinine (SCr) and a higher prevalence of delayed graft function (DGF).[9] The latter often results in postoperative dialysis.

The effect of the donor age on the quality of the graft remains uncertain. Various studies give different outcomes when comparing younger and older donors. This review is written to give an overview of the existing data. The aim of this systematic review is to compare the outcome after transplantation from younger donors with older donors to answer the question if older donors should be considered as a good alternative to expand the current donor pool.

Methods

Literature search

We conducted a systematic review of studies that compared young with old donors. Therefore, we searched the Pubmed database for English-language articles on January 12th, 2018. The following search strategy was used:

"kidney transplantation"[Majr] AND ("old donors"[TIAB] OR "elderly donors"[TIAB] OR "young donors"[TIAB] OR

"Cadaveric donors"[TIAB] OR "old donor"[TIAB] OR "elderly donor"[TIAB] OR "young donor"[TIAB] OR "Cadaveric donor"[TIAB]) AND ("graft survival"[MESH] OR "graft rejection"[MESH]) AND "delayed graft function"[TIAB].

Selection criteria

To include studies we set up certain criteria. We included articles when the outcome of kidney transplantation was determined on the basis of one or more of the following outcome measures: DGF, acute rejection, graft survival, estimated glomerular filtration rate (eGFR) and SCr. Articles of which the full text was not available or were inaccessible for Erasmus MC were excluded. If articles were a review, they were also excluded. The search strategy was restricted to articles written in English. After this, the articles were screened by title and abstract.

Then, articles were excluded when: these articles described outcomes with children as donors, aimed to compare immunosuppressive drug regimens, studied if there was a difference in recipient survival between transplantation of 1 or 2 kidneys, or young and old donors were compared in relation to cold storage time, to name a few. Studies that did not compare young donors with old donors were also excluded at this part. Moreover, we excluded studies when there were no age subgroups defined for expanded criteria deceased donors (ECDD). According to the UNOS definition ECDD is defined as deceased donors older than 60 or deceased donors aged between 50 and 59 with 2 of the following criteria: a history of hypertension, cerebrovascular accident as cause of death or an SCr > 1,5 mg/dL.[10] Furthermore, studies describing the Eurotransplant Senior program were excluded. The idea behind this "old for old" program is to transplant organs from old donors to old recipients. This was not relevant for our review, because they did not compare younger donors with older donors.

Table 1 - Study characteristics

Author	Type of study	Number of patients	Follow-up	Cut-off donor age (years)
Jozwik et al. (2016)	Retrospective study	657	3 years	70
Cheng et al. (2015)	Retrospective study	482	Mean follow-up time: - Young: 59 months (range: 12-86 months) - Old: 31.5 months (range: 6-87 months)	55
Tanrisev et al. (2015)	Retrospective study	258	Mean follow-up time: 83.4 ± 43.1 months	60
Tekin et al. (2015)	Retrospective study	2633	3 years	65
Thornton et al. (2011)	Retrospective study	136	5 years	60
Resende et al. (2009)	Retrospective study	441	Mean follow-up time: 72.0 ± 52.3 months	55
Rossetti et al. (2007)	Prospective study	184	Mean follow-up time: 6.9 years (range = 4.8 to 8.6 years)	60
Emiroglu et al. (2005)	Retrospective study	207	5 years	50
Oppenheimer et al. (2004)	Retrospective study	3365	12 years	60
Fijter, de et al. (2001)	Retrospective study	496	Followed until death, return to dialysis, or June 1, 2000.	50
Carmellini et al. (2000)	Retrospective study	333	5 years	55

Study endpoints

We chose to analyse the following outcome measures to compare studies in this systematic review: DGF, acute rejection, graft survival, eGFR and SCr.

DGF was defined as the need for dialysis within a week after transplantation.[11]

Acute rejection is a cellular immune response of the body of the recipient to the allograft. If the recipient and the donor share little matching human leukocyte antigens (HLA) or the doses of immunosuppressive drugs are too low, the graft may show acute rejection. In kidney grafts the first signs of acute rejection are bloating, anuria and increased serum creatinine. Histologically, an infiltration of leukocytes and damage to the endothelia is visible.

Graft survival is a term used to describe the period a graft keeps functioning after transplantation.

The eGFR is defined as the amount of fluid filtered by the renal glomerular capillaries into the Bowman's capsule per unit time. It is used as a measurement of kidney function.[12]

The SCr is also a measurement for renal function. It is a useful clinical index of GFR.[12] In steady state the urinary creatinine excretion equals the rate of metabolic production. A higher level of creatinine is associated with a lower function of the kidneys.

Statistical analysis

We performed a meta-analysis on one specific outcome measure, namely: DGF. We chose DGF for our meta-analysis because it was reported in all of our included studies. In this way we could compare all articles in a forest plot.

OpenMeta[Analyst] open-source software was used to perform the meta-analysis. We calculated the occurrence of DGF in the older and younger donor groups. We constructed a forest-plot using the random effect model to determine relative risk and corresponding 95% confidence intervals (CI) for DGF. Heterogeneity was assessed using Cochran's Q-statistic and I^2 values. All tests were performed two-sided and $p<0.05$ was considered as statistically significant.

Results

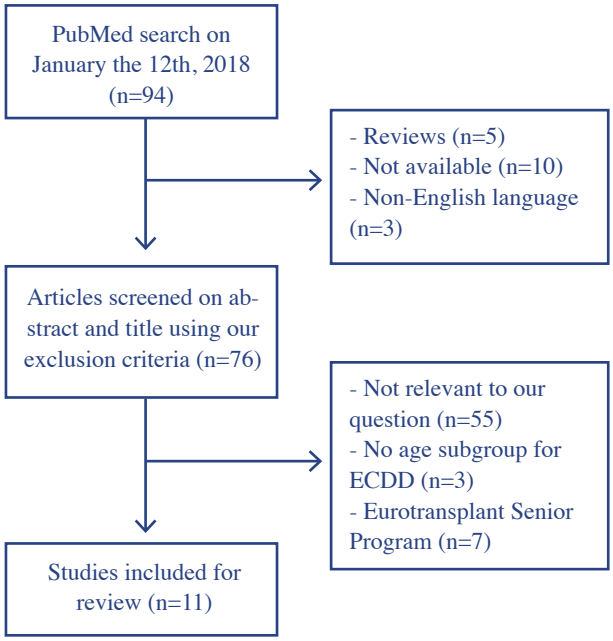
Search strategy

Our PubMed search produced 94 publications. After applying exclusion criteria, 76 articles remained. The titles and abstract of these articles were screened, after which another 65 articles were excluded. 11 articles remained for full reading, all 11 articles were suitable to be included. The flowchart in figure 1 shows how the articles for this systematic review were selected at each stage.

Study Characteristics

The characteristics of the 11 included studies are presented in table 1. The numbers of patients in de studies varied between 136 and 3365. The total gave us a pool of 9192 patients. The cut-off age as of when the donors were considered old ranged between 50 years and 70 years.

Figure 1 - Flowchart of the literature



Delayed Graft Function

All articles [11,13-22] examined the effect of donor age on DGF. The incidence of DGF in the young and old donor groups is given in table 2. Six of the 11 articles [11,15,16,18-20] described a significant higher incidence of DGF in the aged donor group than in the young donor group. With percentages ranging from 15.1% to 68.4% in patients who received kidneys from older donors and 5.2% to 40.2% in patients who received kidneys from younger donors.

Based on our meta-analysis, the pooled overall relative risk was 1.55 (95% CI 1,29 - 1.87) for the old donor group compared with the young donor group. The analysis showed a significant heterogeneity ($I^2 = 60,8\%$, $p = 0.004$, Fig. 2).

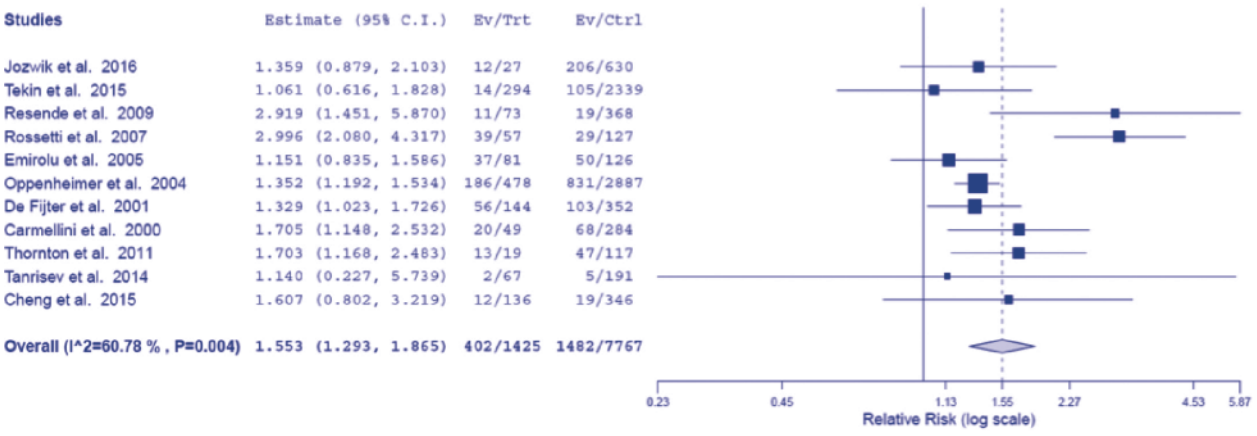
Acute Rejection

In eight of the 11 articles [11,14-19,22], acute rejection was studied as an outcome measure. In 2 studies a significant higher incidence of acute rejection was found in the old donor group. Both de Fijter et al.[19] ($p < 0.005$) and Cheng et al.[22] ($p = 0.01$) showed this significant difference. De Fijter found the following acute rejection percentages when comparing the older donors vs. younger donors: 64,4% vs. 46.7% and 66.7% vs. 53.9%. Cheng et al found 21.32% vs. 13.01%. The other 6 articles that described acute rejection as an outcome measure [11,13-17], showed no significant difference between the young donor group and the old donor group. Tekin et al.[14] and Emiroğlu et al.[17] found no significant difference ($p = 0.115$ and $p > 0.05$), as did Resende et al.[15], Rossetti et al.[16], Oppenheimer et al.[18] and Carmellini et al.[11]

Graft Survival

A total of 10 studies investigated the impact of donor age on graft survival.[11,13-19,21,22] The outcomes of these studies are shown in table 2. Carmellini et al.[11] described the influence of donor age plus the occurrence of DFG on the graft survival. The 1-, 3-, and 5-year graft survival rates of patients who experienced DGF comparing the young donor group versus the old donor group were 73.5% vs. 60%, 71.7% vs. 46.7% and 64.3% vs. 46.7% respectively. The 1-, 3-, and 5-year graft survival rates of patients who did not experience DGF were 89.4% vs. 96.6%, 85.9% vs. 84.5% and 79.6% vs. 72.4% respectively. These differences in graft survival are statistically significant ($p < 0.001$). Two of the 10 articles [14,17,19] examined the graft survival rates with and without the occurrence of acute rejection. Emiroğlu et al.[17] showed that the 1-, 3- and 5-year graft survival rates of patients with acute rejection within the first 6 months in the old donor group are significantly lower than in the younger donor group ($p = 0.005$). However, the 1-, 3- and 5-year graft survival rates of patients without acute rejection in both groups were not significantly different ($p > 0.05$). De Fijter et al. described a significantly lower graft survival rate ($p < 0.02$) in patients with old

Figure 2 - Forest plot of overall DGF relative risk (RR)



donor kidneys and a history of acute rejection. In patients without acute rejection, there was no significant effect of donor age on graft survival (p = 0.84).

The other 7 articles [13-16,18,21,22] described the effect of donor age on the graft survival. Five of 7 [13-16,22] articles found no significant difference between the old donor group and the young donor group. Tekin et al.[14] found no difference in graft survival at 1, 2 and 3 years comparing the old donor group versus the young donor group: 97.5% vs. 97.6%, 96.8% vs. 96.4% and 95.2% vs. 94.1% respectively (p = 0.471). Resende et al.[15] found that the 5- and 10-year graft survival rates were 88% vs. 77% and 82% vs. 68% for younger and older donors respectively (p = 0.294). Cheng et al.[22] found the following 1-, 3- and 5-year graft survival rates comparing the two groups: 97.8% vs. 96.8%, 92.2% vs. 89.1% and 81.7% vs. 75.2% (p = 0.115). Jozwik et al.[13] and Rossetti et al.[16] also found no significant difference in graft survival rates between young and old donors. Two of the 7 articles [18,21] found a significant lower graft survival rate in the old donor group compared with the younger donor group. Oppenheimer et al.[18] found a significant difference between old and young donors. Tanrisev et al.[21] showed a 7-year graft survival rate of 81.6% in the young donor group and 64.8% in the old donor group (p = 0.007).

Glomerular Filtration Rate

The impact of donor age on the eGFR was discussed in 5 of the 11 articles.[13,15,20-22] Four articles found a significantly higher eGFR among the young donors compared to the old donors. [15,20-22] Resende et al.[15] showed a significant difference after 3 months, 1 year and 5 years (all three timepoints p <0.0001). Thornton et al.[20] described a significant difference after 1 month and 1 year (p = 0.0125 and p = 0.05 respectively). In the retrospective study by Tanrisev et al.[21] it was found that the eGFR was significantly lower in the group of older donors after 3 years, 5 years and at the last-follow up (p = 0.004, p = 0.003, p = 0.030, respectively). Cheng et al.[22] also found a significant difference after a median follow-up of 59 months for young donors and 31.5 months for old donors (p <0.01). In contrast, Jozwik et al.[13] found no significant difference in incidence of DGF or graft survival. They concluded that there is no difference in the eGFR between young and old donors.

Serum creatinine

In five of the 11 articles [11,13,16,18,21], creatinine was studied as an outcome measure. In 2 of the 5 articles [18,21] a significantly higher creatinine value was found in the old donor group in comparison with the young donor group. Oppenheimer et al.[18] showed this significance at 3 months and 1 year (both p<0.0001). Tanrisev et al.[21] described a significant difference at 3 years, 5 years and last follow-up (p = 0.002, p = 0.001, p = 0.000). Serum creatinine levels were analysed 1 month, 3 months, 6 months and 12 months post-transplant by Carmellini et al.[11] At 1 and 3 months there were no differences in the mean serum creatinine level. However, at 6 and 12 months posttransplant they found a significant difference between young and old donors. The other 2 articles [13,16] presented no significantly higher creatinine level in the aged donor group. Rossetti et al.[16] found no difference after a median follow-up of 6.9 years. Jozwik et al.[13] found no significant overall difference at 6, 12, 24 and 36 months.

Table 2 - DGF and graft survival in young and old donor kidneys

Author	DGF (%)	Graft survival at 1 year	Graft survival at 2 years	Graft survival at 3 years	Graft survival at 5 years	Graft survival p-value
Jozwik et al. (2016)	32,7% vs. 44,4% p = NS	92.5% vs. 85%	NA	88.6% vs. 80%	NA	p = NS
Cheng et al. (2015)	5.5% vs. 8.8% p = 0.06	97.8% vs. 96.8%	NA	92.2% vs. 89.1%	81.7% vs. 75.2%	p = 0.115
Tanrisev et al. (2015)	2.6% vs. 3.0% p = 0.911	NA	NA	NA	NA	p = 0.007 Lower in the old donor group.
Tekin et al. (2015)	4,5% vs. 4,8% p = 0.778	97.5% vs. 97.6%	96.8% vs. 96.4%	95.2% vs. 94.1%	NA	p = 0.471
Thornton et al. (2011)	40.2% vs. 68.4% p = 0.009	NA	NA	NA	NA	NA
Resende et al. (2009)	5,2% vs. 15,1% p = 0.005	NA	NA	NA	88% vs. 77%	p = 0.072
Rossetti et al. (2007)	22.8% vs. 68.4% p <0.001	NA	NA	NA	NA	p = NS
Emiroglu et al. (2005)	39,7% vs. 45,7% p >0.05	With AR*: 93% vs. 89% Without AR*: 95% vs. 90%	NA	71% vs. 55% 65% vs. 60%	44% vs. 28% 40% vs. 35%	p = 0.005 p >0.05
Oppenheimer et al. (2004)	28.8% vs. 38.9% p <0.0001	NA	NA	NA	NA	p = S Lower in the old donor group.
de Fijter et al. (2001)	29.3% vs. 38.9% p <0.05	With AR: NA Without AR: NA	NA	NA	NA	p <0.02 p = 0.84
Carmellini et al. (2000)	23,9% vs. 40.8% p <0.05	With DGF: 73.5% vs. 60% Without DGF: 89.4% vs. 96.6%	NA	71.7% vs. 46.7% 85.9% vs. 84.5%	64.3% vs. 46.7% 79.6% vs. 72.4%	p <0.001 (overall)

AR = acute rejection; DGF = delayed graft function; NA = not available; NS = not significant; S = significant
*acute rejection within the first 6 months after transplantation

Discussion

Organ shortage is one of the biggest problems for people with organ failure. Therefore, the aim of this study was to investigate whether old donors are a good option to expand the donor pool. Our study outcome suggests that DGF is affected by donor age. A higher incidence of DGF in the older donor group was found in our meta-analysis. Looking at the average, donor age had no influence on graft survival. In two studies acute rejection resulted in a significant lower graft survival rate in the old donor group. This suggests that there is an association between the occurrence of acute rejection and a lower graft survival. In addition, there seems to be a reduced kidney function as suggested by the significant lower eGFR in the old donor group. In general, there seems to be no significant difference in the occurrence of acute rejection.

Limitations

The study has several limitations. It starts with our search method. Having excluded the non-English articles and the articles not available for Erasmus MC excess, we may have missed some viable information for our research. For a more reliable outcome, we should not have excluded these articles. However, we googled most of the unavailable articles, none of these met our criteria, limiting the data missed in this review.

Furthermore, every study except for Rossetti et al.[16] that we used for this review was retrospective. Retrospective studies are known for the inferior level of evidence compared to prospective studies. One of the reasons for this is that retrospective studies are prone to be subject of confounding, meaning there could be other risk factors that have not been measured. In other words, it is not possible to determine the causation, only the association. In retrospective studies there is also more often recall bias, which makes the results less reliable. Another limitation of this review is that we assumed that al cut-off ages to define old donors were the same. However, the cut-off age ranged from 50 years in Emiroğlu et al.[17] and de Fijter et al.[19] to a cut-off age of 70 years in Jozwik et al.[13], giving a maximum gap of 20 years. This difference may have affected the outcomes. Also, there was no accounting for the age difference between the donor and the recipient since the majority of the studies did not give the average age of the younger donors. The age difference may be more of a risk than the actual age of the donor.

Our review could also be limited by the fact that we did not correct for the different transplantation donor types. It is well known that kidney grafts from living donors survive longer than grafts from deceased donors and grafts from DBD donors longer than those of DCD donors. For example: the survival rate of kidneys from living donors, 5 years post-transplant, is 85.6%, while the survival rate of kidneys from deceased donors is reported as 74.4%.[23] This may have caused false significant outcomes in the studies that looked at deceased donors. Also, the follow-up time differed between the studies. Some studies had a follow-up time of 36 months.[13,14] Other studies followed their patients until death. The disadvantage of short follow up periods is that recent studies show that differences in graft function between aged and young donors will appear beyond 3-4 years.[24] Most of the studies describing graft survival show no significant difference between the survival of young and old allografts. Still, the graft survival of older grafts is roughly 5-10% lower than the graft survival of younger donors, as shown in table 2, which can still be considered as a clinical difference.

Also, the heterogeneity of the meta-analysis is with 60,8% quite high, suggesting the outcomes of the studies are not comparable. The heterogeneity came to be because of the great differences between the studies, such as the different cut-off values and the different endpoints. This makes it difficult to draw a reliable conclusion.

Future

For further and higher level of evidence, a large prospective cohort study with a minimum follow-up time of five years should be set. We recommend that the study uses different cut-off ages in different subgroups in order to make comparisons between the different age-groups. We would also recommend that the age-difference between the older donor and younger donor will be analysed further. Because our review did not have enough data to give a conclusion of the measure of SCr and eGFR, we would like to see these further analysed in future studies.

In addition to this, we think that we should look more at the biological age of the donor instead of the calendar age, since a bad lifestyle takes a great toll on your health and organ function.

Conclusions

Based on our results, renal allografts from older donors seem like a good alternative to expand the donor pool, however it may be necessary to change the approach. For instance, shortening the ischemic time to make up for the lower eGFR.

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Pre-heart transplant psychological factors as predictors of post-heart transplant physical outcomes

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Abstract

Objective: **Selection of heart transplant (HTx) recipients includes psychological evaluation, but it remains to be elucidated whether psychological factors could predict physical outcome after transplantation. We performed a systematic review of the literature to investigate whether pre-HTx psychological factors could predict post-HTx physical outcomes.**
Methods: **We systematically searched PubMed for peer-reviewed studies investigating adult HTx-patients that underwent psychological assessment before HTx and a follow-up for physical outcomes after HTx published from inception until 9th of January 2018.**
Results: **After screening and exclusions, we included nine studies, five of which discuss the predictive value of anxiety on post-HTx physical outcomes and unanimously report no statistically significant association. The seven articles discussing depression report mixed findings, three of which report a significant association with post-HTx survival. One study discusses type D personality, which independently predicts post-HTx mortality and early graft rejection.**
Conclusions: **Anxiety is not a predictor for post-HTx outcomes, while depression and type D personality are. Prospective studies with longer follow-ups and consistently used standardized psychological instruments are desired.**

Keywords

Heart transplantation, psychological tests, risk assessment, treatment outcome.

Introduction

Heart transplantation (HTx) is widely known to be a successful form of treatment for patients with end-stage heart failure. However, scarcity of donor organs is a pressing issue, as the number of HTx-procedures is limited to only roughly 5,000 patients each year for a total of approximately 50,000 candidates worldwide (1). This necessitates the selection of recipients who will benefit most from a HTx. The selection of patients who are most eligible for the transplantation waiting list is based upon both medical predictors and psychological risk factors of outcome (2).

In this field, progress has been made in identifying pre-HTx medical factors that could predict post-HTx survival and morbidities, yielding predictors such as heart failure etiology, body mass index and age at time of HTx (3). However, few studies have examined the predictive properties of psychological factors for post-HTx outcomes.

Patients awaiting HTx symptoms of anxiety and depression. It has been reported that 23.7% of waitlisted patients have a major depressive disorder (4). The intensity of such symptoms increases further during this waiting period (5).

In order for the selection of HTx-patients to be both evidence-based and ethically justifiable, not only physical pre-HTx predictors, but also psychological pre-HTx predictors should be taken into consideration when assessing eligibility. It remains to be clarified which pre-HTx psychological factors are predictors of post-HTx physical outcomes. Thus, the aim of this systematic review will be to identify pre-HTx psychological factors that predict post-HTx physical outcomes.

Methods

Search strategy

On January 9th 2018, we systematically searched PubMed for articles, using the following Medical Subject Headings (MeSH terms): ("heart transplantation/psychology"[MeSH Terms] OR ("heart transplantation"[MeSH Terms] AND (("behavioral symptoms"[MeSH Terms] OR "emotions"[MeSH Terms]) OR "personality"[MeSH Terms]))) AND ((((("morbidity"[MeSH Terms] OR "prognosis"[MeSH Terms]) OR "heart transplantation/mortality"[MeSH Terms]) OR "graft rejection"[MeSH Terms]) OR "survival"[MeSH Terms]). Physical outcomes of interest included survival and physical morbidities, e.g. graft rejection, infection and cardiac allograft vasculopathy (CAV). Since the MeSH term 'morbidity' did not provide full coverage of all morbidities we were interested in, we added the MeSH term 'graft rejection'. Due to the fact that not all articles in PubMed are indexed with MeSH terms, especially recent additions to the database that could be important for our systematic review, we also conducted an 'all fields' search: ((((((heart transplant*) AND psycholog*)) AND (((((morbidity) OR mortality) OR graft

reject*) OR prognosis) OR surviv*))) AND (((((waitlist*) OR pretransplant*) OR pre-transplant*) OR preoperative) OR pre-operative)) AND ((((posttransplant*) OR post-transplant*) OR postoperative) OR post-operative). We also reviewed the 'Related Articles' feature on PubMed and reference lists of all relevant studies, so as to ensure that our search included these articles as well.

Inclusion and exclusion criteria

Inclusion criteria were as follows: an article (I) should be written in Dutch, French, Spanish, English or German; (II) should be published in a peer-reviewed journal; (III) should discuss adult HTx-patients; and (IV) should include assessments at a minimum of two time points: a minimum of one pre-HTx psychological assessment, and a minimum of one post-HTx physical assessment.

The exclusion criteria were as follows: (I) it solely included a patient group other than adult HTx-patients, i.e. pediatric heart transplant recipients (patients <18 years), patients undergoing an LVAD implantation, spouses or family of recipients; (II) it is of an unsuitable study type, i.e. it does not include original empirical evidence, specifically review articles, case reports, letters, comments or conference abstracts; and (III) the full text is not accessible.

Study selection

Study selection was done in two stages. First, three authors (CS, DO, and CB) screened all titles and abstracts independently for eligibility based on the aforementioned criteria. Secondly, we did a full text analysis of the potentially relevant articles. After each stage, we discussed discrepancies to achieve consensus.

Table 1 - Studies examining pre-HTx psychological factors and their predictive value for post-HTx physical outcomes

Author	Setting	Pre-HTx psychological factor	Assessment method	Post-HTx physical outcome	Sample size	Follow-up	Results
Delibasic, M. (2017)	USA	Depression	BDI II, evaluation by transplant worker	Survival, graft rejection	43	First year post-HTx	Pre-HTx depression does not predict survival or graft rejection.
Denollet, J. (2006)	The Netherlands	Type D personality	DS14 scale	Survival, graft rejection	51	Mean 5.4 years (range 1-10 years)	Pre-HTx type D personality predicts survival and early graft rejection.
Dobbels, F. (2009)	Belgium, Switzerland	Depression Anxiety	HADS-D HADS-A	Graft loss, graft rejection	28	First year post-HTx	Pre-HTx depression or anxiety does not predict graft loss or graft rejection.
Favaro, A. (2011)	Italy	Depression	SCID	Survival, graft rejection, malignancy	107	Mean 11.3 years (range 8.2-14.1 years)	Pre-HTx depression does not predict survival or graft rejection, but it does predict malignancies.
Owen, J. (2006)	USA	Depression anxiety	Four-page structured evaluation form, semi-structured interview by clinician	Survival, infection	108	Mean 971 days (range 1-2065 days)	Pre-HTx depression predicts survival, but not infection incidence. Pre-HTx anxiety does not predict survival or infection incidence.
Skotzko, C. (1999)	USA	Anxiety	Routine psychiatric consultations	Survival, graft rejection, infection	107	First year post-HTx	Pre-HTx anxiety does not predict survival, graft rejection or infection incidence.
Spaderna, H. (2017)	Germany, Austria	Depression	HADS-D	Survival	148	1-93 months (median 70 moths)	Pre-HTx depression predicts survival.
Sponga, S. (2015)	Italy	Depression Anxiety	CBA 2.0	Survival, graft rejection, infection, CAV	345	Mean 6.2 years	Pre-HTx depression or anxiety does not predict survival, graft rejection, infection or CAV.
Zipfel, S. (2002)	Germany	Depression anxiety	DS STAI	Survival	103	Mean 4.4 years	Pre-HTx depression in ICMP patients predicts survival, but pre-HTx depression in DCMP patients did not predict survival. Pre-HTx anxiety did not predict survival in both ICMP patients and DCMP patients.

Abbreviations: HADS-D: Hospital Anxiety and Depression Scale - depression subscale; BDI II: Beck Depression Inventory II; DS14: Type D Scale-14; SCID: Structured Clinical Interview for DSM-IV; HADS-A: Hospital Anxiety and Depression Scale - anxiety subscale; CBA 2.0: Cognitive Behavioral Scale 2.0; DS: Zerssen depression scale; STAI: State-Trait Anxiety Inventory.

Study quality assessment

Quality of the studies was assessed using a modified version of the Newcastle-Ottawa quality assessment Scale (NOS) for case control and cohort studies (appendix). We added the following criterion about the study design: one star is assigned to a prospective design, no stars are assigned to a retrospective design. This criterion was added because of the fact that a prospectively designed study is ranked higher in the hierarchy of evidence than a retrospectively designed article, on the basis of there being fewer potential sources of confounding (6). Regarding the duration of follow-up, we decided to assign a star to studies with a mean follow-up of at least one year. This cut-off was chosen based on the consideration that a study is more relevant if they do not only allow for the inclusion of acute morbidities that commonly occur within the first year post-HTx, but also ensure that long term unfavorable physical outcomes are taken into consideration (7). All three reviewers (CT, DO and CB) assessed the included articles on their quality, and disagreements were resolved by a discussion between CT and DO to reach a consensus.

Data extracted from each study included: first author, year of publication, setting, pre-HTx psychological factor, psychological assessment method, post-HTx physical outcome measure, sample size, duration of follow-up and individual study results.

We organized the findings of the included articles in sections based on pre-HTx psychological factors.

Results

We identified a total of 192 published studies. After screening the title and abstract, 22 articles remained. A further seven articles were excluded due to unavailability of full texts. After reviewing the remaining fifteen full texts, six articles were subsequently excluded.

A total of 9 articles met the inclusion criteria (Figure 1). Table 1 shows the data extracted from all included articles. Since all included studies are cohort studies, we only utilized the modified NOS regarding cohort studies. Nevertheless, we included the modified NOS regarding case control studies in the appendix for completeness, so that potential future studies on this subject could make use of it. The results of the quality assessment using the modified NOS are shown in table 2.

We organized the findings of the 9 included articles in three sections based on pre-HTx psychological factors: Pre-HTx anxiety, pre-HTx depression and pre-HTx personality traits.

Pre-HTx anxiety and post-HTx physical outcomes

Five of the nine included studies examined the association between pre-HTx anxiety and post-HTx physical outcomes and report similar results. All five articles conclude that pre-HTx anxiety did not correlate with post-HTx outcomes. Dobbels et al., who used the Hospital Anxiety and Depression Scale (HADS) for assessing pre-HTx anxiety, report no statistically significant relationship between anxiety and graft loss or graft rejection during the first year post-HTx (8). Graft rejection was also examined by Skotzko et al., who similarly report no statistically significant relationship with anxiety. However, Skotzko et al. used a different assessment method for anxiety, namely routine pre-HTx psychi-

Figure 1 - Flow chart of the study selection process

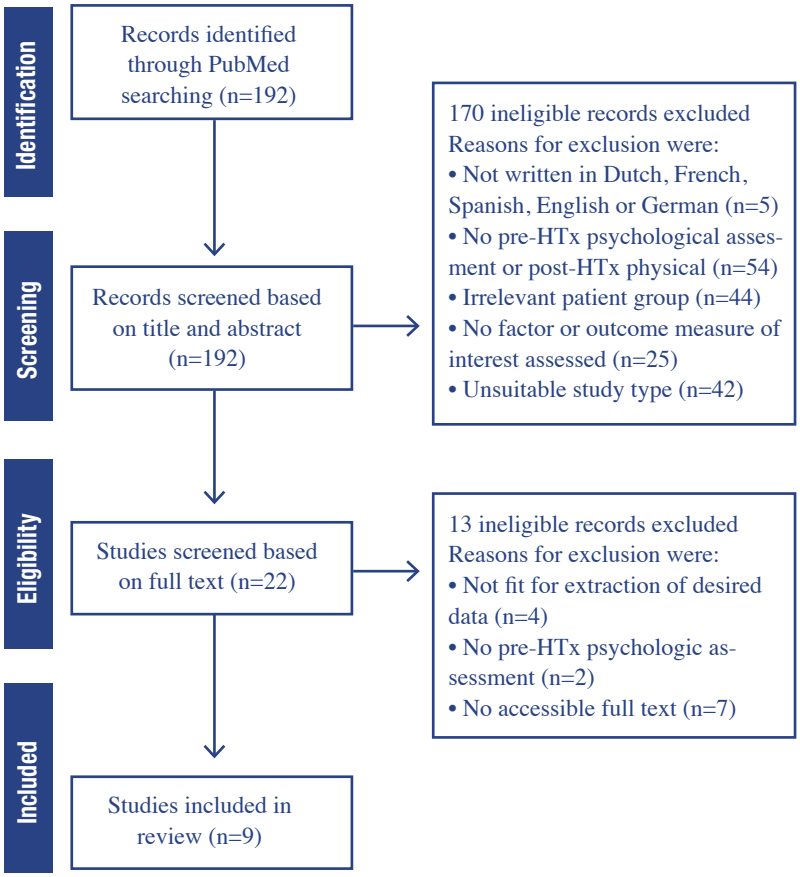

Table 2 - Modified NOS quality assessment scores of included studies

Author	Selection				Comparability	Outcome			Design	Total stars
	1.	2.	3.	4.	1.	1.	2.	3.	1.	
Delibasic, M. (2017)	B★	A★	B★	A★	A★	B★	B	B★	B	7
Denollet, J. (2006)	B★	A★	C		A★	B★	A★	A★	A★	8
Dobbels, F. (2009)	B★	A★	C		A★	B★	B	B★	A★	7
Favaro, A. (2011)	B★	A★	C		A★	B★	A★	A★	A★	8
Owen, J. (2006)	B★	A★	B★	A★	A★	B★	A★	A★	B	8
Skotzko, C. (1999)	B★	A★	C		A★	B★	B	A★	B	6
Spaderna, H. (2017)	A★	A★	C		A★	B★	A★	B★	A★	8
Sponga, S. (2015)	B★	A★	C		A★	B★	A★	B★	B	7
Zipfel, S. (2002)	B★	A★	C		A+B★★	B★	A★	A★	A★	9

atric consultations. Skotzko et al. also found no statistically significant difference between patients with and without anxiety with regards to the outcome variables survival and infection incidence (9). Additionally, out of all studies, Skotzko et al. had the lowest performance on the modified NOS, with a total score of six stars. Owen et al. examined the same association as Skotzko et al. (9), but over a longer period of time (mean follow-up duration of 2.7 years). Skotzko et al. used an unspecified four-page structured evaluation form as well as a semi-structured interview performed by a clinician. Owen et al. did not find a statistically significant association between pre-HTx anxiety disorders and post-HTx survival or infection incidence, either (10). Sponga et al. used the Cognitive Behavioral Assessment (CBA) 2.0 scale to examine pre-HTx anxiety and did not identify anxiety as a predictor for infection incidence, rejection episodes, or CAV. They also did not find an impact of anxiety on survival 1, 5 and 10 years post-HTx (11). Zipfel et al., the study that scored the most stars on the modified NOS, used the State and Trait Anxiety Inventory (STAI) scale to assess anxiety, and reported overlapping results. Zipfel et al. divided their patient population into ischemic cardiomyopathy (ICMP) patients and dilated cardiomyopathy (DCMP) patients and found that during their mean follow-up period of 4.4 years pre-HTx anxiety did not predict survival in either of these patient groups (12).

Pre-HTx Depression and post-HTx physical outcomes

Of the nine included studies, seven studies examined the association between pre-HTx depression and post-HTx physical outcomes. Of these seven studies, four studies found a statistically significant association between depression and post-HTx physical outcomes, and three articles did not.

Spaderna et. al concludes in their study, with a median follow-up of approximately 5.8 years, that pre-HTx depressive symptoms are statistically significantly associated with post-HTx survival, as assessed with a HADS-D (depression subscale) score of 0-21 (HR=1.07; 95% CI 1.01–1.15; P=0.032). However, after dichotomizing depression scores, patients with a high score (HADS-D of ≥9) did not have this statistically significant association (HR=1.62; 95% CI 0.96–2.73; P=0.075) (13). Zipfel et al., who had made a distinction between ICMP and DCMP patients, found that it was the former patient group that had a statistically significantly higher depression score at baseline (10.9 versus 7.6, respectively). ICMP patients, who were also part of the high-depression subgroup, had a higher rate of mortality in comparison with the ICMP patients in the low-depression group (RR=5.06; 95% CI 1.07–23.89; P<0.05). Depression in the DCMP group was not proven to have a statistically significant association with mortality (12). All four studies that are mentioned above were assigned eight or more stars in accordance with the modified NOS.

Of the three articles that did not find a relationship between pre-HTx depression and post-HTx physical outcomes, Sponga et al. showed that depression, like anxiety, did not influence survival at the three follow-ups of 1, 5 and 10 years post-HTx, nor that this pre-HTx factor had a significant association with CAV, acute rejection episodes, and multiple rejection episodes. After multivariate analysis, Sponga et al. also found that depression is not a risk factor for infection (P=0.68) (11). Dobbels et al. also reports not to have found a statistically significant association between the pre-HTx depression and graft loss or graft rejection in the first year post-HTx (8). Similarly, Delibasic et al. did not find a significant relationship between depression, as assessed by the Beck Depression Inventory II (BDI II) scale, and graft rejection or survival in the first year post-HTx (14). All three studies that are mentioned above were assigned seven stars in accordance with the modified NOS.

Lastly, there are two articles that present seemingly mixed evidence of depression as a predictor. Like both Sponga et al. (11) and Dobbels et al. (8), Favaro et al., the study with the longest follow-up of 11.3 years (mean), reports to have found no statistically significant association between depression, as assessed by a Structured Clinical Interview for DSM IV (SCID), and early or late acute rejection. In addition to this, no statistically significant association was found with survival either. However, Favaro et al. did find that pre-HTx depression is statistically significantly associated with post-HTx cancer (OR=3.3; 95% CI 1.2–8.7; P<0.01). This effect remains, even after a control is made for gender, age at HTx, education, type of cardiac illness before HTx, smoking before and after HTx, alcohol use after HTx, previous use of antidepressants, poor adherence, 1-year rejection score, and perceived social support (adjusted OR=5.8; 95% CI 1.6–20.5; P<0.008) (15). Similarly, Owen et al. reports mixed evidence. Owen et al. has a similar conclusion to Spaderna et al. (13), stating that a depressive disorder is indeed associated with survival: HR 2.52 (P<0.01), but also stating that depression has no association with infection (10), like Sponga et al. does(11).

Pre-HTx personality traits and post-HTx physical outcomes

Only one article discusses the association between pre-HTx personality traits and post-HTx physical outcomes. Denollet et al. examined the association of type D personality in HTx candidates with survival and graft rejection over a follow-up of 5.4 years on average. A type D personality is defined as the presence of both negative affectivity (chronic negative emotions, e.g. tendency to worry, easily irritated and a lack of self-esteem) and social inhibition (inhibited self-expression towards others). Type D personality was diagnosed using a Type D Scale-14 (DS14) scale. According to this study, type D recipients had a 4-fold higher mortality rate (5 out of 15 patients, or 33%) compared with non–type D recipients (3 out of 36 patients died, or 8%) (P=0.025). This association was even stronger after adjusting for recipient age at HTx and gender (with a mortality rate of 33% for type D recipients and 3% of non-type D recipients, P=0.013). They did not find a statistically significant difference regarding occurrence of graft rejection. However, with type D recipients rejection occurred statistically significantly earlier (>14 days post-HTx) than non–type D recipients (>50 days post-HTx, P=0.032) (16).

Discussion/Conclusion

In this study, we performed a systematic review to assess the predictive value of several pre-HTx psychological factors on post-HTx physical outcomes. Anxiety is not proven to be a predictor, none of the five studies discussing anxiety found a statistically significant association with the post-HTx outcomes of graft loss, graft rejection, survival, infection, rejection episodes, and CAV (8-12). Furthermore, type D personality is an independent predictor for post-HTx mortality and early graft rejection, based on the

results by Denollet et al. (16). Lastly, the results of the included studies on depression were not similar. When taking the modified NOS quality assessment scores into consideration, we see that the three studies reporting no statistically significant associations with post-HTx outcomes were of lesser quality (seven stars) (8,11,14) in relation to the four studies with one or more statistically significant associations (eight or nine stars) (10,12,13,15). Three of the four studies with higher quality described significant associations with the outcome of survival (10,12,13), which leads us to the conclusion that depression might indeed be a factor of importance with regards to such physical outcomes of HTx.

Mechanisms relating to our conclusions

Various theories exist on the mechanisms contributing to the associations between pre-Htx depression and type D personality and subsequent post-Htx outcomes. These mechanisms may be divided into two groups, namely biological and behavioral pathways. With regards to the biological pathway, studies show that both depression and social inhibition (i.e. lacking social contacts, a characteristic of type D personality) are connected to a deregulation of the hypothalamus–pituitary–adrenal axis, inflammatory reactions, and oxidative stress; all of which also commonly occur in the setting of heart failure (17,18). These biological pathways/mechanisms could thus induce unfavorable physical outcomes. As for the behavioral pathways/mechanisms, depression and social inhibition have also been linked to impaired self-care and a lower adherence to medical regimens, which has been associated with unfavourable physical outcomes (19).

Limitations of this systematic review and recommendations for future research

Our study made a clear differentiation between possible pre-HTx psychological predictors and subsequent post-HTx physical outcomes. Due to this distinction, a gray area of outcomes that could be both psychological and physical were not taken into consideration, including the outcomes 'compliance to medicine' or 'Quality of Life (QoL)'. The former outcome was mentioned in the study of Delibasic et al. (14) and could therefore serve as an example of our reasons for not including this. In this study, depression is correlated with higher rates of admissions for infection. The authors of this study are unaware of why such a result came about, and discuss the fact that patients with depression in their medical history were more likely to be non-compliant. However, as the incidence of rejection was similar between both the depressed and non-depressed group, and just the rates of admissions were increased, the immunosuppression regimen could not have played a major role. We believe it to be imaginable that physicians would experience a lower threshold to admit a patient with an infection suffering from depression as opposed to a patient that is not depressed. Because of these reasons, we have decided not to include such outcomes, as they do not fit the strict criteria of our study in separating purely psychological predictors and their purely physical outcomes. The same could be applied to quality of life as this outcome is interpretable on a psychological as well as a physical level. Some studies used the assessment tool of Health-Related Quality of Life (HRQoL), which is a questionnaire on both the patient's physical and psychological state. Some studies did not specify which results of this questionnaire were based on physical outcomes as opposed to psychological outcomes, making it impossible to examine these aspects independently. The influence of the identified psychological predictors on such borderline outcomes might therefore be an interesting new area to research and review.

Secondly, we have based our conclusion on the topic of personality traits and their relation to post-HTx outcomes on a single study, namely that of Denollet et al. (16) Albeit this study had a considerable quality (eight out of ten stars), the evidence that we found on the predictive value of type D personality - as well as personality traits in general - on adverse outcomes was very limited. In order to draw firm conclusions on whether Pre-heart transplant psychological factors as predictors of post-heart transplant physical outcomes, further research is required.

Another point to take heed of, is the fact that we have only discussed studies on adult HTx-patients. This means that the conclusions in this systematic review are not necessarily applicable to pediatric patients. It is reported that this patient group also faces a psychological experience pre-HTx (20, 21), but its influence on post-HTx physical outcomes could possibly differ from that in adults (22). Therefore, further research in this field can be of great value.

Limitations of the discussed researches and recommendations for future research

The quality assessment that we used in our review allowed for a maximum of ten stars. The highest awarded score was a total of nine stars, which was assigned to Zipfel et al. (12). The lowest score of six stars was assigned to Skotzko et al. (9). The remaining seven articles scored either seven or eight stars (8,10,11,13-16). The main reasons why most articles missed out on stars, can be found in the categories questioning the ascertainment of exposure, follow-up length and the study design. Most stars were lost on 'ascertainment of exposure', given that only 2 studies (10,14) received a star on this aspect because of the fact that they had assessed pre-HTx psychological predictors using interviews. The remaining seven studies (8,9,11-13,15,16) all used a self-report instrument. Relying on the trustworthiness of a self-report could negatively affect the diagnostic validity and reliability. Self-report instruments can introduce bias since some patients might naturally feel less restrained to report their symptoms. This in consequence might lead to more alertness in caregivers, which in return could lead to better clinical outcomes. A higher level of quality according to the NOS could be achieved using structured psychiatric interviews, performed by trained clinicians. With respect to the follow-up length of the included studies, three studies (8,9,14) did not have a follow-up that was longer than 1 year, which can result in limited predictive value for outcomes that predominantly manifest after a longer period of time (e.g. mortality or malignancies). This could explain why all three of these studies did not find any significant association between pre-HTx psychological factors and post-HTx physical outcomes. Furthermore, four studies (9-11,14) missed out on a star due to their retrospective study design. This retrospective design can introduce different sources of bias (6), like we mentioned before. In order for future research to be of a higher quality, we recommend having a pre-HTx psychological evaluation by a trained clinician, longer follow-ups, and a prospective design.

The question remains as to whether the conflicting findings of the included studies are a true reflection of the association of interest. It could be that the differences in results are influenced by the lack of a consistently used standardized psychological assessment of the pre-HTx patients. It may well be possible that the various assessment methods of the pre-HTx psychological factors play a role in the inconsistent findings, as a large variety of tests were used, ranging from structured interviews to various types of self-administrable tests (e.g. the aforementioned HADS, DS or STAI tests). We recommend one psychological assessment tool to be used amongst all future researches that aim to find psychological predictors for post-HTx outcomes, so results are more generalizable between studies.

Clinical implications

Including depression and type D personality as psychological predictors in a consistently used, standardized pre-transplant assessment tool could lead to the allocation of donor hearts to be done in an ethically justifiable, and evidence-based manner. Knowing who is at risk opens up the possibility of intervention by extending the given medical and psychological care.

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Appendix

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE – MODIFIED VERSION – CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ★
   b) yes, e.g. record linkage or based on self reports
   c) no description
2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ★
   b) potential for selection biases or not stated
3) Selection of Controls
   a) community controls ★
   b) hospital controls
   c) no description
4) Definition of Controls
   a) no history of disease (endpoint)★
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for candidacy for HTx ★
   b) study controls for any additional factor ★

Exposure

1) Ascertainment of exposure
   a) secure record (e.g. surgical records)★
   b) structured interview where blind to case/control status★
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description
2) Same method of ascertainment for cases and controls
   a) yes ★
   b) no
3) Non-Response rate
   a) same rate for both groups ★
   b) non respondents described
   c) rate different and no designation

Design

1) Type of study design
   a) prospective ★
   b) retrospective

NEWCASTLE - OTTAWA QUALITY ASSESSMEN T SCALE – MODIFIED VERSION – COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average HTx candidates in the community ★
   b) somewhat representative of the average HTx candidates in the community ★
   c) selected group of users e.g. nurses, volunteers
   d) no description of the derivation of the cohort
2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ★
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort
3) Ascertainment of exposure
   a) secure record (e.g. surgical records) ★
   b) structured interview ★
   c) written self report
   d) no description
4) Demonstration that outcome of interest was not present at start of study
   a) yes ★
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for candidacy for HTx ★
   b) study controls for any additional factor ★

Outcome

1) Assessment of outcome
   a) independent blind assessment ★
   b) record linkage ★
   c) self report
   d) no description
2) Was follow-up long enough for outcomes to occur
   a) yes (min. a mean of 1 year follow-up) ★
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ★
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > 80 % follow up, or description provided of those lost ★
   c) follow up rate < 80% and no description of those lost
   d) no statement

Design

1) Type of study design
   a) prospective ★
   b) retrospective

Arthroscopic meniscectomy or conservative treatment for degenerative meniscal tears: *a systematic review*

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Abstract

Background: **Meniscus injuries are the most common cause of disability of the knee. Nowadays meniscectomy is the favorable treatment, but it has become controversial. Exercise therapy could have the same results as meniscectomy.**
Objective: To find out if a patient with a degenerative meniscal tear should be treated with conservative treatment or be treated with a meniscectomy.
Methods: **We systematically searched the database of PubMed for relevant articles on October 4, 2017. We only included (prospective) randomized controlled trials that assessed degenerative meniscus tears and mentioned either 'meniscectomy', 'conservative treatment' or 'placebo surgery', all other study designs were excluded. Two reviewers screened all titles and abstracts of the found publications individually and in duplication.**
Results: **The search strategy identified 128 articles of which 8 randomized controlled trials were included in this systematic review. There were 6 studies that compared meniscectomy to a conservative treatment and 2 that discussed a placebo surgery in comparison to meniscectomy. When looked at primary outcomes such as the Knee injury and Osteoarthritis Outcome Score (KOOS), there was no significant difference between patients treated with meniscectomy, placebo surgery or conservative treatment. There was a significant difference in thigh muscle strength in favor of the conservative treatment.**
Conclusions: **Meniscectomy and conservative treatment yielded comparable results on KOOS. However, when looked at the thigh muscle strength conservative treatment was beneficial over meniscectomy.**

Keywords

Knee injuries, meniscus, exercise therapy, arthroscopy

Introduction

Knee injuries are very common in the general population; in the Netherlands the incidence of traumatic and non-traumatic knee injuries is 22.5 per 1,000 persons per year. [1] One of the categories of knee injuries are meniscus injuries. They are also the most common cause of knee disability [2] and the most common injury in sportsmen. Yet, only 30% of all tears are seen in sportsmen, so the remaining 70% occur in the general population. [3] Meniscus injuries are not always symptomatic. No less than 35% of all persons older than 50 years has a meniscal tear on imaging, but only a third of these tears are symptomatic. [4] Meniscal tears can be the result of a trauma or of a degenerative process. [5] An example of a degenerative process is osteoarthritis. It is unknown whether the meniscal tear is caused by osteoarthritis or the other way around, which are both reasonable options. [5-7] Because of the high prevalence and incidence of meniscal tears, arthroscopic (partial) meniscectomy (APM) is often performed as a procedure. More than 350.000 APM's are performed in the United states annually. [8] However, meniscectomies have become controversial, because the long-term benefits of meniscectomies in middle age patients has not been proven over non-surgical treatment such as exercise therapy. [9,10] An advantage of an operation is that it is less time-consuming for the patient. Although, in the revalidation period the symptoms such as pain and functional limitations can increase, resulting in sick leave after the operation. [11,12] Sick leave increases the costs in addition to the already high costs of the operation itself. [13] On the other hand, an advantage of exercise therapy is an improvement of function and activity levels. [14] Especially neuromuscular and structural improvements are seen in patients who followed an exercise program. [15] An important finding of Østerås et al. [16] was that exercise programs which contained a higher number of repetitions in sets, were more beneficial for neuromuscular outcomes. Therefore, the use of physical therapy as first line treatment grows. In addition, more guidelines refrain from recommending APM as first line therapy. [17-22] Meniscectomy is still a widely used operation, although the findings do not underline the benefits for patient with a degenerative meniscal tear. Therefore, the objective of this systematic review was to find out if a patient with a degenerative meniscal tear should be treated with conservative treatment or be treated with a meniscectomy.

Methods

Eligibility

Studies were considered for inclusion if they: were published in English, were a (prospective) randomized controlled trial, assessed degenerative meniscal tears and mentioned two of the following treatments: meniscectomy, a placebo surgery or conservative therapy. No restriction was made regarding publication date, length of the follow-up or a specific study outcome. The exclusion criteria of this systematic review were studies that did not specify the meniscal tear as degenerative, case reports, prospective studies, meta-analysis and systematic reviews.

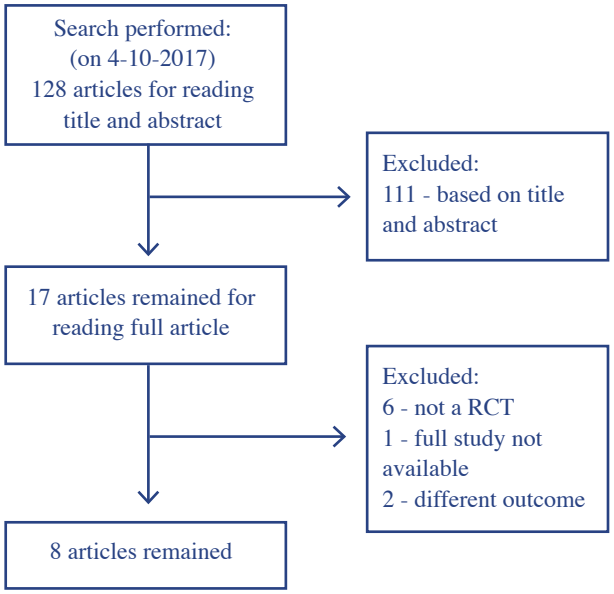
Literature search

We systematically searched the database of PubMed for relevant articles on October 4, 2017. The database was explored using the combination of the following Mesh terms and their entry terms, search terms and Boolean operators: (Meniscus OR Tibial Meniscus Injuries) AND (Rupture OR Lacerations OR Tibial Meniscus Injuries) AND (Meniscectom* OR Meniscus/Surgery OR Cartilage, Articular/Surgery) AND (Conservative Treatment OR Exercise Therap* OR Physical Therap*). Furthermore, we searched the reference lists of the identified publications to find publications with useful information about the treatment for a degenerative meniscal tear. The detailed search strategy can be found in Appendix 1.

Selection process

Two reviewers screened all titles and abstracts of the found publications in the PubMed database individually using Microsoft Excel. After the initial screening, the two reviewers discussed their findings and discrepancies were resolved by consensus. The titles and/or abstracts had to discuss degenerative meniscal tears and two of the treatments mentioned above. When the articles were likely to be eligible the reviewers screened the full texts individually. After screening the whole article, the reviewers compared the results and uncertainties were discussed.

Figure 1 - Flowchart of the literature search on PubMed



Data extraction and information about outcomes

The authors collected all relevant information and reported outcome data from the studies individually. If data were unclear the authors discussed it and tried to find the correct data in the article. The data extracted from the articles were about the effectiveness of the treatments, the Knee injury and Osteoarthritis Outcome Score (KOOS) and costs of the treatments.

Results

Using the above-mentioned search strategy, 128 records were identified from the PubMed database. After reviewing the titles and/or abstracts 17 articles were retrieved for full text evaluation. Finally, 8 [23-30] met the inclusion criteria and were included in the review (Fig. 1).

Table 1 - Design of the included studies

Author (Year Published)	Study Design	Arthroscopic (Partial) Meniscectomy	Conservative Treatment	Placebo Surgery	Primary Outcome Measure
Herrlin et al. (2013)	Prospective	X	X		KOOS at 60 months
[23]	Randomized Trial				
Katz et al. (2013)	Randomized	X	X		WOMAC at 6 months
[24]	Controlled Trial				
Stensrud et al.	Randomized	X	X		Isokinetic knee
(2015) [25]	Controlled Trial				extension peak torque at 3 months
Jullum Kise et al	Randomized	X	X		- KOOS at 24 months
(2016) [26]	Controlled Trial				- Peak Torque + Total Work for knee
					extension and flexion at 3 months
Katz et al. (2016)	Randomized	X	X		≥10 point improvement of the KOOS
[27]	Controlled Trial				Pain score
Sihvonen et al	Randomized	X		X	- WOMET at 24 months
(2017) [28]	Controlled Trial				- Lysholm knee scores at 24 months
Sihvonen et al	Randomized	X			- Knee pain after exercise at 24
(2016) [29]	Controlled Trial				months
				X	Mechanical symptoms at 12 months
Herrlin et al (2007)	Prospective	X	X		KOOS at 6 months
[30]	Randomized Trial				

Abbreviations: KOOS, Knee injury and Osteoarthritis Outcome Score ; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index ; WOMET, Western Ontario Meniscal Evaluation Tool

Table 2: Patient characteristics of the included studies

Study	Group	Patients (n)	Mean age (SD)	Sex (m/w)	Osteoarthritis* (yes/no/both)
Herrlin et al. (2013) [23]	Meniscectomy	47	54 (5)	28/19	Yes
	Conservative treatment	49	56 (5.8)	30/19	Yes
Katz et al. (2013) [24]	Meniscectomy	161	59 (7.9)	71/90	Both
	Conservative treatment	169	57.8 (6.8)	72/97	Both
Stensrud et al. (2015) [25]	Meniscectomy	42	48.6 (6.4)	27/13	Both
	Conservative treatment	40	49.2 (6.4)	26/16	Both
Jullum Kise et al (2016) [26]	Meniscectomy	70	48.9 (6.1)	43/27	Yes
	Conservative treatment	70	50.2 (6.2)	43/27	Yes
Katz et al. (2016) [27]	Meniscectomy	161	59 (7.9)	71/90	Both
	Conservative treatment	169	57.8 (6.8)	72/97	Both
Sihvonen et al (2017) [28]	Meniscectomy	70	52.1 (6.9)	42/28	Both
	Placebo surgery	76	52 (7.2)	47/29	Both
Sihvonen et al (2016) [29]	Meniscectomy	70	52.1 (6.7)	42/28	Both
	Placebo surgery	76	52.0 (7.2)	47/29	Both
Herrlin et al (2007) [30]	Meniscectomy	47	54	28/19	Both
	Conservative treatment	43	57	27/16	Both

* studies with "both" used the Kellgren-Lawrence grade, the others were distracted from the text.

Study characteristics

Characteristics of the included studies are summarized in Table 1. All included studies are (prospective) randomized controlled trials (RCTs). [23-30] Studies were published from 2007 to 2017. The primary outcome measures in the 8 studies varied: the Knee injury and Osteoarthritis Outcome Score (KOOS) [31]), the peak torque, the Western Ontario Meniscal Evaluation Tool (WOMET) [32], the Lysholm Knee Scoring Scale [33], the presence or absence of mechanical symptoms and knee pain after exercise.

Characteristics of treatments

All included studies contained a meniscectomy group. There were 2 studies, Shivonen et al 2016 and 2017 [28,29], that compared meniscectomy to placebo surgery. The 6 other studies compared meniscectomy to a conservative treatment. This conservative treatment was an exercise program supervised by physical therapists or a program to do at home. [23-27,30]

Patient characteristics

The 8 studies meeting the inclusion criteria ranged in size from 83 to 351 patients (Table 2). In total, combining the 8 studies, 1,319 patients underwent a treatment for a degenerative meniscal tear. Out of the 1,319 patients, 645 patients had a meniscectomy, 152 patients underwent placebo surgery and the rest of the patients (522 patients) received conservative treatment. All 8 studies contained patients with osteoarthritis of the knee besides the degenerative meniscal tear.

Effectiveness of exercise therapy versus meniscectomy

Studies comparing meniscectomy to conservative treatment showed no significant difference in primary outcome. [23-27,30] Stensrud et al. [25] showed that a 12-week supervised neuromuscular and strength exercise therapy program yielded clinically relevant and statistically significant improvements in isokinetic quadriceps muscle strength immediately after completion of the program. This result of improved thigh muscle strength in the short term of 3 months with exercise therapy is also shown in the study of Jullum Kise et al. [26]

Effectiveness of meniscectomy versus placebo surgery

The outcomes after arthroscopic partial meniscectomy showed no significant improvement compared to the outcomes after placebo surgery. [28,29] Resection of a torn meniscus has no benefit over sham surgery to relieve knee catching or occasional locking. [29]

Table 3: KOOS4 in treatments

Study	Group	KOOS at baseline						KOOS at the end of the follow-up					
		Pain	Symptoms	ADL	Sport/Recr	Quality/Life	Koos	Pain	Symptoms	ADL	Sport/Recr	Quality/Life	Koos
Herrlin et al. (2013) [23]	Meniscectomy	56	64	68	20	31	NR	94	93	98	91	82	NR
	Conservative treatment	64	71	76	35	38	NR	100	96	98	80	82	NR
Jullum Kise et al. (2016) [26]	Meniscectomy	67.6	77.4	79.6	47.8	45.6	59.6	NR	NR	NR	NR	NR	84
	Conservative treatment	63.4	69.8	75.0	44.0	40.0	54.3	NR	NR	NR	NR	NR	79.6
Herrlin et al. (2007) [30]	Meniscectomy	56	64	68	20	31	NR	89	89	84	70	69	NR
	Conservative treatment	62	71	79	30	38	NR	86	86	96	65	63	NR

The variables are presented as median.

KOOS subscales: Pain, Symptoms, Activity in Daily Living (ADL), Sport and Recreation (Sport/Recr) and Quality of Life (Quality/Life) which relates to the knee. KOOS4 = average score for four of the five KOOS subscales covering pain, symptoms, Sport/Recr and Quality/Life. (34)

Abbreviations: KOOS, Knee injury and Osteoarthritis Outcome Score ; NR, not reported

Knee injury and Osteoarthritis Outcome Score (KOOS) in treatments

An example of the many primary outcome measures of the included studies is the Knee Injury and Osteoarthritis Outcome scores. The KOOS is a questionnaire (see Appendix 2) that evaluates knee-related problems. The scores are transformed to a 0-100 scale, where 100 represents no knee-related problems. [31] Table 3 shows the KOOS of the meniscectomy treatment and conservative treatment in 3 out of the 8 included studies. Both studies of Herrlin et al. [23,30] used the KOOS subscales to grade the difference from baseline to follow up. For every subscale in both, the meniscectomy and the conservative treatment group, the KOOS are higher, which implies that knee-related problems are better. The study of Jullum Kise et al. [26] used the KOOS4 to compare the baseline to the follow-up. The KOOS4 is 54.3 at baseline, while at follow-up it is 79.6, which is an improvement and this implies that the knee-related problems are better than when the population entered the study. In Katz et al. (2016) [27] APM and the exercise therapy had comparable results in the proportion of patients, who reached an ≥ 10 point improvement of the KOOS Pain scale (82% for APM vs. 73% for the physical therapy).

Other outcome measures in meniscectomy versus exercise therapy

Besides the KOOS, there were many other outcomes measures. Katz et al. (2013) [24] described an difference of 2.4 (CI 95%: –1.8 to 6.5) in improvement of the WOMAC at 6 months. At 12 months the difference was even less: 0.7 (–3.5 to 4.9). Stensrud et al.[25] showed an significant difference in favor of exercise therapy in isokinetic knee extension peak torque: 24.7 Nm (14.0 to 35.3; p<0.0001). Jullum Kise et al. did not only use the KOOS at 24 months as primary outcome, but also the Peak Torque and Total Work for knee extension and flexion at 3 months. The Peak Torque flexion improved more in the exercise group compared with the APM group with a difference of 7.8 Nm. (2.9 to 12.7) A similar result was seen in the other 3 outcomes: Total work flexion: 49.4 J (16.0 to 82.9); Peak Torque extension: 23.3 Nm (14.7 to 31.9); Total work extension: 110.4 J (67.5 to 153.3). Overall an significant difference was seen between APM and exercise therapy in muscle strength variables (p<0.004).

Other outcome measures in meniscectomy versus placebo surgery

Sihvonen et al. (2017) [28] had 3 outcome measures. The WOMET score improved similar in APM and placebo surgery with a difference of –4.3 (–11.3 to 2.6). The Lysholm knee score and the pain after exercise score improved also similar; –3.2 (–8.9 to 2.4) and –0.4 (–1.3 to 0.5) respectively. Sihvonen et al. (2016) [29] investigated the mechanical symtoms after (sham)surgery. The risk difference between the two procedures at 12 months was 0.07 (–0.06 to 0.21).

Costs of meniscectomy versus conservative treatment

The procedure of meniscectomy involves an arthroscopy of the knee. An average arthroscopy of the knee costs €4500 [13], this excludes the revalidation. The costs of the conservative treatment, a physical therapy session, are about €35. [35]

Discussion/Conclusion

The most important finding of our systematic review is that there is no significant difference in outcome between a conservative treatment or meniscectomy in patients with a degenerative meniscal tear. There is not even a difference in outcome between meniscectomy or a placebo surgery in these patients. Therefore we suggest to treat patients with a degenerative meniscal tear with physical therapy firstly. If, unfortunately, the physical therapy fails, meniscectomy is proven to be as effective as been treated with meniscectomy in the first place. [27] Nevertheless, treating a degenerative meniscal tear with meniscectomy is less cost-effective than physical therapy. As physical therapy induces lower costs. To cover the costs of one operation (€4500), a patient can take around 125 physical therapy sessions. Besides the costs of the meniscectomy, the patients will need after care such as physical therapy and these costs are additional to the €4500. Besides the cost-effectiveness, physical therapy also reduces anxiety and depression. Østerås et al. [36] described a significantly reduction in patients receiving medical exercise therapy in comparison with arthroscopic surgery.

Finally, physical therapy also shows significant improvements in thigh muscle strength [26] and improvement in isokinetic quadriceps muscle strength immediately after completion of a 12-week supervised neuromuscular and strength exercise therapy program. [25]

Generally, the included studies in this review were of good quality, however there are a few limitations that need to be addressed. Firstly, most of the primary outcomes varied a lot, which made it difficult to draw a straightforward conclusion. The conclusion is more gathering of results of similar outcomes.

Secondly, the studies did not have a homogenous study population, for example

if you want to know about the link between osteoarthritis and the best treatment.

Thirdly, the follow-up of the included studies varied a lot. The shortest follow-up was 3 months [25,26] and there was one study with a follow-up of 60 months. [23] Therefore it is difficult to conclude about the long term effects and when surgery should be considered.

At last, most of the time there was not a 100% certainty all patient had a meniscal tear. In most studies MRI was used to determine if a patient had a meniscal tear. Yet, some patient were diagnosed false positive. For example in Herrlin et al. (2013) [23] in 3 out of 47 patient no meniscal tear was found during the arthroscopy. This could lead to a distorted view on this study.

A recommendation for future studies is to investigate the effects of osteoarthritis and degenerative meniscal tears over a longer period of time (24-36 months), with a reliable outcome measure such as the Knee injury and Osteoarthritis Outcome Score (KOOS) and mechanical measurements/symptoms.

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Appendix

1. Detailed search strategy in PubMed database

(meniscus[mh] OR menisc*[tiab] OR semilunar cartilage*[tiab] OR tibial meniscus injuries[mh]) AND (rupture [mh] OR rupture*[tiab] OR lacerations[mh] OR laceration*[tiab] OR tear[tiab] OR tibial meniscus injuries[mh]) AND (meniscectom*[tiab] OR meniscus/surgery[mh] OR cartilage, articular/surgery[mh]) AND (conservative treatment[mh] OR conservative*[tiab] OR exercise therap* [tiab] OR physical therap* [tiab])

1. KOOS Knee Survey Questionnaire (34)

KOOS KNEE SURVEY

Today's date: _____/_____/_____
Date of birth: _____/_____/_____
Name: _____

INSTRUCTIONS: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to perform your usual activities.

Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Symptoms

These questions should be answered thinking of your knee symptoms during the last week.

S1. Do you have swelling in your knee?
Never / Rarely / Sometimes / Often / Always
S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?
Never / Rarely / Sometimes / Often / Always
S3. Does your knee catch or hang up when moving?
Never / Rarely / Sometimes / Often / Always
S4. Can you straighten your knee fully?
Never / Rarely / Sometimes / Often / Always
S5. Can you bend your knee fully?
Never / Rarely / Sometimes / Often / Always

Stiffness

The following questions concern the amount of joint stiffness you have experienced during the last week in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

S6. How severe is your knee joint stiffness after first wakening in the morning?
None / Mild / Moderate / Severe / Extreme
S7. How severe is your knee stiffness after sitting, lying or resting later in the day?
None / Mild / Moderate / Severe / Extreme

Pain

P1. How often do you experience knee pain?
Never / Monthly / Weekly / Daily / Always
What amount of knee pain have you experienced the last week during the following activities?
P2. Twisting/pivoting on your knee
None / Mild / Moderate / Severe / Extreme
P3. Straightening knee fully
None / Mild / Moderate / Severe / Extreme
P4. Bending knee fully
None / Mild / Moderate / Severe / Extreme
P5. Walking on flat surface
None / Mild / Moderate / Severe / Extreme
P6. Going up or down stairs
None / Mild / Moderate / Severe / Extreme
P7. At night while in bed
None / Mild / Moderate / Severe / Extreme
P8. Sitting or lying
None / Mild / Moderate / Severe / Extreme
P9. Standing upright
None / Mild / Moderate / Severe / Extreme

Function, daily living

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your knee.

A1. Descending stairs
None / Mild / Moderate / Severe / Extreme
A2. Ascending stairs
None / Mild / Moderate / Severe / Extreme

For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your knee.

A3. Rising from sitting
None / Mild / Moderate / Severe / Extreme
A4. Standing
None / Mild / Moderate / Severe / Extreme
A5. Bending to floor/pick up an object
None / Mild / Moderate / Severe / Extreme
A6. Walking on flat surface
None / Mild / Moderate / Severe / Extreme
A7. Getting in/out of car
None / Mild / Moderate / Severe / Extreme
A8. Going shopping
None / Mild / Moderate / Severe / Extreme
A9. Putting on socks/stockings
None / Mild / Moderate / Severe / Extreme
A10. Rising from bed
None / Mild / Moderate / Severe / Extreme
A11. Taking off socks/stockings
None / Mild / Moderate / Severe / Extreme
A12. Lying in bed (turning over, maintaining knee position)
None / Mild / Moderate / Severe / Extreme
A13. Getting in/out of bath
None / Mild / Moderate / Severe / Extreme
A14. Sitting
None / Mild / Moderate / Severe / Extreme
A15. Getting on/off toilet
None / Mild / Moderate / Severe / Extreme

For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your knee.

A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)
None / Mild / Moderate / Severe / Extreme
A17. Light domestic duties (cooking, dusting, etc)
None / Mild / Moderate / Severe / Extreme

Function, sports and recreational activities

The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the last week due to your knee.
SP1. Squatting
None / Mild / Moderate / Severe / Extreme
SP2. Running
None / Mild / Moderate / Severe / Extreme
SP3. Jumping
None / Mild / Moderate / Severe / Extreme
SP4. Twisting/pivoting on your injured knee
None / Mild / Moderate / Severe / Extreme
SP5. Kneeling
None / Mild / Moderate / Severe / Extreme

Quality of Life

Q1. How often are you aware of your knee problem?
Never / Monthly / Weekly / Daily / Constantly
Q2. Have you modified your life style to avoid potentially damaging activities to your knee?
Not at all / Mildly / Moderately / Severely / Totally
Q3. How much are you troubled with lack of confidence in your knee?
Not at all / Mildly / Moderately / Severely / Extremely
Q4. In general, how much difficulty do you have with your knee?
None / Mild / Moderate / Severe / Extreme

Thank you very much for completing all the questions in this questionnaire.

Osteoarthritis in the temporomandibular joint: *a review*

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Abstract

Like other joints, the Temporomandibular joint (TMJ) can suffer from degenerative disorders such as osteoarthritis (OA). However, the etiology of this disorder is still unclear. The incidence in the world's population concerning the TMJ OA is approximated at 15%. TMJ OA is classified in different stages of progression, based on clinical signs and histopathological findings. Despite the several radiographic modalities for the imaging of the TMJ, the Computed Tomographic (CT) and Magnetic Resonance Imaging (MRI) have shown superior sensitivity concerning the identification of OA. Treatment of patients depends on the severity of the OA and the symptoms and signs of the patient in the clinical setting. Non-invasive treatment does not show superiority to conservative treatment. Invasive treatment should only be considered in late stages of TMJ OA. More research on auto- and allografts is necessary.

Introduction

The temporomandibular joint is a bilateral synovial articulation formed between the temporal bone of the skull and the mandible. [1] Disorders, and more specifically osteoarthritis (OA) of the temporomandibular joint (TMJ) are abundant, but little is known about this subject. People with this disorder suffer in everyday actions like chewing and talking. The etiology and diagnostics of the TMJ OA has been poorly understood in today's literature. This also accounts for the choice of the several treatment modalities. Thus, in this review we present a broad overview of the etiology and diagnostics and treatment based on the known literature concerning the OA in the TMJ. We will be discussing the epidemiology, etiology and physiology, diagnostics and treatments regarding this interesting disorder.

Methods

We gathered data by searching articles in Medline and Google Scholar involving reviews and trials related to the TMJ Disorders and Osteoarthritis. Most used terms while searching were: "TMJ osteoarthritis", "TMJ degenerative joint disease", "TMJ imaging", "TMJ treatment". Articles were screened on title and abstract and relevant articles were read in full. References of these articles were also screened. Data was finally extracted from several articles that were considered to be relevant for this paper. Next to this, medical dictionaries were utilized for definitions and books with chapters about TMJ disorders were screened for relevant information.

Epidemiology

Pathologies in the temporomandibular joint have been identified and are known as Temporomandibular Joint Disorders (TMD). TMD are clinical conditions involving the surrounding soft tissue and bony components, but also the musculature and the joint itself. Furthermore, the muscle tissue and joint components can suffer from degeneration.[2] OA of the TMJ is a subset of TMD, which involves a degeneration of the adjacent tissues around the TMJ.[1, 3] This may cause alterations in the joint components such as the synovial membrane, cartilage and the subchondral bone. [3-6]

The incidence in the world's population concerning the TMJ OA is approximated at 15%. [7] However, several studies have been published that claim to have found different numbers, and therefore the incidence varies. This varies for the main reason that each study uses different diagnostic criteria as definition of OA.[8, 9] OA can be presented at any age, but with age the risk of obtaining OA increases.[10]. Women suffer more from TMJ OA, possibly because of Estrogen Receptor alpha polymorphism and an increased susceptibility for women with TMJ OA.[11]

Diagnostics

Diagnosing TMJ osteoarthritis is a combination of a review of the patient's history, physical examination and additional research. Within the umbrella group of TMD, TMJ OA is initially an articular, non-inflammatory disorder. Patients present themselves with myofascial pain during masticating and a restricted function of the joint, causing trismus. Clicking, popping or crepitus sounds may also be present, but are not diagnostic when appearing as a single symptom.[12]

Three phases of OA have been identified. The early phase, the beginning of the degeneration, lasts about 2.5 to 4 years and is associated with clicking sounds and intermittent locking. The intermediate phase is characterized by further TMJ destruction and lasts six months to a year. Clinically, patients have spontaneous joint pain at rest and limitation in mouth opening. The late phase is called the stable burn-out phase. It lasts about six months and will stabilize after that.[13]

The TMJ pain, caused by synovitis, is mostly dull and may lead to disuse of the joint; the disuse induces stiffness and muscle weakness. This can lead to a vicious circle, with further joint de-

generation as a result. TMJ OA can become painless as the time passes. Other symptoms are similar to artrosis in the rest of the body: morning stiffness of the joint for more than 30 minutes, joint crepitus and absence of joint warmth. NSAIDs can help to relieve the pain. In the advanced stages, patients may have remodelling of the facial bones, with malocclusion and subsequent overbite or chin deviation to the side of the affected TMJ.[3]

The differential diagnosis for TMJ OA includes articular and nonarticular disorders. Nonarticular disorders can be acute muscle strain or muscle spasms of the masticatory muscles, fibromyalgia, myotonic dystrophy or just myofascial pain.[14]

Articular disorders can be divided in two groups: inflammatory, including rheumatoid arthritis (RA), ankylosing spondylopathies or infectious arthritis, and noninflammatory, such as joint damage due to trauma or prior surgery, bone disorders or TMJ OA. RA can be excluded from the differential diagnosis with a C-reactive protein test.[7]

The physical examination should include a general assessment of the head and neck, palpation of the masticatory muscles and the TMJ and a check of the occlusion and the jaw opening and closing. Palpation of the masticatory muscles may evoke pain, which can indicate a muscle disorder.

Schiffman et al. presented diagnostic criteria for TMJ degenerative joint disorders, which includes TMJ OA. These clinical criteria can be found in figure 1.[15]

Next to the history and physical examination, imaging is a crucial part in diagnosing TMJ OA.

For classifying TMJ articular disorders, the Wilkes' Staging Classification can be used. It includes five stages (I-V); I being the least severe and V being the most severe. Every stage describes a clinical, radiographic and anatomic aspect.[16]

Imaging and other additional research

Imaging has been found useful as supplement for diagnostics regarding arthritis. There is a variety of methods to image the TMJ. These methods can be classified as invasive and non-invasive imaging. The non-invasive imaging includes conventional radiographs and ultrasonography radiographs, Computed Tomography (CT) and MRI. The more invasive imaging tools are methods such as arthrography.[17] Supplement 1 demonstrates the anatomic structures of the TMJ joint after radiographic imaging.

Ultrasonography

First of all, the ultrasonography imaging is the least invasive and expensive imaging tool that can easily be performed to inspect the TMJ. The ultrasonography imaging is used to find signs of joint effusion. Ultrasonography has also been found to show promising results regarding revealing different morphological changes of the bony but also the soft tissue components of the TMJ. For example, the cartilage and the possible articular disc displacement can be assessed by this type of imaging. Klatkiewicz 2018 et al. [18] found a sensitivity for articular disc displacement using ultrasonographic imaging at 75.6% and a specificity of 69.1%. During the ultrasonic imaging, the TMJ can be moved, hence also providing a more dynamic imaging result. The ultrasonic imaging is also used for guidance in therapeutic purposes.

Radiographic imaging

The conventional radiographs can only assess the bony elements because soft tissue can hardly be identified and is therefore limited in the evaluation of the TMJ. Soft tissue such as the cartilage cannot be assessed.[19, 20]

Figure 1 - Diagnostic criteria for degenerative joint disease.

Degenerative joint disease (ICD-9 715.18; ICD-10 M19.91)

Description		A degenerative disorder involving the joint characterized by deterioration of articular tissue with concomitant osseous changes in the condyle and/or articular eminence.
Criteria	HISTORY	Positive for at least one of the following: 1. In the last 30 days[1] any TMJ noise(s) present with jaw movement or function; OR 2. Patient report of any noise present during the exam.
	AND	
	EXAM	Positive for the following: 1. Crepitus detected with palpation during at least one of the following: opening, closing, right or left lateral, or protrusive movement(s).
Validity		Without imaging: sensitivity 0.55; specificity 0.61. Imaging is the reference standard for this diagnosis.
Imaging		When this diagnosis needs to be confirmed, then TMJ CT criteria[106] are positive for at least one of the following: Subchondral cyst(s), erosion(s), generalized sclerosis or osteophyte(s). Note: Flattening and/or cortical sclerosis are considered indeterminant findings for degenerative joint disease (DJD) and may represent normal variation, aging, remodeling, or a precursor to frank DJD.

A panoramic evaluation is one of the different types of conventional radiographic imaging which is generally used for screening of the bony joint structures by clinicians. In this way, the overall status of the maxillo-mandibular complex can be assessed, subsequently, other potential disease etiologies can be excluded. Another type of radiographic imaging is a TMJ conventional tomogram.[21] During a conventional tomogram the area of interest is moved through a plane of focus. Normally, several undistorted slices of the joint are produced in the coronal or sagittal plane which allows assessment of the joint.[22]
This tomogram of the TMJ can reveal osseous abnormalities in different parts of the joint, specifically regarding the condyle. The transpharyngeal and the transcranial TMJ tomographic projection of the joint has been found to be limited and is therefore no longer included diagnostic imaging tool concerning the TMJ osteoarthritis.[21] Although TMJ tomograms are used as diagnosticians for TMJ OA in other projections, a study has shown that the reliability and sensitivity was limited for the panoramic radiography.[7]

Cone beam CT
Cone beam CT is an imaging technique that produces multiple images in different projections: axial, coronal and sagittal planes of the TMJ.[23] These multiple images provide a thorough inspection of the osseous components as well as the adjacent soft tissues of the TMJ. The cone beam CT is ideal for evaluating different abnormalities such as erosion, flattening, irregularities, subchondral cysts, osteophytes and resorption and infections of the TMJ.[17, 24] The sensitivity of the CT scan was the most sensitive technique after the MRI with a sensitivity of 83.33% for soft tissue interpretation.[25]

MRI
The MRI has proven to demonstrate an excellent reliability for revealing disc displacements and degenerative bony changes.[23] The MRI provides imaging with high resolution and a great contrast for tissues.[19, 21, 23] Radiographic signs of inflammation on the MRI can demonstrate joint effusions of the TMJ. Inflammation may indicate a transition from adaptive to pathologic changes in the TMJ. Although the MRI is a great radiographic modality to reveal the abnormalities in the joint, clinicians should not dictate their treatment strategies on the MRI findings alone. The MRI has a 95% accuracy in assessing the form of the disc and its position. Moreover, the osseous changes can be assessed with an accuracy of 93%.[17] They should combine the MRI findings with the clinical presentation, signs and symptoms to establish a treatment strategy.[3, 26]

Arthrography
Arthrography is an invasive method of imaging that requires the clinicians to inject a contrast in the TMJ. The injected contrast fluid will spread around the TMJ. This enables the clinician to thoroughly evaluate the adhesions, disc dysfunction and perforations. Though this technique provides great imaging results, this technique is rarely used nowadays, because the MRI provides great imaging, without being invasive and thus avoiding the risk of harmful radiation.[17]

Arthritis imaging
Like other synovial joints, the TMJ suffers from arthritis. This can be degenerative or secondary to another disease such as RA (Rheumatoid arthritis) or an infection.[17] In this review, we will be discussing the degenerative OA. Several studies have shown that in 35% of asymptomatic patients and 11% of the symptomatic patients flattening of the condyle can be found.[12] An important radiologic marker for degenerative OA is the irregular surface of the cortical bone in the TMJ. Furthermore, erosion (27%), osteophytes (13%) and sclerosis (less common 9%) can be found during imaging.[27, 28] The erosion is focally and can be identified as a spot with decreased density in the articular cortex surface of the condyle and the subchondral region. The osteophytes are formed in a later stage of the disease. The formed osteophytes lead to a more broaden articular surface area in order to attempt a more stable joint surface and a better withstand to the axial forces of the joint.[29] Several imaging methods are used to identify these abnormalities but there is no consensus to which imaging method should considered to be the golden standard. The selection of the imaging modalities should depend on the clinical signs and symptoms. MRI can be used for assessment of the articular disc, derangement of the joint and the adjacent soft tissues. A CT scan can be considered for evaluation of the bony structures in the TMJ. However, since the CT scan is associated with radiation risk, the indication should be considered judiciously. [12] Supplement 2 and 3 show radiographic markers for degenerative arthritis in the TMJ.

Clinical management:
Patients that suffer from simple TMJ OA and show signs of the OA should initially be treated with non-invasive modalities.[3] However, most patients who find themselves in a advanced stage of the disease require invasive modalities for treatment.[3] All of the modalities intend to increase the mandibular range of motion and function, decrease the joint and masticatory muscle pain and inflammation, improve the quality of life and reduce the related morbidities and prevent further degenerative change and (in)direct damage in the tissues adjacent to the joint.[30] The least invasive and most reversible method should be applied first. Only if the conservative and less invasive methods fail to succeed, more invasive and less reversible treatments are allowed to be used.[30, 31]

Noninvasive
Noninvasive modalities cover physical therapy, occlusal splints and pharmacologic treatments. Firstly, the (electro)physical therapy and manual exercise techniques have been shown to be successful. Besides the relieve of the masticatory muscle and joint pain, it also improves the range of motion of the TMJ and reduces the inflammation.[3, 32] Therefore, physical therapy is nowadays added to all treatment modalities concerning TMJ OA and other TMJ disorders. [3] Additionally, changing the posture, diet and stress related habits have also been found to be effective.[33] Electrophysical therapy can relieve the orofacial pain, reduce the inflammatory etiology, increase the blood flow adjacent to the joint and stimulate relaxation of the muscles that are associated with the TMJ by using TENS (transcutaneous electric

nerve stimulation), ultrasound and lasers.[34] The manual therapies, which involve exercise techniques, work by strengthening and improving the mobility in the musculature. This modality is intended to also relieve pain and increase the range of motion of the TMJ.[4] However different patients require different treatments. Therefore, the non-invasive therapy may involve a combination of modalities but have still to be patient specific.[35] Acupuncture and thermal therapy are associated with symptoms reduction of swelling and pain and restricted mobility, but the evidence that is presented by systematic reviews is little.[32, 36, 37]

The occlusal splints and adjustments are meant to create a balance in the occlusion of the TMJ. These non-invasive modalities intend to achieve a more stable and less joint-traumatizing bite position. Eventually, the splints should reduce the pain of the muscles next to the joint and in the joint itself. Furthermore, the occlusal splints and adjustments reduce the malocclusion in TMJ OA patients. However, from a Cochrane review 2014, the evidence is insufficient to support for the splints as treatment for the patients [38] Qvintus et al found that after a long-term evaluation, 27.6% of the patients that received splint treatment and 37.5% of the patients that received counseling and instructions for masticatory muscle exercises reported "very good" treatment effects.[39] The long-term effectiveness of the splints remains controversial. [40]

Pharmacologics are often used in conjunction with other treatments. This pharmacologic therapy aims to treat the underlying disease process and alleviate the associated symptoms as pain and swelling. A combination of pharmacologics is prescribed to target the goals of the pharmacological therapy.

This includes non-steroidal anti-inflammatory drugs (NSAID's) that provide minimization of the inflammation. Kopp et al showed that an injection of corticosteroids can induce a decrease in signs of clinical dysfunction, pain and an increase in ability to open. However, it is still unclear whether the advantages of the NSAID's outweigh the disadvantages.[41] Corticosteroids have a critical effect on the gastrointestinal tract. NSAIDs can induce gastric erosion and lead to ulcers and bleeding. This also tends to be more severe in elder patients. Severe adverse reactions of NSAIDs also include the interaction with multiple medications, which can lead to an unwanted effect. For instance, NSAIDs can cause a decreased clearance of lithium.[42] This is important because a high proportion of patients with chronic pain tend to develop a type of depressive syndrome concomitantly with the pain.[43]

Likewise, the discussion regarding the effectiveness of muscle relaxants, that are used to treat spasm and muscle pain, prevails. [43-46] Several studies have demonstrated that benzodiazepines have a therapeutic-effects for musculoskeletal pain. Therefore, drugs of the benzodiazepines class are frequently prescribed for patients with chronic pain. Dionne et al. suggests that the muscle relaxants can reduce the tone of the muscles and consequently alleviating the orofacial pain. However, the efficacy of benzodiazepines for chronic pain is currently not recognized and can produce dependence. Also, the decrease in the muscle tone may induce unacceptable levels of central nervous system depression doses that is unacceptable (by depression of polysynaptic reflexes).[43, 47] Nonetheless, a combination of the NSAID's with the muscle relaxants may work synergetic.[4]

Literature of drugs that are used for TMD does not reveal upon to base therapy does not reveal a wealth of data upon which we can base the therapy. The drugs can have a potential serious toxicity and still lack a demonstrated efficacy. Therefore, a patient may be at risk without any therapeutic benefit. There is a need for well-controlled studies regarding the drugs that are used for orofacial pain. Care must be taken regarding pharmacologics such as analgesics, as a prolonged use of these medications can cause tolerance and dependency. The medications should only be prescribed and used to relieve the active symptoms, so that the disease cycle can be interrupted, and a potential permanent improvement may be established.[3]

Minimally invasive:

One of the minimally invasive modality include injections of different solutions such as corticosteroids, high molecular weight sodium hyaluronate and others.[3] Generally, injections into the superior articular cavity/fossa of the TMJ should treat the osteoarthritic symptoms. The injections are designed to stimulate the regeneration of the joint cells. However there is insufficient evidence to support the injections.[48]

For instance, a review of Li C, Zhang Y, Lv J et al. claims that an inferior injection or simultaneous injections of the upper and lower cavities is associated with a greater increase of the mobility of the TMJ and reduction of the disease associated pain. [49] Furthermore, several studies indicate that this treatment may be more effective in the early stages of degeneration and inflammation.[50, 51]. Contrary to this, Stoustup et al. found no scientific evidence that substantiates the effect of this treatment. There was no significant effect on the ability to open the mouth, reduction of disease progression and increasing efficacy upon repeated injections.[48]

Arthrocentesis is another method that is classified as minimally invasive. During arthrocentesis of the TMJ, the joint is drained from fluid. Consequently, the joint is rinsed with a sterile solution to remove inflammatory cytokines and debris.[52]

Arthroscopic surgery is a more invasive procedure and is also performed to identify TMJ OA and attribute its current stage. Both modalities are designed to lubricate the joint surfaces and reduce the inflammation.[53,54] The arthroscopic surgery and arthrocentesis are often combined with the occlusal splints and/or pharmacologic therapy. Both treatments are indicated if the patient shows resistance to the less invasive treatment modalities as discussed in the previous section.[3, 55]

Invasive

5% of the patients with TMD will require surgical methods to restore the motion of the TMJ and relieve the orofacial pain.[56]

Arthroplastic treatment

Arthroplasty contains disc repositioning, disc replacement, discectomy alone and disc repair. During a TMJ arthroplasty, the articular surface of the TMJ is reshaped by removing the irregularities that are due to the formation of osteophytes and the erosions. A patient that shows signs of degeneration of the disc will undergo surgery that will reposition, repair or remove the

disc. An open surgical approach is performed through peri-auricular incision of the skin.[3, 57] Disc repositioning is indicated and most effective if the articular disc is normal in appearance (shiny; white and firm) and minimally displaced. Hereby, the disc is replaced to its anatomic position.[3] Complications of a arthroplasty are rare but include infection of the wound, VII nerve injury and occlusal changes and joint pain.[3] Therefore, early postoperative physical therapy and exercises are imperative to a success of the treatment.[3]

Discectomy and disc replacement

The discectomy is a type of arthroplasty that involves a removal of the articular disc and is required when the disc is severely perforated, if there is a recurrence of symptoms after repositioning or a considerable loss of flexibility of the disc.[3, 58] The discectomy provides an improvement in the motion of the TMJ and relief in the orofacial pain. However, studies have also found that patients show newly formed fibrotic adhesions, a narrowed joint space and osteophyte formations on MRI.[59-61].

A disc replacement may follow after a discectomy. The graft replacement aims to prevent degeneration of the joint and formation of the fibrotic adhesions.[3] Studies have found that a discectomy after a five to ten years post-operative follow-up results in greater increases to the mandibular motion in patients that failed to thrive with the non-invasive methods.[62, 63] A discectomy should therefore be indicated when non-invasive modalities tend fail. Radiographic imaging in the long term demonstrates formation of osteophytes and flattening of the surfaces of TMJ. However, it is defended that this should be recognized as adaptive change rather than a degenerative abnormality.[62-64] Patients that do not respond correctly to this surgical modality will need autologous or alloplastic disc substitutes. Autologous disc replacements include subcutaneous fat, and are designed to provide a cushioning as protection during articulation of the joint. Yet in practice, the alloplastic discs along with the autologous replacement have not been very successful and often tend to fail. The substitutes failures are mainly associated with the different responses to the material. The autologous disc substitutes may not provide the required protection during motion, such as rotation and translation of the TMJ. The autogenous grafts reduce the crepitus that is seen after discectomy but did not prevent the remodeling of the joint [65, 66] The autogenous graft does significantly improve the pain relieve, chewing and overall condition of the patient's health.[3] The autogenous grafts - including temporalis flaps, auricular cartilage and dermal grafts - are still found to be superior to the alloplastic grafts.[67] The alloplastic substitutes tend to cause a foreign body reaction by degradation and the debris of the respective material used. According to the latest studies, the response to the foreign material could lead to degeneration and resorption of the mandibular caput and the fossa itself, thus creating perforations in the medial cranial fossa. Apart from that, clinical success has been compromised as result of displacement of the graft to the posterior of the condyle. More inert materials (silicone based) were not associated with resorption of the bony structures, but did provoke a fibrotic response that led to a fibrotic capsule near the alloplastic disc. This affected the mobility of the TMJ due to restriction of the movement caused by formation of an intra-articular band. This also accounts for the autologous fat grafts. This subcutaneous fat could become devitalized, following a transformation to fibrotic tissue and restriction of the TMJ.[68] Although the discectomy with graft replacement has significantly better clinical outcomes than the other arthroplasty methods, there is no consensus of which treatment is first choice.[3] Because of the different indications for the arthroplasty, each patient should be assessed individually in order to assign the first-choice treatment.

Joint reconstruction

Reconstructions of the TMJ can be divided in total and sub-total reconstructions.[4] The sub-total reconstruction is performed by using hemi-arthroplasty to replace the superior joint articular surface. Joint adhesions are lacerated. Subsequently, a vitallium alloy prosthesis of the fossa-eminence is implanted to restore the temporal joint component.[4] McLeod et al. found that a hemiarthroplasty can effective in patients that have an unaffected mandibular condyle that suffer but suffer from severe degenerative changes. [69] The degenerative condyle however, is often associated with a degenerative temporal joint component. When both components are affected, a total joint reconstruction may be required.[4]

Total joint reconstruction

A total joint reconstruction is indicated when a considerable fragment of the joint is missing.[4] The joint must be severely damaged and the disease should be recognized in its end stage. During this end stage, other treatments fail to thrive.[3] A loss of a substantial portion of the joint can cause malocclusion and other pathologies, hence the total joint is reconstructed.[4] The reconstruction is designed to primarily restore the form and function of the joint. Relieving the disease associated pain is a secondary goal.[28] Acute OA can be accompanied with serious degeneration of the cartilage and the bone. If there is no presence of an immune-mediated processes (as seen in rheumatoid disease), costochondral grafts can be used as a replacement of the condyle. The histology and morphology of the costochondral grafts are akin to the condyle of the mandible.[4] In addition, the costochondral grafts lack the potency to induce an immunogenic response, therefore they are superior to alloplastic materials. Furthermore, the autogenous costochondral bone grafts show growth potential which is favorable for juvenile TMJ OA group. [70] Although, there have been signs of progressive resorption of the graft in the long-term, great results are found regarding the autologous grafts treatment of patients with TMJ OA and an underlying pathology or preceding trauma. The nearby musculature and dentition compensate for the loss of the graft. However, the negative sides of the autologous grafts are that the resorption of the graft can lead to loss of height which can be accompanied with joint and muscle pain.[30, 51] The alloplastic graft is an alternative modality especially for patient with immune-mediated degenerative processes. Alloplastic grafts have become more popular with regards to the adult population. This is due to the autologous potential harvest site morbidity failure during transplantation and the functional loading.[67] A downside of these allografts is that they have a lifespan of 10 to 15 years, conse-

quently requiring a secondary surgery for the relatively young patients with TMJ OA.[40] Another flaw of these allografts is the early degradation, as aforementioned, that can lead to early debris. This debris can cause several complications and often requires an early secondary surgery.

Current allografts consist of stock or custom titanium joint designs and include a temporal fossa and mandibular condylar component that uses screws for fixation.[3] Several studies found that the custom and stock allografts have shown significant improvement in pain and mobility of the jaw.[71,72]

Especially for young patients, improved grafts and treatments methods are necessary. These improved grafts should take in the movements of the TMJ and the dynamic adjacent soft tissue in consideration. The challenge might be designing a tissue engineering technique that can enables fragments of the TMJ to adapt to mechanical and chemical stimuli from the articular joint.[4]

Conclusion/discussion:

Osteoarthritis of the TMJ remains a poorly understood condition. It is a condition which involves degeneration of the several essential joint components. The patient may suffer from symptoms and show clinical signs caused by the reduced adaptive capacity and subsequent degeneration of the joint. There is a variety of diagnostic modalities available but the CT and MRI have been found to be superior to any other type of imaging. Treatment should be specifically tailored for each patient in order to establish a successful treatment. Therefore, more research to allo-and autogenous grafts and tissue-engineering is necessary in order to treat the rather young patient population sufficiently. In addition, universal criteria may be designed for identification of the TMJ OA in order to improve the diagnostics.

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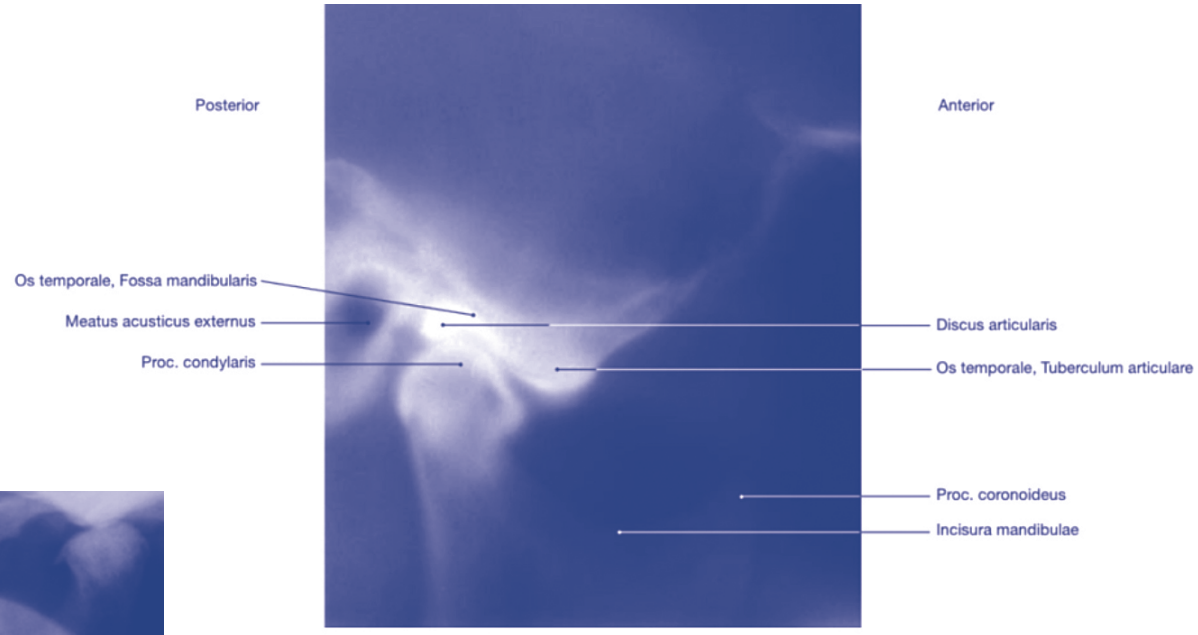
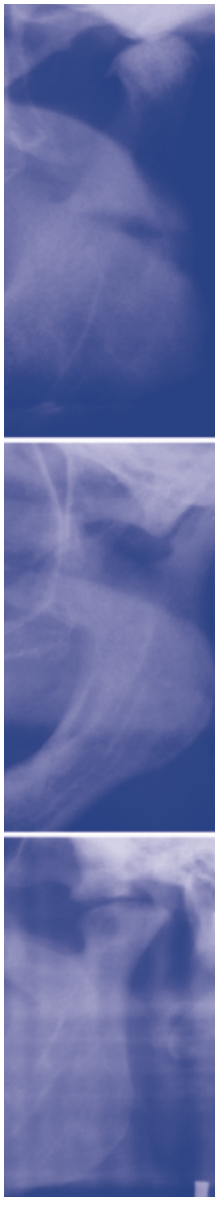
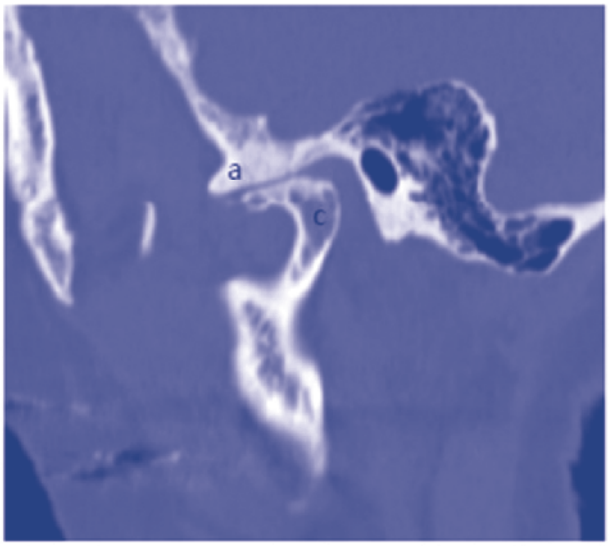
SUPPLEMENT:

Supplement 1: Imaging of the TMJ joint and its components. [72]





Supplement 2: OPG imaging is used and the radiographic signs/markers of osteoarthritis can be identified. There is a severe loss of joint space and an extensive sclerosis of the TMJ. Furthermore, 2c shows a flattening of the mandibular condyle. [10]



Supplement 3: This CT scan also demonstrates degenerative changes in the TMJ, including flattening of the condyle (letter c) and severe loss of the joint space and vast sclerosis (letter a). [17]

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Clinical lesson/question - A clinical lesson should present a scenario and a concrete related question about a disease or condition, the article should elaborate on possible approaches or treatment options for this disease or condition. Conclusion should provice a solid evidence based conclusion on the preferred approach or treatment. Number of words: 1000 + 1 figure or table.

Case reports - A case report consists of the initial presentation, medical history, examination, tests performed, eventual outcome and discussion on the case backed up by scientific literature. Number of words: 900 + 1 figure or table.

Clinical quiz - A clinical quiz should present a scenario and a concrete related question about the disease or condition, preferably accompanied by a clinical image, and four plausible treatment options or courses of action. Conclusion should elaborate on which is the correct option and why. Number of words: 600 + 1 figure or table.

Clinical images - Clinical images should present a typical abnormality on a photograph/imaging tests of a patient or on an additional investigation. It must be accompanied by an elaboration on the clinical diagnosis. Number of words: 350 + 1 figure. Make sure that the patient is not identifiable or that the data presented traceable to the patient. Additionally, written consent should be obtained from presented patient. We expect the author to refer to scientific literature to back up their case presentations.

Comments - In this section editors, or faculty staff, as well students are invited to write a short critical comment on a paper, putting it into perspective for a broader medical public readership. Number of words: 350.

Letters to the editor - The editorial board encourages students to write a letter to the editor to comment on published papers, or on the journal in general. These will be published on the website of the journal. Letters should not exceed 200 words and may be abbreviated by the editor.

The review process

Papers may be submitted to the editorial office. Please indicate which author will act as corresponding author. We expect this author to maintain contact with the other authors and to speak and decide on their behalf.

Each paper will be assigned to a team consisting of a managing editor and an associate editor. Each submitted paper will be checked for compliance with the author instructions. If this is not the case, the paper may be returned to the author.

Instructions for EJM authors

When the paper is taken into review, it will be sent out to two external reviewers, a student and a staff member of Erasmus MC. Based upon these reviewers comments, their recommendations and the opinion of the editorial team, a decision will be made: reject, major revision, minor revision, accept with or without minor changes.

The paper will then be returned to the corresponding author, along with the recommendation. We try to return papers within 3 weeks after submission. When a paper is rejected, it cannot be resubmitted, but we encourage resubmissions when we recommend major or minor changes to a paper. Resubmitted paper will be reviewed again by the same reviewers and editorial team.

Before a paper can be accepted for publication, we will need a statement that the staff member that supervised your work agrees with the submission of your paper. Moreover, we need a signed Copyright Transfer Agreement (CTA) and a signed Conflict of Interest statement. When your research project involves patients or volunteers, we need a statement in the paper that the research protocol has been reviewed by a Medical Ethics Committee. Failure to provide this information at an early stage of the submission may impair the review process.

When a paper is accepted for publication, it will often be forwarded to our language editing and restructuring editors. They will each in turn give recommendations and ask the author adapt the paper accordingly. When this phase is completed, the paper will be forwarded to the publisher. Page proofs will be sent to the author for a final check.

Formatting instructions

Entry format - Papers should be submitted by email, to ejm@erasmusmc.nl. Word 2007 files are preferred for the initial submission. The file should include all figures and tables.

Title page - The title page should clearly identify the authors, the institute where the research project was carried out, as well as the staff member who supervised the project. The corresponding author name (first name and family name), email address, student id, should be clearly indicated. In case of multiple authors, state functions and departments only in superscript in alphabetical order.

Example:
First name A.G. Family name[a] and First name W.F. Family name[a] Supervisor: First name R. Lastname[b]
[a] Medical students, Erasmus MC University Medical Center Rotterdam, the Netherlands
[b] Dept. of Internal Medicine, Erasmus MC University Medical Center Rotterdam, the Netherlands
Correspondence: First name A.G. Family name, email: FirstnameFamilyname@me.com.

Structure - Please use the following sections in all papers (except in comments and opinion papers): Abstract, Introduction, Methods, Results, Discussion, References, Tables, Figures.

References - Number references in order of appearance. References should have the following format:
Rothwell, P. M. Medical and surgical management of symptomatic carotid stenosis. Int J Stroke. 2006; 1: 140-149. (I.e. year;vol:ppp-ppp) In case of more than 3 authors, name the first 3 and insert "et al.". Limit the number of references to 30. References should appear in the text as follows: "… treatment is of proven benefit.[1]"

Tables and figures - Tables and illustrations (both numbered in Arabic numerals) should be prepared on separate pages. Number tables and figures separately and consecutively. Tables require a heading and figures a legend, also prepared on a separate page and should be formatted with a text editor (example). Figures should be submitted electronically. B/w half-tone and color illustrations must have a final resolution of 300 dpi after scaling, line drawings one of 800-1,200 dpi (jpg and tiff is an acceptable format). Please note that all color-figures will be converted to gray tones. Please adapt graphs to suit this format, i.e. make use of dotted and dashed lines and hatched bars instead of colored items.. The final submission should contain figures as JPG or TIFF files.

Page layout
- Standard margins
- no headers or footers
- no columns
- left align (ragged right)
- font: 12pt Arial
- single line spacing
- main headings 14 pt bold; subheading 12 point italic
- indent every paragraph, except after headings, tables, bulleted lists or figures

Other formatting
- number all tables and figures sequentially
- place tables and figures at the end of article; insert captions at correct locations in body text
- no text boxes
- no footnotes or end notes
- do not submit figures with text as drawing objects (they cannot be edited)
- limit the use of italics and do not use italics for simple emphasis; do not italicize quotations; quotation marks are sufficient
- do not use italics for commonly understood Latin expressions such as "in vitro"
- use italics for other foreign words, such as expressions in Dutch
- no "sub-paragraphs"
- no hyphenation (afbreking)

Language
US English spelling and punctuation

The template for authors

Introduction

1. *What is the health-related problem that your research helps to solve?*

2. *What is your strategy to solve the problem?*

3. *What is your research question/hypothesis?*
   Whether a question or a hypothesis, state it in terms of 2 items:
   - variables: the measurable/observable independent and outcome variables that you measured/observed and
   - relationships: the relationships between those variables that your data analyses were designed to determine.

4. *The core concept of the methods you used to answer the research question*
   Briefly describe the core concept of the methods at the end of the Introduction section. This helps readers to understand the complex details that are then presented in the Methods section

Methods section

Organize the details of the Methods section under subheadings. Possible subheadings:

What was studied and study design (subheading)

Describe the details of
- what was studied: sample from a patient/animal population, and
- the design of the study: case-series, cohort study, case-control study, randomized trial, etc.

Data collection (subheading)

Describe the details of how the data was collected/observed

Note
Observable variables will be credible only if qualified observers and validated instruments were used to assess them. Examples of observable variables include patient symptoms, subject responses to open interviews/ questionnaires, ultrasound/MRI/CT images, assessments of articles in a literature review etc. In such cases, build credibility in the Methods section; report "who" observed and interpreted the data. For example, "An experienced radiologist interpreted the images."

Note
When reporting on decisions/judgments that were made, use the "we" form—take responsibility for what you did.

Note
The Methods section reports historical facts and must be in past tense.

Data analysis (subheading)

Results section

5. *The core concept of the Results*
   Briefly describe the core concept of the results in a short paragraph at the beginning of the Results section. This helps readers to understand the details that follow. Note just as in the Methods section, this section reports historical facts and must be in past tense.

Then organize the details of your Results under sub-headings, for example:

Patient/animal characteristics
Data
Statistical results

Discussion section

Structure your Discussion to focus on 4 core concepts (6, 7, 8, and 9 below).

6. *The answer to your research question*
   Present this right at the top of the Discussion section—the very first sentence, a present tense statement that expresses—to the best of your knowledge—how the world works as related to your research question/hypothesis. It is a direct answer to the question/hypothesis stated in the Introduction.
7. *Support that answer?*
   a) how your factual findings, (expressed in past tense), support your answer.
   b) relating the findings of others to your answer.
   c) theoretical considerations that support your answer.

Limitations (subheading)

8. *The limitations to that answer*
   Focus explicitly on limitations related to possible confounders:
   - sample size
   - specific locations/medical centers of your study,
   - possible ethnic/cultural variables,
   - uncontrolled patient/subject characteristics and
   - underlying assumptions.

Conclusions (subheading)

The Conclusion is not a summary, but should focus on the consequences of your work. Structure this subsection using separate paragraphs that state 2 main messages (9 and 10)

9. *What are the practical/theoretical consequences of your answer?*
   The value—relevance— of your work: how it helps to solve the problem described at the beginning of the Introduction.
10. *What is a next step to help solve the original problem?*
    - a new research question to be answered
    - a refinement of the present study to reduce limitations
    - a protocol to implement the findings in the clinic

Advice to the reviewers of EJM

For the convenience of our future contributors and our readers, we publish here the advice we give to our reviewers.

In the process of reviewing a paper, please refer to the following points:

- Your first step should be to evaluate your relationship with the authors. To ensure the credibility of the process, reviewers should not have a conflict of interest with the authors. If this is a case, the paper should be appointed to other reviewers. Please keep us informed whether conflict of interest is an issue for you as an appointed reviewer.
- Is this work relevant and interesting for EJM?
- Are the objectives appropriate and clearly stated?
- Are the data valid?
- Are the conclusions valid and properly supported?
- Is the already existing work described adequately?
- Paper structure/organization; is this logical?
- Does abstract clearly convey meaning of the paper?
- Is the paper well written and can be easily understood? (Please keep in mind that students don't have the experience to reed throughout the paper very quickly and to understand everything in a research paper at the first glance)
- Are all sections really needed, or could they be shortened?
- Is the science reliable? Please, be aware of ethical issues such as plagiarism!

Comments should be detailed and specific. Mentoring the authors includes helping authors improve their paper under review even if these papers will/could not be accepted for publication in our journal. By careful reviewing, you will help improving the quality of papers published elsewhere too. Avoid vague complaints and provide appropriate citations if authors are unaware of the relevant work.

Please consider a manuscript received for reviewing as a confidential document and do not discuss the content of this paper with others. To maintain the validity of this process, you should never contact the authors about the paper under review.

The review process serves two important goals: providing guidance to the authors to improve the quality of their paper, and providing the editor or editorial board with valuable recommendations regarding the acceptance or rejection of the peer-reviewed papers (along the whole spectrum of major revision- minor revision- rejection). So it is important that you give comments to the authors, and to the editor in separate sections. Please use the provided form, because this makes life easier for you, the editor and the authors.

EJM is committed to rapid editorial decisions and publication. We request that reviewers return their comments within the time indicated at invitation. If any unanticipated difficulties arise that may prevent you from submitting the review on time, contact us by sending an email to the editorial office at ejm@erasmusmc.nl. You are welcome to contact us if you have any questions.

For more information about guidelines for the review process, please visit our website: www.erasmusmc.nl/ejm. We also recommend you to view the presentations of the EJM workshop on our website. Here you can find instructions about how to scan through a paper and grab its essence, and how to structure your comments to the authors and to the editor.

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