Evaluation of the effectiveness of oral treatments and accuracy of oral diagnostics using in silico methodology

PhD thesis booklet

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1. Introduction

As a result of the evolvement of healthcare, evidence-based medicine become the basis of modern clinical practice. Evidence-based clinical practice integrates the patient values with clinical expertise and research evidence. As a consequence, the need for practice-driven research increased. As a result, the number of new publications in the last decades increased exponentially.

Researchers and healthcare providers are overwhelmed with the enormous amount of information being produced. Systematic reviews can provide efficient interpretation, integration and evaluation of already available information to provide results for coherent decision making. A systematic review attempts to find and collect all experimental evidence that fulfils a predefined eligibility criteria with the aim of answering a particular research question. Systematic reviews assess consistency and generalisability of scientific findings. It also investigates the variability over various subsets.

Several systematic reviews include meta-analyses (MAs). Meta-analysis is the utilization of statistical methods to synthesize new data from the results of included individual studies. Meta-analysis particularly, can increase statistical power. In simpler terms, power is the likelihood of finding a significant result when there is truly an effect or association in the population. Some studies are too small to detect effects, however when many small studies are combined in a meta-analysis there is a higher probability of detecting an effect. Additionally, meta-analysis may improve the estimation of an intervention effect as it is based on more data.

In addition, meta-analysis with a selection of studies for sub-group analyses may help to answer questions not proposed by individual records. For example to evaluate the effect of intervention in various sub-group populations. Moreover, meta-analyses may help to resolve controversies caused by opposing study results or aid in formulating new hypotheses. Furthermore, methods used in a meta-analysis are explicit, as a result, they aid in increasing accuracy, limiting bias, and improving reliability of conclusions.

1.1. Rationale for meta-analysis in the topic of dental implants

During the last decades, the focus from machined implants moved to implants with moderately rough surfaces such as sand-blasted surface, however, the scientific justification behind this shift is not well-grounded. No robust evidence exists for clinical practice to support the utilization of sand-blasted implants over implants with smooth surface in healthy people. The randomized controlled trials (RCT) conducted on the healing of sand-blasted implants utilized a relatively small number of participants, yielding weak evidence.

Performing a meta-analysis may eliminate the drawbacks of RCTs as it could increase the number of participants involved in the analysis and also improving the validity of the result by other means mentioned earlier. Numerous reviews are available on the topic Doornewaard et al. 2017, Wennerberg et al. 2018, Papaspyridakos et al. 2014, Esposito et al. 2014. However, these did not conduct statistical calculations based on meta-analysis or included various studies with different methodological designs, generating a high level of heterogeneity.

Ostensibly, there has been no meta-analysis performed including exclusively RCTs: investigating the effect of sand-blasted surface of titanium implants on osseointegration compared to machined titanium implants. Identifying all eligible records and performing a meta-analysis may overcome the limitations of individual RCTs and increase the level of evidence on the topic.

1.2. Rationale for meta-analysis in the topic of hyaluronic acid dermal fillers in the oral cavity

Lips are part of the oral cavity and its surrounding anatomical region. Lips have a fundamental functional role in mastication and vocalization. Furthermore, they have a crucial importance in the aesthetic appearance of the face. Specifically, lip fullness is essentially connected with youth, beauty and attractiveness. Hereditary and several harmful factors promote the deterioration of the tissues related to the perioral region with age. As a result, the volume of the lips may shrink with various other signs of ageing.

Within the non-surgical treatment modalities, hyaluronic acid (HA) dermal filling is among the most often used treatment techniques. The use of

non-animal-based HA was first approved in 2004. Since that time various clinical trials aimed to reveal the true potential of HA dermal fillers. However, short follow-up times and small sample sizes of clinical trials investigating the effectiveness yielded findings with weak evidence and a high level of uncertainty.

With the methodological approach of meta-analysis, one could overcome the limitations of individual clinical studies i.e. to increase precision and power of the estimated effect of HA dermal fillers on lip augmentation. Additionally, a systematic review may help to explore the type and frequency of rare adverse effects (AEs) associated with HA dermal fillers.

1.3. Rationale for meta-analysis in the topic of oral diagnostics

As the population exponentially increases on the globe and most of the people live and work in crowded areas, the risk of air-born pandemics drastically increasing. Such as COVID-19, caused by the SARS-CoV-2 virus. Globally, as of 19 July 2023, there have been 768,237,788 confirmed cases, including 6,951,677 deaths. Quick diagnosis and early isolation of infected people will play an important role in stopping the further escalation of any disease.

Mass screening with the gold standard technique (nasopharyngeal swabbing) is expensive and poses an extra risk on the healthcare system as more medical personnel are needed. Furthermore, nasopharyngeal swabbing has several contraindications, such as anticoagulant therapy, coagulopathy, significant septum deviation.

To overcome these limitations diagnosis from saliva specimen is under continuous development. Numerous studies have been published on the possible use of saliva specimens for detecting COVID-19. However, the published papers use small sample sizes, resulting in a low level of evidence, high uncertainty and weak statistical power to detect significant differences. Conducting a meta-analysis on the topic could overcome the limitations of a small sample size, and also reveal regional or age differences among populations.

2. Objectives

In the last decade, the number of published papers on clinical trials exponentially increased. The large number of original studies became more than that clinicians and research groups can comprehensively assess and process to implement these findings into practice.

Conducting a meta-analysis on a given topic helps to elevate the level of evidence and clarify questions within a research area. This is achieved by systematically finding and assessing each eligible record in the topic. The present scientific work aimed to utilize the methodology of meta-analysis in order to assess the available evidence and clarify practice-related issues and questions in clinically important dental areas which were not assessed by the means of meta-analysis.

A. First objective of the present scientific work was to conduct a meta-analysis to investigate the performance and healing potential of two different types of commercially pure Titanium implant surfaces, smooth (machined) and moderately rough, sand blasted surface.

B. The next aim was to investigate the effectiveness of HA for lip augmentation and to verify its long-term aesthetic results using the methodology of meta-analysis. Additionally, the nature and number of adverse effects of HA in the literature were also reviewed. systematically.

C. Finally, a meta-analysis was conducted to estimate the diagnostic sensitivity of saliva-based detection of the SARS-CoV-2 virus. Additionally, various factors related to the methodological differences used in COVID-19 tests were explored.

Thus, the present scientific work aimed to apply the methodology of meta-analysis in three important topics of dentistry lacking strong evidence and to overcome the limitation of small sample sizes and high uncertainty, as well as weak statistical power, to increase the level of evidence aiding clinical and research decision in these particularly important themes.

3. Methods

3.1. Protocol and registration

The present work was conducted according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) checklist and guideline. The methodology for each dental topic was registered prior to conducting the meta-analysis in the PROSPERO or Open Science Framework database.

3.2. Eligibility criteria

In each case clinical question was formulated with the aid of the PICO format (population, intervention, control, and outcome).

In the case of dental implants, the following question was formulated. Are there significant differences concerning implant failure rates and marginal bone level loss between machined and sandblasted dental implants among healthy patients? {Czumbel, 2019 #1} Studied meeting the following requirements were considered for inclusion: **P:** participants with partial edentulous or edentulous jaws, with no systemic diseases affecting the healing of the implants. **I:** treatment of tooth loss with sandblasted endosteal dental implants. **C:** treatment of tooth loss with machined endosteal dental implants. **O:** implant failure rates (IF) and MBL (marginal bone level) changes using x-ray images to measure changes. Only RCTs, using similar implant macro design, written in English were included.

Exclusion criteria were defined as studies other than RCTs, studies applying growth factors, or bone augmentation, implants with modified neck macrostructure, participants with systemic or local diseases affecting implant healing, gray or black literature.

In the case of HA dermal fillers in the perioral region, the following questions were formulated. (1) To what extent are hyaluronic acid dermal fillers effective for lip augmentation? (2) What are the common and also the rare treatment-related adverse effects of HA application? {Czumbel, 2021 #25} Studied meeting the following requirements were considered for inclusion: **P:** participants at age 18 or older with minimal, mild or moderate levels of lip fullness based on a validated lip fullness scale. **I:** the use of injectable HA in the perioral region and lips to enhance lip fullness and

aesthetics of the face. **C:** baseline controlled. The values of lip fullness of each participant were recorded before and after treatment and these were compared. **Primary O:** measurement of effectiveness expressed as the rate of responders. Participants with one or more levels of improvement based on a validated lip fullness scale were defined as responders. **Secondary O:** Frequency and type of treatment-related AEs. Case series, cohort studies, and RCTs, written in English or available in English translation were considered for inclusion. Studies investigating other filling materials, treatment of other areas than the perioral region and the lips were excluded,

In the case of oral diagnostics publications satisfying the following research question was formulated. *Are saliva specimens reliable for detecting SARS-CoV-2 in COVID-19 patients confirmed by nasopharyngeal swab testing? E*ligibility criteria were as follows. **P:** records published in clinical trial registries or scientific journals, participants diagnosed with COVID-19. **Index test:** PCR diagnostics of saliva samples for detecting SARS-CoV-2. **Comparator test** (reference standard): PCR diagnostics of NPS samples for diagnosing SARS-CoV-2. Records in English language or with available English translation. Records such as reviews, guidelines, recommendations or publications before 01.01.2020 and after 25 04.2020 were excluded. Additionally, grey and black literature were also excluded. {Czumbel, 2020 #789}.

3.3. Information sources and search
In each meta-analyses, a preconstructed search query was used to perform the literature search in several databases, at a minimum of three databases, such as Cochrane Central Register of Controlled Trials (CENTRAL) Library, Embase and Medline via Pubmed. In the case of the meta-analysis on the topic of oral diagnostics two other databases were also used Scopus, Web of Science. Additionally, the reference list of the included records and relevant articles were also used to find records for inclusion.

3.4. Study selection and data collection process and data items
In each topic, records were managed using EndNote (Clarivate Analytics, Philadelphia, US, version: X9.3.3) reference manager software. Collected data

on each topic was organized into preconstructed and standardized data extraction tables. Study selection and data collection were carried out by two authors independently. Disagreements within selection were resolved by discussion or by consulting with a third author.

3.5. Risk of bias assessment

Risk of Bias (RoB) assessment was performed based on guidelines published in the literature. The guideline outlined in the Cochrane handbook {Higgins, 2011 #252} were followed to assess RoB in the case of RCTs. For cohort studies the Newcastle Ottawa Scale (NOS) was used {Deeks, 2003 #2441}. For diagnostic accuracy studies the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool was used.

3.6. Summary measures and synthesis of results

In the topic of dental implants, weighted mean difference (WMD) with 95% confidence intervals (CIs) were calculated for continuous outcome – MBL changes. Pooled Risk Ratio (RRs) with 95% CIs were calculated for the dichotomous outcome – IF rates. The statistical unit of calculations was the implant numbers.

In the topic of HA dermal fillers in the perioral region for the rate of responders, the untransformed proportions were calculated with 95% CIs. A responder is defined as a participant with at least one-grade improvement on a validated lip fullness scale compared to its baseline value. Descriptive statistics were used to analyse the distribution and frequency of AEs.

In the topic of oral diagnostics, patient-based data was included from consecutive case series. Analyses were performed according to the recommendations of the working group of the Cochrane Collaboration. In each case series sensitivity of saliva and NPS tests were evaluated in participants who were confirmed to be infected (diagnosed by NPS test and also clinical signs.) The sensitivity of the NPS test was based on the matching NPS tests when saliva tests were also performed.

To estimate the intervention effect and the pooled effect the random effect model with DerSimonian-Laird estimation was used in each meta-analysis. All statistical analyses were performed using STATA 15.0.

4.1.3. Risk of bias in studies

Two records Vroom et al. 2009 and Gotfredsenet al. 2001 had high risk of allocation concealment, as they utilized a predictable random sequence generation process. Other two publications did not clearly present the random sequence generation process used Steenberghe et al. 2000 and Tawse-Smith et al. 2002. No intext evidence of selective reporting bias was found, although there was no access to study protocols or trial registers.

4. Results

4.1. Results of the meta-analysis on the topic of dental implants

4.1.1. Study selection

The systematic search and selection process yielded a total of 188 records. Out of these records, seven RCTs were eligible for quantitative and qualitative analysis.

4.1.2. Characteristics of the included studies

All included records were randomized controlled trials (RCTs). The analysis included 722 implants (362 sandblasted and 360 machined). The included participants in these studies were uniform. Population with excessive drug and alcohol consumption or participants with systemic diseases that might influence the process of osseointegration were excluded.

4.1.4. Results of data synthesis – IF rate

Moderately rough surface (sandblasted) implants have significantly lower implant failure rates than smooth surface implants at 1, 2, and 5/6 years.

Data for meta-analysis of implant failure after one year of follow-up were pooled from five eligible studies. The analysis indicated that there is an 80 % lower risk of implant failure among sandblasted implants after one year of use. RR = 0.20; 95% CI: 0.06– 0.67; statistical heterogeneity: $I^2 = 0.0\%$ p = 0.986).

Analysis of pooled data of cumulative implant failure after two years reveals the risk of implant failure is 81% lower in the case of moderately rough surface than in the case of machined implants. (Risk Ratio = 0.19; 95% CI: 0.05–0.64; statistical heterogeneity: $I^2 = 0.0\%$ p = 0.977).

Meta-analysis of data on cumulative implant failure after five or six years of follow-up reveals that there is a 74 % lower risk of implant failure among moderately rough implants. (Risk Ratio = 0.26; 95% CI: 0.09–0.74; statistical heterogeneity I2 = 0.0% p = 0.968).

Data on cumulative implant failure after 12 to 15 years were pooled from three studies. Analysis indicates no significant difference between smooth and moderately rough surfaces after 12-15 years of follow-up. Risk Ratio = 0.68; 95% CI: 0.29–1.57; statistical heterogeneity I2 = 0.0% p = 0.590).

4.1.5. Results of data synthesis – MBL change

No significant difference in marginal bone loss between moderately rough (sandblasted) and smooth (machined) surface after 5 years.

Meta-analysis of marginal bone levels was conducted on data after one and five years after the delivery of the final prosthesis. Analysis reveals no significant difference between the two implant types after one year of use. Weighted mean difference = -0.10 mm; 95% Confidence Interval: -0.20–0.01; statistical heterogeneity: $I^2 = 0.0\%$, p = 0.560). Analysis of 5-year data also indicates no significant results between moderately rough and smooth implant surface. Weighted mean difference = 0.00 mm; 95% Confidence Interval: -0.13–0.14; statistical heterogeneity $I^2 = 26.2\%$, p = 0.258).

4.2. Results of the meta-analysis on the topic of hyaluronic acid dermal fillers in the oral cavity
4.2.1. Study selection

The study selection process identified a total of 326 records. After rigorous selection 10 records were included in the quantitative synthesis assessing the effectiveness of lip augmentation and 32 records were included in the qualitative synthesis.

4.2.2. Characteristics of included studies

To analyze the effects of HA on lip augmentation 5 RCTs and 5 cohort studies were included. Additionally, to assess the AEs 14 case reports six additional cohort studies and two additional RCTs were included.

A total of 1228 participants were included in the effectiveness analysis. Average subject age was between 41 and 54 years within the studies. In the included population all Fitzpatrick skin types were represented {Roberts, 2009 #2455}. Participants with an allergy to injectable HA or a history of any permanent or semi-permanent aesthetic tissue augmentation were excluded. The sites of injection in all studies were the perioral lines and the lips.

4.2.3. Risk of bias in studies

All included RCTs used means of random sequence generation. Yet, in the case of Dayan et al. 2015 and Carruthers and coworkers 2010 the methods of allocation concealment were not described clearly. Blinding of personnel giving the injection could not be carried out, however, blinded evaluators were used to assess the outcome.

The Newcastle Ottawa Scale was used to assess the bias in the observational studies. These studies had no control groups. They utilized baseline control, meaning that in the treated group the so-called "rate of responders" was compared to the baseline values.

4.2.4. Results of data synthesis – Effectiveness of HA

Three months after HA injection the rate of responders to HA treatment, i.e. the percentage of participants with at least one-grade improvement on a validated lip fullness scale was calculated including eight records. Pooled data showed that 71% of the HA-treated participants were responders, meaning that 71 out of 100 experienced a substantial, at least one grade increase in lip fullness 3 months after the initial treatment (ES=0.71, 95% CI: 0.55—0.87; $I^2 = 97.91\%$, p = 0.00).

Six months after treatment, the overall rate of responders was synthesized from five studies. The statistical analysis indicated that 74% of those who received the one dose of HA treatment maintained their lip fullness (ES=0.74, 95% CI: 0.66—0.82; $I^2 = 66.88\%$, p = 0.02).

Lip fullness data of 12 months follow-up was available in four studies. Pooled data revealed that the rate of responders was 46% even after one year of a single HA injection (ES=0.46, 95% CI: 0.28—0.65; $I^2 = 93.21\%$, p = 0.00).

4.2.5. Adverse effects related to hyaluronic acid injection

The analysis showed that the five most frequent AEs were tenderness (n = 1320, 88.7 %), injection site swelling (n = 1105, 74.3 %), contusion (n = 725, 48.7 %), injection site mass (n = 406, 27.3 %) and injection site pain (n = 293, 19.7 %). More severe AEs were rare.

Among them worth mentioning herpes labialis (n = 9, 0.6 %) and granulomatous foreign body reaction (n = 9, 0.6 %). Life-threatening angioedema was reported in four cases out of the 1 488 participants (0.3 %).

4.3. Results of the meta-analysis on the topic of oral diagnostics
4.3.1. Study selection
After duplicate removal 96 records remained for appraisal. Out of these 5 were included in quantitative synthesis.

4.3.2. Characteristics of included studies
The five studies included in the quantitative analysis were consecutive case series with 123 participants. Another consecutive case series Wyllie et al. 2020 was also included in the qualitative synthesis. However, it cannot be included in the quantitative work as no clear patient-wise data was reported for comparison with the rest of the studies.

4.3.3. Risk of bias assessment in the studies
Quadas-2 tool was used to assess the risk of bias in the included six case series. Overall, the risk of bias analyses demonstrated a moderate level of bias in both the individual and the overall aspects of the studies.

4.3.4. Results of data synthesis - sensitivity
Among the included studies the sensitivity of saliva tests ranged between 78% to 100% among the SARS-CoV-2 infected participants.

Pooled event rates (negative and positive saliva test results) indicate a sensitivity of 91% (CI 80-99%) among COVID-19 patients. Pooled event rates of NPS tests taken at the same time as saliva specimens show that the sensitivity of NPS test was 98% (CI 89-100%) (*Figure 16B*). As the confidence intervals of the two tests overlap, it suggests that the percentage of positive tests from the NPS and saliva tests are not very different. However, to strengthen our observation larger clinical studies are needed.

Evidence exists that in some cases NPS tests sometimes give negative results while the saliva test is positive. Wyllie and coworkers 2020 in a sample-based study out of 38 participants in eight (21%) detected the virus based on saliva

specimens, while the virus was not detected in the corresponding NPS samples. Whereas only in three instances (8%) happened that NPS was positive but saliva tests gave a negative result.

Specificity was assessed in two studies. In the study of Williams et al. 2020 SARS-CoV-2 was detected in 2% (CI 0.1-11.5%) of PCR-negative patients (n=50) (test was taken by nasal swab). The study by Wyllie and coworkers in 2020 included 98 asymptomatic healthcare personnel in their analysis. Saliva and NPS tests were taken in parallel. All tests turned out to be negative for NPS and two were positive for saliva.

5. Conclusions

The present PhD work applied the methodology of meta-analysis in three extremely important, controversial and unsettled dental topics, dental implant surface modifications, application of hyaluronic acid dermal fillers in the perioral region and oral diagnostics for COVID-19 identification. Analyses were performed to obtain a high level of evidence and to outline possible directions for further research in these specified fields of dentistry. As a result, the following conclusions were drawn.

1. The data revealed that there is an important and significant difference between moderately rough (sandblasted) and smooth (machined) implant surfaces in terms of implant failure rate after five years of follow-up. Sandblasted implants performed significantly better. On the other hand, no significant difference was found in marginal bone level loss between the two implant surfaces.

2. From the findings it can be also concluded that there is a need for comprehensive protocols to perform standardized clinical trials in the field of oral implant dentistry. Consistent reporting on several clinical outcomes is needed. Such as pocket probing depth, bleeding on probing and implant success.

3, Additionally, we found evidence that hyaluronic acid dermal filler injections are greatly efficient for at least up to six months. The present work also provided evidence that the lip volume was still significantly increased after a year in almost half of the participants.

4. Moreover, our analysis revealed that most of the AE related to HA injection were moderate or mild, however, due to the lack of a longer follow-up period possible delayed reaction could not be revealed. Longer follow-up periods are needed to establish the long-term effect of HA dermal filler injection.

5. Furthermore the present work provided evidence that saliva-based tests are promising candidates to replace nasopharyngeal swab tests for diagnosing COVID-19.

6. Enhanced and standardized saliva assays may offer a safe collection and reliable diagnosis of SARS-CoV-2 virus in the future. However

further validation and standardization are still needed for saliva-based tests before they become the standards of clinical practice.

Overall, in the three studies high level of scientific evidence was provided by systematically finding and selecting all eligible articles, and then synthetizing them by meta-analyses, and also applying an extremely rigorous quality control.

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