EVALUATION OF GLYCEMIC CONTROL OF TYPE 2 DIABETIC PATIENTS AFTER PERIODONTALLY INVOLVED TOOTH EXTRACTION

Doctoral Dissertation

Ljubljana, 2018
Evaluation of glycemic control of type 2 diabetic patients after periodontally involved tooth extraction

Doctoral Dissertation

Ocena urejenosti glikemije pri sladkornih bolnikih tipa 2 po izdrtju parodontalno prizadetih zob

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**Abbreviations:**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>HbA1c</td>
<td>Glycated hemoglobin</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>High sensitivity C-Reactive Protein</td>
</tr>
<tr>
<td>T2DM</td>
<td>Type 2 Diabetus Mellitus</td>
</tr>
<tr>
<td>ND</td>
<td>Non Diabetic</td>
</tr>
<tr>
<td>PPD</td>
<td>Periodontal Probing Depth</td>
</tr>
<tr>
<td>BoP</td>
<td>Bleeding on Probing</td>
</tr>
<tr>
<td>mCAL</td>
<td>Mean Clinical Attachment Loss</td>
</tr>
<tr>
<td>mPI</td>
<td>Mean Plaque Index</td>
</tr>
<tr>
<td>SRP</td>
<td>Scaling and Root Planing</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
</tbody>
</table>
Extended Summary

Background

Well-controlled diabetic adult patients were three times less likely to have periodontal disease than those with diabetes. Also, the glycated hemoglobin level correlates with the severity of periodontal disease. Otherwise, in a patient with periodontal disease, C-reactive protein levels are higher compared to healthy patients. Hence, the control of chronic periodontal disease is mandatory for achieving long-term control of diabetes, defined by the reduction in glycated hemoglobin levels.

It is well known that routine oral prophylaxis plays an important role in periodontal health but it not shown significant improvement of glycated hemoglobin levels. On the contrary, a full-mouth desinfection approach showed beneficial effects on diabetic metabolic control. Although non-surgical periodontal therapy resulted in improvement of glycated hemoglobin control, different periodontal treatment approaches were used.

Taking this into consideration together with the necessity for further investigations for T2DM and periodontal disease, the aim of this doctoral thesis was to evaluate the improvement of the glycemic, systemic inflammation levels according to the main biomarker analysis and periodontal parameters through clinical examinations of healthy and type 2 diabetic Kosovo patients after non-surgical periodontal therapy and extraction of periodontally compromised teeth, or periodontally compromised teeth extraction alone. The rationale of this doctoral thesis was that periodontal disease is most common in Kosovo due to the high poverty level and individuals rarely seek medical attention. The present study was undertaken according to the CONSORT statement to improve the quality of reports of parallel-group, randomized trials (http://www.consort-statement.org/), and it was registered on Clinical.Trials.gov (NCT02874963). The null hypothesis was that non-surgical periodontal treatment and extraction of periodontally compromised teeth may not reduce tissue glycemic levels and systemic inflammation in diabetic patients, that might reflect in better glycemic control.
Participants and methods

This study was designed as a cluster-randomized trial of parallel-group design conducted at endocrinology department of Peja’s Regional Hospital and the Dental Polyclinic in the city of Peja, between December 2015 and February 2017. Surgical procedures were performed by one expert clinician (DB). Participation of every candidate was voluntary according to the principles embodied in the Declaration of Helsinki of 1975 for biomedical research involving human subjects, as revised in 2013. All of the patients were informed about the nature of the treatment and their written consent was obtained. The study was approved by Ethical-Professional Board at University Clinical Centre of Kosovo based on Administrative Instruction Nr.05/2012 for Supervision of Professional Ethics, decision dated October 21st, 2014 Org.Unit.01, Nr. Prot., 4212/2. With further additional approval of the Ethical-Professional Board at University Clinical Centre of Ljubljana, decision dated May 31st, 2016; (KME 73/01/16). A priori sample size calculation was performed given Effect size d=0.5, alfa error probability 0.08 and power 0.8 resulting in 26 patients for the group. Due to the availability of patient in this period of time to increase the statistical power we have almost doubled the selected patients for the type 2 diabetes as the main research investigation indicator in this doctoral thesis (n=50).

Patients were selected if they met the following inclusion criteria: any partially edentulous patient (had at least 10 teeth in the functional dentition excluding third molars, aged 18 years or older, able to sign an informed consent form, with a clinical diagnosis of chronic periodontitis, as determined by the presence of at least 1 site with a periodontal probing depth (PPD) ≥ 5 mm, two teeth with attachment loss ≥ 6 mm, positive bleeding on probing (BoP), and at least 1 periodontally compromised tooth, was considered eligible for this study. A periodontally compromised tooth was noted when two or more of the following characteristics were present: loss of more than 75% of supporting bone, probing pocket depths ≥ 8 mm, class III furcation, hypermobility, and non-treatable endodontic issues. Hemoglobin (HbA1c) levels and of high-sensitivity C-reactive protein (hs-CRP) were collected from clustered patients with type 2 diabetes (diabetes mellitus) and non-diabetic patients. The cut-off value used to clustered patients with diabetes was HbA1c ≥ 6.5% and hsCRP ≥ 1.5 % in both groups.
Information about diabetes including duration, type of treatment, diabetes self-care management, blood glucose testing, patient's adherence to their current medications, diet therapy, and any physical activities was also collected. In addition, body mass index (BMI) changes, medications, smoking status and weight were noted.

Personal interviews were performed to collect baseline data from each participant using a pre-structured questionnaire. Basing on the questionnaire, patients were not admitted to the study if any of the following exclusion criteria were present: general medical contraindication to oral surgery (American Society of Anesthesiologists [ASA] Physical Status Class III or IV), irradiation of the head and neck area less than 1 year before research, alcohol or drug abuse, pregnant or nursing, severe bruxism or clenching, major diabetic complications and history of antibiotic therapy or non-steroidal anti-inflammatory drug therapy 4 months before the first visit.

Detailed medical history, socio-demographic data (age, sex, level of education and income), preoperative photographs, periapical radiographs, and model casts were obtained for initial screening and evaluation. The periodontal clinical examination was performed according to the periodontal chart, School of Dental Medicine (ZMK), University of Bern, Department of Periodontology (http://www.periodontalchart-online.com/uk/index.asp).

All patient characteristics and baseline characteristics of biochemical and clinical data's from the patients are recorded.

All the patients underwent professional oral hygiene prior to the surgeries and received prophylactic antiseptic (chlorhexidine mouthwash 0.2%, Listerine, Johnson & Johnson, UK). Patients were treated under local anesthesia using articaine hydrochloride with adrenaline 1:100000 (Orabloc, Pierrel, Milan, Italy).

Fifty patients with type 2 diabetes and 30 non-diabetic patients received non-surgical periodontal therapy before extraction of periodontally compromised teeth(test groups). Non-surgical periodontal therapy consists in instrumentation of all pockets (full mouth scaling and root planing [FMSRP]) with local antiseptics. Ultrasonic device (UDS-J Ultrasonic Scaler, Guilin Woodpecker Medical Instrument) and periodontal curettes (1/2 Gracey Curette, SGR 1/24; 1/2 Mini Fie Graey Curette SAS1/2C8; 1/2 After Five Gracey Curette; CL866, Hu-Friedy) were used for the mechanical debridement of supra- and subgingival plaque and calculus. The others 50 and 30 patients in each cluster (diabetic and non-diabetic) received periodontally compromised teeth extraction alone (control groups).
Afterwards, in both groups, periodontally compromised teeth extractions were performed asatraumatically as possible, with the aid of a periosteum and atraumatic elevators (PT1 and EPTSMS, Hu-Friedy, Milan, Italy). Multiple-rooted teeth were sectioned at the furcation and the roots were individually extracted. Then, the residual extraction socket was washed with physiological solution and debrided thoroughly from granulation tissue and residual periodontal ligament fibers with a curette (CL866, Hu-Friedy). Painkillers were administered as needed. Post-operative rinsing was followed by the use of the antiseptic solution Listerine (Johnson & Johnson, Berkshire, UK) as a mouthwash thrice a day for 3 weeks. Follow-up visits were scheduled every 3 months up to 1 year after treatment.

**Outcomes measure were:** Periodontal clinical parameters plaque index [PI], bleeding on probing [BOP], probing depth [PPD] and clinical attachment level [CAL] were collected into the online periodontal chart (Department of Periodontology, School of Dental Medicine (ZMK), University of Bern) at baseline and 3 months after the periodontal treatment. All the parameters were recorded for six measurement points (mesial buccal, buccal, distal buccal, mesial lingual, lingual, distal lingual) on all teeth (excluding 3rd molars) during each of two visits, using a periodontal probe (PCP UNC-15, Hu-Friedy).

The levels of HbA1c and hs-CRP were measured using venous blood collected from patients at baseline and 3 months after the study procedures. All biochemical analyses were conducted in a biochemical laboratory in Peja (Laboratory Diagnostic Center, Peja, Kosovo) using a biochemistry analyzer (Select Pro XS, ELITech Clinical Systems, Paris, France) and enzyme-linked immunoassay kits (ELITech Clinical Systems, Paris, France).
**Statistical analyses**

All data were reported as means±standard deviation (SD); 95% confidence interval (CI). Before the statistical analysis was performed, the normal distribution and homogeneity of the variances were tested. Associations between the experimental parameters were investigated over time for using paired t-tests. Differences of means at patient level for continuous outcomes between groups were compared by unpaired t-tests. The results were considered significant when the P value was P<0.05 (GraphPad Prism 5.0 software, San Diego, CA, USA).
RESULTS

A total of 200 consecutive patients were screened for eligibility. After clinical examination, 160 patients aged from 30 to 70 years old (59.49±10.82) were selected for this cluster-randomized trial. Patients were clustered in type 2 diabetic (n=100) and non-diabetic (n=60) patients and then randomized in two parallel groups. Patients with type 2 diabetes received non-surgical periodontal therapy and extraction of periodontally compromised teeth (n=50; 87 extracted teeth; test group), or extraction of periodontally compromised teeth alone (n=50; 88 extracted teeth; control group). Non-diabetic patients received non-surgical periodontal therapy and extraction of periodontally compromised teeth (n=30; 54 extracted teeth; test group), or periodontally compromised teeth extraction alone (n=30; 49 extracted teeth; control group). At the end of the study, no drop-out occurred and no deviation from the original protocol occurred.

The diabetic type 2 patients have shown a significant improvement in the HbA1c plasma serum levels compared to the baseline which was founded in both groups. In the test group (with non-surgical periodontal therapy-test), non-surgical periodontal therapy before periodontally compromised teeth extraction improves HbA1c plasma serum levels. In the control group (without non-surgical periodontal therapy-control), periodontally compromised teeth extraction alone improves HbA1c plasma serum levels, with a tendency for more improvement in the test group, however, the difference between test and control group was not statistically significant. Significantly reductions of hs-CRP were founded in both groups and also the difference between test and control group was statistically significant with better value for the test group.

Non-Diabetic patients have shown a statistically significant reduction in the HbA1c plasma serum levels which was found during the study period in the test group but not in the control group, however, the differences between test and control group were not statistically significant. The variation in the serum levels of hs-CRP in non-diabetic patients during the study period was statistically significant in the test group, while in the control group it was sustained the same and the differences between test and control group were statistically significant with better value for there testing group.
The periodontal parameters in the diabetic type 2 patients including:

- The mean PI (mPI) values statistically decreased in both groups and the difference between test and control group was statistically significant with better value for the test group.
- The mean BoP (mBoP) values statistically decreased in both groups and the difference between test and control group was statistically significant with better value for the testing group.
- The mean mPPD (mPPD) values statistically decreased in both groups and the differences between test and control group were not statistically significant.
- The mean CAL (mCAL) values statistically decreased in the test group but not in control the group, however, the differences between test and control group were not statistically significant.

The periodontal parameters in the non-diabetic patients including:

- The mPI values statistically decreased in both groups and differences between test and control group was statistically significant with better value for the test group.
- The mBoP values statistically decreased in both groups and differences between test and control group was statistically significant with better value for the test group.
- mPPD values statistically decreased in both groups and the differences between test and control group was statistically significant with better value for the test group.
- The mCAL values was not statistically significant in both groups and the differences between test and control group was statistically significant with better value for the test group.

Conclusions

The results of the present doctoral thesis demonstrated that non-surgical periodontal therapy and extraction of periodontally compromised teeth may improve glycemic levels and periodontal parameters of both non-diabetic and type 2 diabetic patients with chronic periodontitis. Further follow-ups, as well as larger investigational studies aimed at evaluating the impact of non-surgical and surgical approaches to the clinical management of periodontal disease and diabetic patients, need to confirm these results.


*Answers to research hypothesis*

1. Non-surgical periodontal therapy reduced significantly glycemic levels in type 2 diabetic patients and non diabetic patients with extraction of periodontally compromised teeth which were associated also improvement of periodontal status.

2. Non-surgical periodontal therapy reduced significantly systemic inflammation in diabetic patients which were accompanied with the better glycemic control in type 2 diabetic patients and non diabetic patients with extraction of periodontally compromised teeth which were associated also improvement of periodontal status.
**Razširjeni povzetek**

**Izhodišča**

Bolniki z dobro urejeno sladkorno boleznijo so trikrat manj podvrženi razvoju parodontalne bolezni kot tisti s slabo urejenostjo glikemije. Tudi delež glikiranega hemoglobina A1c (HbA1c) je v povezavi z napredovalostjo parodontalne bolezni. Pri bolnikih s parodontalno boleznijo je raven C-reaktivnih proteinov višja kot pri zdravih osebah. Zato je pri bolnikih s kronično parodontalno in sladkorno boleznijo pomembna vzdrževalna faza parodontalnega zdravljenja. S tem dosežemo dobro presnovno urejenost sladkornih bolnikov, kar se lahko kaže z manjšimi vrednostmi HbA1c.

Vzdrževanje dobre ustne higiene je pri bolnikih s sladkorno boleznijo pomembno za zdravje obzobnih tkiv, ne vodi pa v zmanjšanje deleža HbA1c. Izboljšanja urejenosti glikemije dosežemo z uporabo metode dezinfekcije celotne ustne votline ter nekirurškimi in kirurškimi metodami zdravljenja parodontalne bolezni.

To nas je vodilo k nadaljnem raziskavam, ki so bile namen te doktorske dizertacije: da z biomarkerji in parodontalnimi kliničnimi parametri ocenimo izboljšanje urejenosti glikemije ter sistemskih vnetij pri osebah s sladkorno boleznijo tipa 2 in zdravih prebivalcih Kosova, po nekirurškem zdravljenju parodontalne bolezni ter ekstrakciji parodontalno prizadetih zob, in ekstrakciji parodontalno prizadetih zob brez predhodnega nekirurškega zdravljenja parodontalne bolezni.

Parodontalna bolezen je zelo pogosta na Kosovu, kjer je prisotna visoka stopnja revščine in posamezniki zelo redko poiščejo medicinsko pomoč.

Raziskava je potekala v skladu s zgoščenimi standardi za poročilo raziskav COMPASS (http://www.consort-statement.org/) in je bila registrirana na Clinical.Trials.gov (NCT02874963). Ničelna hipoteza je bila, da nekirurško parodontalno zdravljenje in ekstrakcija parodontalno prizadetega zoba nista povezana z zmanjšanjem sistemskega vnetja, ki bi se odražalo v izboljšanju urejenosti glikemije.
Preiskovanci in metode

Opravili smo kontrolirano randomizirano raziskavo na Endokrinološkem oddelku deželne bolnišnice v Peči in Zobne poliklinike v Peči na Kosovu med decembrom 2015 in februarjem 2017. Vse kirurške posege je opravil isti zobozdravnik (DB). Sodelovanje v raziskavi je bilo prostovoljno v skladu s smernicami Helsinške deklaracije za biomedicinske raziskave, v katerih sodelujejo ljudje, iz leta 1975, posodobljene leta 2013. Vsi preiskovanci so bili podučeni o namenu in poteku raziskave in so pisno privolili v sodelovanje. Raziskavo je odobrila komisija za medicinsko etiko Kosova (Ethical-Professional Board at University Clinical Centre of Kosovo based on Administrative Instruction Nr.05/2012 for Supervision of Professional Ethics, decision dated October 21st, 2014 Org.Unit.01, Nr. Prot., 4212/2) in tudi Komisija Republike Slovenije za medicinsko etiko May 31st, 2016; (KME 73/01/16).

Velikost vzorca, šestindvajset bolnikov v vsaki od dveh skupin, je bila izračunana tako, da je bil učinek velikosti 0.5 pri stopnji tveganja (α=0.08) in moči testa (β=0.8). Zaradi velikega števila ustreznih bolnikov in z željo izboljšati statistično moč testa se je število preiskovancev povečalo na 50.

Vključitveni kriteriji za sodelovanje v raziskavi so bili prisotnost vsaj 10 zob v funkcionalni denticiji brez tretjih kočnikov, starost 18 let ali več, sposobnost razumeti in podpisati pisno privolitev. Diagnoza kronične parodontalne bolezni, določene s prisotnostjo vsaj enega zoba z enim mestom z globino sondiranja večjo od 5 (GS ≥ 5 mm), dveh zob z izgubo epitelijanskega prirastišča več kot 6 mm (IEP≥ 6 mm), prisotnostjo krvavitve na sondiranje (KS) in vsaj enim parodontalno prizadetim zobom. Za parodontalno prizadet zob z brezupno prognozo se je štel zob, kjer sta bila prisotna dva ali več kriterijev: izguba več kot 75 % podporne kosti, GS ≥8 mm, stopnja prizadetosti razcepisč III, stopnja majavosti III, endodontsko brezupna prognoza.

Delež HbA1c in raven visoko občutljivega C-reaktivnega proteina (hsCRP) smo izmerili tako preiskovancem s sladkorno boleznijo tipa 2 kot tudi osebam brez sladkorne bolezni. Za skupino oseb s sladkorno boleznijo sta bili vrednosti HbA1c ≥ 6,5 % in hsCRP ≥1,5 % pogoja za vključitev v raziskavo.
Zbrali smo tudi podatke o poteku sladkorne bolezni, njenem trajanju, načinu zdravljenja in samovodenja bolezni. Izračunali smo indeks telesne mase (ITM), zabeležili smo vsa zdravila, ki jih bolnik jemlje ter preverili status kajenja. Podatke smo pridobili v razgovoru z bolnikom po v naprej določenem protokolu in vprašalniku. Izključitveni dejavniki za sodelovanje v raziskavi so bili kontraindikacije za kirurški poseg (American Society of Anesthesiologists [ASA] Physical Status Class III or IV), radiološko zdravljenje področja glave in vratu manj kot eno leto pred raziskavo, uporaba drog in prekomerno pitje alkohola, nosečnost in dojenje, huda oblika bruksizma, hudi zapleti sladkorne bolezni, antibiotično ali nesteroidno protivnetno zdravljenje 4 mesece pred prvim obiskom.

Odvzeli smo natančno medicinsko anamnezo, pridobili smo socio-demografske podatke (starost, spol, stopnja izobrazbe, socialno ekonomski status), naredili smo rentgenološko diagnostiko s pomočjo periapikalnih posnetkov z uporabo nosilcev. Klinične meritve je vselej opravil isti pregledovalec in jih zabeležil na standardiziran protokol (protocol-periodontal chart, School of Dental Medicine (ZMK), University of Bern, Department of Periodontology) (http://www.periodontalchart-online.com/uk/index.asp). Zabeležili smo tudi biokemične in klinične podatke bolnika.

Pred kirurškimi posegi smo pri bolnikih naredili profesionalno začetno fazo parodontalnega zdravljenja z uporabo antiseptične ustne vode (chlorhexidine mouthwash 0.2%, Listerine, Johnson & Johnson, UK).

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Localno zdravljenje smo opravili v lokalni anesteziji z uporabo articain hidroklorida z adrenalino 1:100000 (Orabloc, Pierrel, Milan, Italy).

Petdeset oseb s sladkorno boleznio tipa 2 in trideset oseb brez sladkorne bolezni je prejelo nekirurško parodontalno zdravljenje pred izruvanjem parodontalno prizadetih zob (testna skupina). Z nekirurškim parodontalnim zdravljenjem smo odstranili trde in mehke zobne oblobe po metodi dezinfekcije celotne ustne votline (full mouth disinfection [FMD]). Uporabili smo ultrazvočni odstranjevalec oblog (UDS-J Ultrasonic Scaler, Guilin Woodpecker Medical Instrument) in parodontalne kirete (1/2 Gracey Curette, SGR 1/24; 1/2 Mini Fie Graey Curette SAS1/2C8; 1/2 Gracey Curette; CL866, Hu-Friedy) za glajenje korenin. Pri ostalih 50 in 30 preiskovancih v vsaki skupini (sladkorni in nesladkorni bolniki smo opravili zgolj ekstrakcijo parodontalno prizadetih zob (kontrolna skupina).
Ekstrakcijo zob smo napravili atravmatsko z uporabo periotoma in atravmatskih pripomočkov (PT1 and EPTSMS, Hu-Friedy, Milan, Italy). Korenine večkoreninskih zob smo ločili v razcepniščih in vsako korenino ekstrahirali posebej. Ekstrakcijsko rano smo izprali s fiziološko raztopino, ostanke vnetega tkiva smo odstranili s kireto (CL866, Hu-Friedy). Po potrebi smo bolnikom predpisali tudi protibolečinske tablete. Po ekstrakcijah so bolniki ustno votlino spirali trikrat dnevno naslednje tri tedne z Listerinom (Johnson & Johnson, Berkshire, UK). Kontrolni pregledi so bili načrtovani na tri mesece prvo leto po zdravljenju.

**Meritve:**

Parodontalni klinični parametri: indeks plaka (IP), krvavitev na sondiranje (KNS), globina sondiranja (GS), nivo kiničnega prirastišča (NKI), so bili izmerjeni in zabeleženi s tabelo-online periodontal chart (Department of Periodontology, School of Dental Medicine (ZMK), University of Bern) na začetku raziskave in 3 mesece po opravljeni začetni fazi parodontološkega zdravljenja. Klinični parametri so bili izmerjeni na 6 merilnih točkah (meziobukalno, bukalno, bukodistalno, meziolingvalno, lingvalno, distolingvalno, na vseh zobeh razen na tretjih kočnikih ob vsakem od dveh obiskov. Za meritve je bila uporabljena parodontalna sonda (PCP UNC-15, Hu-Friedy). Delež HbA1c in raven hs-CRP sta bila izmerjena v vzorcu periferne venske krvi, odvzete pred in tri mesece po ekstrakciji parodontalno prizadetih zob. Vse biokemične analize so bile opravljene v biokemičnem laboratoriju v Peči (Laboratory Diagnostic Center, Peja, Kosovo) z uporabo biokemičnega analizatorja (Select Pro XS, ELITech Clinical Systems, Paris, France) in encimskega imunskega testa (ELITech Clinical Systems, Paris, France).

**Statistična analiza**

Vsi podatki so predstavljeni kot povprečna vrednost ± standardna deviacija (x±SD); 95 %interval zaupanja (CI). Pred statistično analizo je bila testirana normalna distribucija in homogenost variance. Povezanost med eksperimentalnimi parametri je bila analizirana z uporabo t-testa. Razlika povprečij pri preiskovancih je bila primerjana z neparnim t-testom. Meja signifikance je bila postavljena na 0.05 (P<0.05, GraphPad Prism 5.0 software, San Diego, CA, USA).
REZULTATI

Za vključitev v raziskavo je bilo pregledanih 200 zaporednih preiskovancev. Po kliničnem pregledu je bilo za to kontrolirano randomizirano raziskavo izbranih 160 preiskovancev, starih od 30 do 70 let (59,49 ± 10,82 let). Preiskovanci so bili razporejeni v skupino oseb s sladkorno boleznijo tipa 2 (n = 100) in skupino oseb brez sladkorne bolezni (n = 60), nato pa so bili naključno razdeljeni v dve vzporedni skupini. Bolniki s sladkorno boleznijo tipa 2 so bili deležni nekirurškega parodontalnega zdravljenja in ekstrakcije parodontalno prizadetih zob (n = 50; 87 ekstrahiranih zob, testna skupina) ali zgolj ekstrakcij parodontalno prizadetih zob (n = 50; 88 ekstrahiranih zob, kontrolna skupina). Osebe brez sladkorne bolezni so bile deležne parodontalnega zdravljenja in ekstrakcij parodontalno prizadetih zob (n = 30; 54 ekstrahiranih zob, testna skupina) ali zgolj ekstrakcij zob (n = 30; 49 ekstrahiranih zob, kontrolna skupina). Pri raziskavi ni prišlo do odstopanj od prvotnega protokola, do konca raziskave so sodelovali vsi vključeni preiskovanci.

Pri bolnikih s sladkorno boleznijo tipa 2 je v testni in kontrolni skupini prišlo do pomembnega izboljšanja urejenosti glikemije. V testni skupini je ne-kirurško parodontalno zdravljenje pred ekstrakcijo parodontalno prizadetih zob izboljšalo urejenost glikemije zmanjšalo delež HbA1c. V kontrolni skupini je že sama ekstrakcija parodontalno prizadetih zob izboljšala urejenost glikemije, s trendom ugodnejšega vpliva v testni skupini, vendar razlika med testno in kontrolno skupino ni bila statistično pomembna.

Statistično značilno zmanjšanje hs-CRP je bilo ugotovljeno v obeh skupinah, prav tako pa je bila razlika med testno in kontrolno skupino statistično pomembna z boljšo vrednostjo za testno skupino.

Pri bolnikih brez sladkorne bolezni je prišlo do statistično pomembnega zmanjšanja deleža HbA1c, kar je bilo ugotovljeno med časom trajanja raziskave v testni skupini, ne pa v kontrolni skupini, vendar razlike med testno in kontrolno skupino niso bile statistično značilne. Spreminjanje serumskih koncentracij hs-CRP pri bolnikih brez sladkorne bolezni v času trajanja raziskave je bilo statistično značilno v testni skupini, v kontrolni skupini je vrednost ostala enaka, razlike med testno in kontrolno skupino pa so bile statistično pomembne z boljšimi vrednostmi pri testni skupini.
Parodontalni parametri pri bolnikih s sladkorno boleznijo tipa 2:

-povprečne vrednosti PI (mPI) so se statistično pomembno zmanjšale v obeh skupinah, razlika med testno in kontrolno skupino je bila statistično pomembna z boljšo vrednostjo za testno skupino.

-povprečne vrednosti BoP (mBoP) so se statistično pomembno zmanjšale v obeh skupinah, razlika med testno in kontrolno skupino je bila statistično pomembna z boljšo vrednostjo za testno skupino.

-povprečne vrednosti PPD (mPPD), so se statistično pomembno zmanjšali v obeh skupinah, vendar razlika med testno in kontrolno skupino ni bila statistično pomembna.

-povprečne vrednosti CAL (mCAL) so se statistično pomembno zmanjšali v testni skupini, vendar pa razlike med testno in kontrolno skupino niso bile statistično pomembne.

Parodontalni parametri pri bolnikih brez sladkorne bolezni:

-povprečne vrednosti PI so se statistično pomembno zmanjšale v obeh skupinah, razlika med testno in kontrolno skupino je bila statistično pomembna, pri čemer je bila boljša vrednost za testno skupino.

-povprečne vrednosti BoP so se statistično pomembno zmanjšale v obeh skupinah, razlike med testno in kontrolno skupino pa so bile statistično pomembne z boljšo vrednostjo za testno skupino.

-povprečne vrednosti PPD, so se statistično pomembno zmanjšali samo v testni skupini, vendar je bila razlika med testno in kontrolno skupino statistično pomembna.

-povprečne vrednosti CAL v obeh skupinah niso bile statistično pomembne, razlika med testno in kontrolno skupino pa je bila statistično pomembna, pri čemer je bila boljša vrednost za testno skupino.
Zaključki

Rezultati te doktorske disertacije so pokazali, da lahko ne-kirurško parodontalno zdravljenje in ekstrakcija parodontalno prizadetih zob izboljšata urejenost glikemije in parodontalne parametre oseb brez sladkorne bolezni in oseb s sladkorno boleznijo tipa 2 s kroničnim parodontitisom. Nadaljnje spremljanje in tudi večje raziskave, usmerjene k ocenjevanju vpliva nekirurških in kirurških pristopov h kliničnemu obvladovanju parodontalne bolezni in oseb s sladkorno boleznijo, morajo potrditi te rezultate.

Odgovori na zastavljene hipoteze

1. Ne-kirurško parodontalno zdravljenje je pri bolnikih s sladkorno boleznijo tipa 2 in pri osebah brez sladkorne bolezni z ekstrakcijo zob statistično pomembno zmanjšalo delež HbA1c, kar je bilo povezano tudi z izboljšanjem parodontalnega stanja.

2. Ne-kirurško parodontalno zdravljenje je statistično pomembno zmanjšalo sistemsko vnetje pri bolnikih s sladkorno boleznijo. Prišlo je tudi do izboljšanja urejenosti glikemije pri bolnikih s sladkorno boleznijo tipa 2 in pri osebah brez sladkorne boleznij z ekstrakcijo zob, kar je bilo povezano tudi z izboljšanjem parodontalnega stanja.
Introduction

Diabetes Mellitus and Dentist Role

Diabetes mellitus is a group of metabolic diseases characterized with hyperglycemia resulting from absolute or relative defects in insulin secretion, insulin actions or both, based on this chronic hyperglycemia in diabetes result in long-term organ damages and failures including macrovascular and microvascular complications: eyes, kidneys, nervous system, heart and blood vessels with the nephropathy, atherosclerosis, hypertension, foot ulcer, and retinopathy. It is associated with symptoms of polyuria, polydipsia, weight loss, blurred vision, hunger, diabetic ketoacidosis, hyperosmolar coma and susceptibility to infections (1). The prevalence of diabetes is increasing worldwide in both developed and developing countries (accounting 75 % of the population in low and mild income countries) accounting with 416 million of people with dominating type 2 diabetes mellitus as one of the most common types with 90 % with equal rates in women and man. The obesity contributes significantly to the burden of diabetes (44 %). The type 2 diabetes mellitus is known to be caused due to progressive loss of insulin secretion (progressive loss of Beta-cell mass and/or function) and insulin resistance, excessive body weight, not enough physical activity and it is diagnosed with appropriate clinical and biochemical screening, glucose plasma levels and more often with its biomarker glycated haemoglobin test HbA1c as a simple, inexpensive screening test that can be automated using existing clinical blood samples (2). Recent studies have shown that HbA1c values from 5.5-6.0 % have a higher tendency for development of diabetes; however, the values with 6.5 % or higher HbA1c are diagnosed as diabetes mellitus. The common risk factors for the development of diabetes include family history, over 50 years old, obesity and body mass index (higher than 25), physical inactivity, lifestyle component, despite its symptoms and disease progression the lifestyle modification, education, and motivation including diets and reduced sugar intake, weight loss and physical activity must be undergone with its therapeutic treatment approaches including oral antidiabetics and insulin. Patients need to avoid certain medications including glucocorticoids, thiazide diuretics, and atypical psychotics.
Oral antidiabetics which are used in common are biguanides (metformin) as first-line treatment approach accompanied with sulphonylureas, meglitinides, thiazolidines. The appropriate management of diabetes and its comorbidities were shown to reduce its complication and mortality (3). Moreover, surgical treatment interventions are shown to be promising in the type 2 diabetic patients undergoing also bariatric surgery interventions, which has shown to reduce the complications and improve the prognosis of the disease even though the recurrence of the disease is still present in 40 % of the patients after follow up (4,5).

Management of every patient should commence with a detailed assessment of the initial diagnosis including an appraisal of diabetes complications and risk factors for complications. This provides the basis for continuing care that includes a treatment plan, treatment administration, monitoring, and review. The T2DM patients need to do an initial assessment step (through medical history, physical examination, laboratory evaluation which would bring to a potential treatment plan through individualized treatment targets, diet, exercise, antidiabetic, prevention and treatment of its complications, continuous education. Treatment administration consists appropriate instructions for use in educated patients which are accompanied with an appropriate monitoring of the compliance with the treatment plan, outcomes, adverse effects, patient comprehension. A further review of a treatment plan is also necessary to adjust further (6).

Since the diabetes is an associated risk factor for periodontal disease including periodontitis associated with dry mouth and oral infections the dentist has been shown to play an important and expanding role in the early screening and appropriate management of diabetes and its related complications which is shown to be also in the patient's best interests (7).

The dental practitioner must pay special attention to the detection of diabetes and the dental setting strategies and tendencies in the management of periodontal and associated systemic disease include the smoking cessation strategies, reduction of sugar consumption, weight control in patients with periodontal disease, caries, diabetes, heart disease and certain cancers (8).
Dentist screening of diabetes consists careful consideration of the following clinical signs includes the: hyperplastic gingiva, inflammation and tissue proliferation of the margins, periodontal disease, mobile teeth, conventional treatment response and the wound healing after oral surgical interventions, abnormal responses to a plaque which persists after tooth scaling.

Moreover, the typical oral symptoms which are reported by the diabetic patients include burning mouth, dry mouth, and altered taste which are related from the neuropathy.

Recently there has been a greatful interest for using the gingival blood samples for the glucose measurement which consists a simple screening for the diabetes diagnosis (9).

Recently there has been a great interest in running a campaign to raise awareness of the increased risk of periodontal disease people living with diabetes. Moreover, most of these patients experience bleeding when brushing, even though only 50 % of them received information about the periodontal disease from a dentist, doctor or pharmacist. Taking this into consideration dentist might help these patients through asking symptoms and also better screening for periodontal disease and examinations in patients with diabetes mellitus and if there might not exist the possible diagnosis the patients should be placed on a preventive care programme and monitored regularly for any changes in the periodontal status and can help patients living with diabetes by giving them information they need to take responsibility for their oral health (10,11).
Periodontal diseases

Inflammatory process and the response includes different acute and chronical immune reaction from the vascular and also cellular level accompanied with the signs and symptoms such as redness, increased temperature and fever, tissue enlargement and pain. The further progress includes the increased CRP levels which could lead to a sepsis. The oral health and it's infections are also an important triggers in this process which may impact also the other systemic diseases such as cardiovascular disease, respiratory etc) (12,13). The oral pathogenic bacteria released from the dental plaque with its endotoxins, cytokines are the main indicators for the induction of inflammation process and immunopathogenesis (immune defenses of the host) which result in the gingivitis. Moreover the inflammation of the periodontal ligaments followed by the bone resorption results in the periodontal disease which result with the increased proinflammatory mediators including CRP, fibrinogen, and IL-1, and 6 which usually respond to the periodontal treatment therapy. The periodontitis is aggravated further through the host risk factors such as family history, hormonal variations, systemic disease, stress, nutritional deficiencies, medications (calcium channel blockers, immunomodulatory agents, anticonvulsants, drug-induced xerostomia, smoking, genetic susceptibility, poor oral health and hygiene (14). The above mentioned risk factors such as proinflammatory mediators and enzymes, diabetes, host response and poor compliance play role in the diseased periodontium, and in the other side the reduction risk factors such as increased host-derived antiinflammatory mediators, host modulatory therapy, SRP, surgery, antibiotics and antiseptics are more defending factors to remain a healthy periodontium, which are shown in more details in the (Figure 1).
Previously the 5-15 % of the adult global population (around 50-60 years old) in more industrialized countries with severe periodontitis and even though there is still no definitive data in the first decade of the 21st century regarding the status of populations globally, there has been an oral assessment in more developed countries (16). Clinical diagnosis is based on the features such as texture changes, enlargement of the tissues, redness, gingival bleeding on probing, increased periodontal pockets and depth, supporting structure destructions, tooth mobility and loss). Moreover, the pain may arise also with acute exacerbations owing to abscesses or dislodgement of teeth caused by weakening tooth support, even though typical periodontitis is painless.
The diagnostic procedures and the main parameters include the clinical attachment level (CAL), bleeding on probing (BoP), probing depth (PD), radiographic findings, patient history, plaque progression and its quality. Important observation should be done in the identifying aetiological factors; screening and prevention with daily home care include brushing teeth, fluoride toothpaste, and balanced diet with limited between-meal snacks. In addition, appropriate management consists gingivitis treatment with non-surgical, adjunctive therapies and local delivery of drugs, systemic antibiotics, systemic host response modulation and surgical therapy (17,18).

Periodontal diseases are generally shown as acute, chronic and aggressive which varies in terms of clinical features and treatment approaches. Periodontal destruction includes the subdivision with no more than 1 to 2 mm of clinical attachment loss, moderate 3-4 mm and severe when 5 mm or more of clinical attachment loss.

It starts with an early gingivitis and then with abscess and chronic periodontitis with the localized and generalized, pericoronal abscess, necrotizing periodontal and periodontal-endodontic lesions (17,19).

Acute lesions in the periodontitis and oral mucose are expressed with pain which could lead to a rapid destruction of the periodontium. Some other lesions are accompanied with fever, malaise and lymphadenopathy. Also the abscesses in the deeper periodontium and may compromise the affected tooth which may result in the systemic infection. This are manifested usually with pain and swelling and tenderness to palpitation.

Necrotizing periodontal diseases (gingivitis, periodontitis, stomatitis) are tissue dependent (20,21). However, the chronic periodontitis involves the inflammation of periodontium (loss of teeth if not treated) and is widespread in different ages, even though it affects more the adults. Its progression is dependent of the subgingival plaque, pathogenic bacteria, comorbidities (diabetes, HIV, inflammation), smoking, stress.

The aggressive periodontitis (localized and generalized) and is well established in early childhood and adults with low incidence level. It can be manifested also with multiple teeth and clinical attachment, bone, periodontal attachment loss. The above mentioned clinical differences exist in an age of onset, a rate of progression, patterns of destruction, clinical signs of inflammation, the relative abundance of plaque and calculus (22–24).

The progression of stages of periodontitis, starting from healthy to the mild to severe periodontal disease, with graphics and periodontal tissue overview, is shown in additional (Figure 2).
Figure 2. The main stages of periodontal disease. This includes healthy for gingivitis, mild-moderate and severe periodontitis and also healthy and diseased periodontium from healthy to the chronic periodontitis. Modified from Kinane (2017) (14)
**Diabetes and Periodontal Disease**

The two-way relationship of diabetes and periodontal disease includes the diabetes role in the periodontal health and in opposite side the periodontal health and infection in the diabetes which may contribute as risk factor, diabetic complication and management. The main indicators are wound healing, microangiopathy, microflora, and immunopathogenesis.

The dentist role helps the physicians in the better management of the oral health in diabetic patients which may result in their quality of life improvements (15).

Since the diabetic patients are prone for the periodontal disease, accounting as the sixth complication, the appropriate management of periodontitis impact the diabetic complications also.

There are different study reports that this group of patients are more prone with high glycemic levels, inflammation and periodontal disease progression (25).

According to the more scientific approaches regarding this correlation, an evidence for the mechanisms that may link periodontitis and diabetes showed that elevated pro-inflammatory markers, mediators including IL1-β, TNF-α, IL-6, RANKL/OPG, CRP, nuclear factor-kappa B ligand/osteoprotegerin ratio, oxidative stress and Toll-like receptor (TLR) 2/4 expression in poorly controlled diabetes and in the other side the systemic inflammatory burden in periodontitis has the potential role in the diabetes control, but no studies addressed the impact of successful periodontal therapy on the pathophysiological mechanisms involved in systemic complications of diabetes (26,27).

Taking this into the consideration the periodontal disease and its related inflammation could worsen also the insulin resistance which may reflect the glycemic levels in diabetic patients. The periodontal disease and insulin resistance and decreased β-cell function, increased prevalence of impaired fasting glucose and diabetes has been shown a bidirectional relationship (28). Moreover the type 2 diabetic patients are characterized more with periodontal disease severity (29).

These findings highlight the fact of appropriate oral health management and effect in general health (30–32).

There are different study approaches in different population which have been shown in another study that the diabetes association with periodontitis remains unclear in the New Zealand population according to one national survey which suggests also that this relationship argument is also mattered of analysis method used in the survey (33).
These data’s were not replicated in an additional Greenland population even though the method of analysis were different the periodontitis was common among patient with diabetes and the relationship between diabetes mellitus and periodontitis is widely reported also in another study which recommends to the patient for more increased awareness of the oral health and the appropriate collaboration between the medical diagnosis and dental professionals is an important step for the management of the affected individuals (34,35).

According to this, there are also different study approaches which have shown a beneficial cooperation regarding also to the screening for diabetes mellitus in the dental health care and was reported to be a feasible method for the early diagnosis and prevention of diabetes, which may impact also the disease progression and treatment prognosis (36).

**Treatment and management of Periodontal Diseases**

Oral health is essential and detrimental to the general health and standard of life. It plays role in the prevention of oral health diseases including periodontal disease which affects the general well being. Wrong techniques in the maintaining the proper oral health such as teeth cleaning was shown even in the educated level (medical students) which requires awareness for the appropriate teeth cleaning (37).

Oral health in the elderly patients is also an important factor in the prevention of the periodontal disease, and based on this an interesting study suggests that despite their information about the basic dental health, patients were unfamiliar with the definition of the periodontal diseases which showed the necessary educational messages to facilitate the understanding in the elderly patients (38). The periodontal disease treatment prognosis are also shown to be improved within the visit to the clinical periodontology specialist (39).

The impact of sugar consumption in the damage of the tooth enamel is a widespread and well-known problem which requires national and international approaches for the reduction of dental caries. Due to this World Health Organization (WHO) have created guidelines for the reducing sugar intake especially in pediatric age (40).
Moreover, the periodontal disease has been linked with poor oral health in the diabetic patients which require further attention by the dental hygienist which consists a regimen of brushing and glossing, use of dentifrices, mouthrinses containing antiseptics (41).

Periodontal disease management, in general, includes patient education, oral hygiene instruction, the rationale for the adjunctive treatment, scaling and root planning, intensive local or systemic antimicrobial, periodontal surgery, risk factor modification. Periodontal treatment and maintenance consist the removal of bacterial and calculus from the subgingival part with using hand instruments, ultrasonic devices which can be arranged by surgically or non-surgically procedures.

Treatment should be introduced in early procedures, including prevention when the gingival abscess is present and it includes the drainage to relieve acute symptoms, restoration of gingival function, prevention of possible recurrence, remove of irritations, appropriate debridement, and diagnosis, additional therapy in more unmanaged cases.

Moreover, the periodontal abscess treatment includes also relieve of acute signs and symptoms, drainage through debridement of the pocket and also a plaque, calculus and other irritants removal, irrigation of the pocket, antimicrobials, surgical procedure to access for the debridement, tooth extraction and resolution of the acute condition. Necrotizing periodontal disease treatment considerations are irrigation and debridement of the necrotic areas and tooth surfaces, oral hygiene, oral rinses, pain and systemic infection management with antimicrobial therapies, appropriate nutrition, oral care and smoking cessation. Periodontal endodontic lesions must also include the drainage by debridging the pocket or by incising the abscess, endodontic therapy, irrigation of the pocket, occlusal adjustment, patient comfort and antibiotic use, surgical procedure for access to the debridement, tooth extraction (19).

Surgical and nonsurgical therapies are an important treatment approach in the management of periodontitis, however, the more severe disease tends to be beneficial for the surgical therapy. About 20-30 % of patients with chronic periodontitis do not respond to the conventional periodontal therapy, which reason remains to inappropriate removal of bacterial and calculus deposits, deeper pockets and intrabony defects, poor plaque control, difficulties in access and operatory skills, systemic conditions which lead to the impaired immune response, defective restorations, periodontal and endodontic involvement, smoking, occlusal dysfunction which increase the challenge on its appropriate management (42).
The appropriate treatment of periodontitis with the antimicrobial therapy and nonsurgical approaches in the developing countries is also inexpensive which can significantly reduce the grade of progressive periodontitis (43).

Surgical periodontal therapy (Widman Flap Surgery) with and without initial SRP in the chronic periodontitis were shown to improve periodontal parameter (probing depth reduction) suggesting an importance of combination in corresponding periodontal treatment approaches. Regenerative surgery with tissue regeneration, grafting (44).

Many clinical studies have shown a different application treatment protocols in the periodontal-endodontic lesions. These include a non-surgical treatment approaches as initial steps which appears to be a reasonable step and required (45).

Even though new technology approaches in non-surgical periodontal treatment, the periodontal debridement (remove of accumulated plaque and calculus in the teeth) is a primary and fundamental treatment modality and is still the treatment choice in the periodontal disease including periodontal inflammation (46).

Since the periodontal status reduce the quality of life in this group of patients (47–49), due to this, there are different studies which provided positive scientific evidence that the nonsurgical periodontal therapy and oral hygiene instruction responses have a direct impact also in the health quality of the patients with periodontal disease (48–51).

The use of ultrasonic and manual instrumentation was provided to be similar, however, the combination is necessary when there is a periodontal defect, increased sticking deposits, and patient comfort. The full-mouth debridement includes the use of antiseptics which produce more significant results, even though the chooses procedures remain on the individual basis (42).

The use antimicrobial therapy for the periodontal disease is also a non-surgical approach for the management of the periodontitis induces inflammation and bacterial infection. The additional benefit of antibiotic use is shown in chronic periodontitis, even though it's treatment remain more in the mechanical therapy and antibiotics should be used with caution due to a concern about the antimicrobial resistance.
There are different antimicrobial prescription related to pathogenic cause and course of treatment which could respond to those patients which do not respond to common mechanical therapy. Moreover, there is not a single antibiotic which could respond in all these patients, and there are also many problems with the susceptibility testing and sample preparation procedures which can make a doubt choice from the clinicians. Despite the surgical treatment, an early prevention in the acute dentoalveolar treatment as an empirical form of prescription and also respond to antibiotic treatment showed to be successful and reduced the clinical symptoms of acute odontogenic infections (52,53).

At the present the use of antibiotics in chronic periodontitis include the combination amoxicillin (250-500 mg) and metronidazole (250-500 mg) three times daily (reported from 3 to 10 days in different studies) which is usually a prefered treatment when the scaling and root planning is accompanied (in allergic to penicillin, doxycycline, minocycline may be beneficial also. No major side effects were reported and this is a minimally invasive, practical and also economical approach to periodontitis therapy. In Pseudomonas and A. acinomycetemcomitans, the combination of ciprofloxacin or levofloxacin and metronidazole may be considered as an option. Also, the local delivery antibiotics (including also atridox - locally delivered tetracycline, arrestin-minocycline) in the individual pockets is shown also to become attractive with potential lower side effect profiles (54–56). Treatment of aggressive periodontitis with systemic antibiotic combination with SRP resulted in a significant benefit compared to SRP alone (57).

Adjunctive antibiotics may be used only in the cases of aggressive, refractory and immunocompromised (heavy smokers and poorly controlled diabetics) periodontitis patents which should be done under microbial testing results and clinicians decisions (58). Moreover, a recent study showed that benefits of the bacteriology clinical protocols are not impressive and the colonization with microbiota is another problem which suggests that more should be done in terms of limiting the use of antibiotics or their harmful effects by the repeated therapy (59). The non-surgical periodontal treatment alone affects the glycemic control in T2DM, even though the mechanisms are still not clear enough (60).
Moreover a recent performed study in the type 2 diabetes patients including 6 month nonsurgical periodontal therapy such as: oral hygiene instructions in combination with SRP resulted with a significant improvements of HbA1c suggesting once again the importance of periodontal treatment (61). Similar data were reproduced even in the patient without diabetes and with periodontal disease (with higher HbA1c and not confirmed diabetes), suggesting the improvement periodontal status role in the glycemic levels (62).

The non-surgical periodontal treatment approaches were widespread further with laser therapy. Even though many studies are ongoing there is still insufficient to support the greater benefits of the lasers over the other periodontal treatment and also the additional benefits when using combined therapy. Based on this different study approaches have been developed which showed the positive effects with the low-level laser therapy as adjuvant therapy to the common scaling and root planning (SRP) treatment in periodontitis, which are represented with the antioxidant potential therapy reduction of alveolar bone loss in experimental induced periodontitis (63).

Moreover, in another study, clinical outcomes of chronic periodontitis were improved when using the laser therapy in combination with SRP treatment (64).

In another study in the patient with the periodontal disease, the supportive role of laser in the periodontal sonic treatment similar clinical and microbiological results was obtained suggesting divergent data's in corresponding treatment (65). Also, treatment with a thermal diode laser (wavelength 808-980 nm) resulted to not become difference when compared with the SRP treatment alone in the clinical parameters of periodontal inflammation (66).

However despite the appropriate evidence of the non-surgical SRP periodontal therapy, a development techniques with a combination with the antimicrobial photodynamic therapy (local noninvasive treatment) which might have impact also in reduction of antimicrobial side effects have been shown to be successful treatment approach in patients with localized chronic periodontitis especially during the maintained phase in non-surgical treatment (67).

Moreover, clinical trials based on this combined therapy approach to SRP treatment with low-level laser therapy and high-level laser therapy, antimicrobial photodynamic therapy did not provide well enough evidence for the reduction of proinflammatory cytokines in the gingival crevicular from the patients with chronic periodontitis and requires further well-designed randomized clinical trials (68).
Even though it provided a beneficial effects compared to ultrasonic scaling or SRP alone only in the bleeding on probing, Treponema denticola, and resulted in a greater reduction of Aggregatibacter actinomycetemcomitans (AA), Tannerella forsythia (TF), and TD compared to mechanical debridement alone (69).

Moreover, aPDT therapy with the combination with SRP for three months provided also adequate treatment of the aggressive periodontitis with the following improvement of the clinical, microbiological and immunologic effects (70).

Also alternative approaches in the treatment of the chronic periodontitis including the probiotic lozenges-L-reuteri showed to slow the re-colonization and the further clinical features improvements (71). Moreover honeybee propolis extract alteratives was found to play significant role in the periodontal treatment when combined with SRP (72).

The statin role including rosuvastatin as gel pharmaceutical composition 1.2 % locally delivered in combination with SRP has improved the probing depth and gingival index in a patient with chronic periodontitis (73). Similarly, the atorvastatin 2 % dentifrice improved periodontal clinical parameters as a complement to nonsurgical periodontal treatment (74). Beneficial effects have been observed also in as gel pharmaceutical form with antidiabetic medication metformin 1 % (75). Moreover, the host modulating therapy includes antimicrobials which reduce bacterial products, nonsteroidal anti-inflammatory drugs which reduce proinflammatory mediators, biphosphonates which reduce bone resorption and connective tissue breakdown. Bone morphogenetic proteins, platelet-derived growth factors (PDGF), enamel matrix protein (Emdogain), resorbable synthetic bone matrix growth-factor enhanced matrix (GEM 21S) which assists in regenerative procedures, recombinant human bone morphogenetic protein-2 (rhBMP-2) (76).

Taken this data together the well plaque controlling, pathogenic bacteria, granulated tissue removal the non-surgical approaches mechanically still consists an effective approach in reduction of the clinical signs and symptoms of inflammation in the chronic periodontitis.

Early diagnosis, management of the influencing factors, increased numbers of clinical trials for further clarifying in the periodontitis management to enable the clinicians for the increased rates of successful periodontal treatment and also additional supportive care.
The therapeutic management of the chronic periodontitis patients includes the diagnosing of periodontitis, scaling and root planing which is accompanied by the evaluation of the clinical improvement. If so the periodontal debridement need to performed at regular intervals and evaluation of the disease, however, if the disease is not well controlled further diagnostic for localized or generalized procedures need to be done for potential local delivery drugs or periodontal surgery (localized) or systemic antibiotics, host response modulation or periodontal surgery (generalized). The decision algorithm is shown in the diagram in the (Figure 3).

**Figure 3.** Decision algorithm for the therapeutic management of chronic periodontitis. Modified from Kinane (2017) (14)
**Reason for our study**

Diabetes mellitus is a chronic disease which comprises a heterogeneous group of metabolic disorders with altered glucose tolerance or impaired carbohydrate metabolism. The prevalence of diabetes has drastically increased over the past decade especially in Kosovo whereby a majority of the population live in poverty and therefore cannot access medical health (77–79). In diabetic patients with poorly controlled metabolism complications are more rapidly and in more severe forms. The goals of diabetes education are to optimize metabolic control, prevent acute and chronic complications, and optimize the quality of life while keeping costs acceptable (80). Systemic complications include retinopathy, nephropathy, neuropathy, macrovascular and microvascular disease. Individuals with diabetes may have a higher mortality rate as they may develop macrovascular and microvascular problems that generate permanent impairment of the kidneys, eyes, heart and the nervous system. Any reduction in HbA1c and glycemic control was proven to reduce the risk of complications (81).

Dental practitioners as professional healthcare providers play an important role in the early diabetes diagnosis and management. DM is a relatively common condition and, thus, is one that practicing dentists may encounter frequently (82). Type 2 diabetes mellitus (T2D) is a growing healthcare burden based on its long-term complications and glycemic control plays an important role in prevention and management, an early introduction of insulin may be more cost-effective than maintaining patients on multiple oral agents. Generally, patients with diabetes exhibited poor oral health (83), and are more susceptible to periodontal diseases and tooth loss and such problems might be aggravated by aging (84). Poorly controlled type 2 diabetes affects periodontal health in patients with generalized chronic periodontitis. The association between glycemic control of type 2 diabetes mellitus (type 2 DM) and severe periodontal disease which provides population-based evidence to support an association between poorly controlled type 2 diabetes mellitus and severe periodontitis (85,86). Diabetes increases the risk of periodontal diseases, and biologically plausible mechanisms have been demonstrated in abundance. The impact of periodontal diseases on glycemic control of diabetes and the mechanisms through which this occurs is still not fully understood.
Inflammatory periodontal diseases may increase insulin resistance in a way similar to obesity, thereby aggravating glycemic control. Further research is needed to clarify this aspect of the association between periodontal diseases and diabetes but several studies showed that type 2 diabetes patients were three times more susceptible to develop periodontal oral complications and loss of teeth as compared to individuals without diabetes (87–89). Therefore this implies that glycemic control is generally affected by oral complications such as periodontal infection.

Periodontal disease has been recognized as the sixth complication of diabetes (87). Well-controlled diabetic adult patients were three times less likely to have periodontal disease than those with diabetes. Also, the glycated hemoglobin level correlates with the severity of periodontal disease (90). The analysis of the data also shows that the prevalence of diabetes in patients with periodontitis is double that seen in the non-periodontitis patients (12.5% versus 6.3%) and that this difference is also statistically significant. Otherwise, in a patient with periodontal disease, C-reactive protein levels are higher compared to healthy patients. There is strong evidence from cross-sectional studies that plasma CRP in periodontitis is elevated compared with controls. There is modest evidence on the effect of periodontal therapy in lowering the levels of CRP (91). Hence, the control of chronic periodontal disease is mandatory for achieving long-term control of diabetes, defined by the reduction in glycated hemoglobin levels. In those, it will be paramount to control other factors that may affect HbA1c levels, such as diabetic medication, diet and physical exercise (92).

It is well known that routine oral prophylaxis plays an important role in periodontal health but it not shown significant improvement of glycated hemoglobin levels. Routine prophylaxes every 3 months significantly improve periodontal health and prevent progression of CP in both poorly controlled and well-controlled patients with T2DM (93). Some studies demonstrated that local mechanical periodontal treatment and systemic antibiotics might improve the level of metabolic control in patients with diabetes. On the contrary, a full-mouth disinfection approach showed beneficial effects on diabetic metabolic control. Metabolic control was measured by the serum level of HbA1c (94). Although non-surgical periodontal therapy resulted in improvement of glycated hemoglobin control.
The meta-analysis showed that non-surgical periodontal treatment improves metabolic control in patients with both periodontitis and diabetes and showed that non-surgical periodontal treatment is associated with the improved glycemic control in type 2 patients and could be undertaken along with the standard measures for the diabetic patient care (95,96), different periodontal treatment approaches were used.

Taking this into consideration together with the necessity for further investigations for T2DM and periodontal disease.

The aim of this doctoral thesis was to evaluate the improvement of the glycemic, systemic inflammation levels according to the main biomarker analysis and periodontal parameters through clinical examinations of healthy and type 2 diabetic Kosovo patients after non-surgical periodontal therapy and extraction of periodontally compromised teeth or teeth extraction alone. The rationale of this doctoral thesis was that periodontal disease is most common in Kosovo due to the high poverty level and individuals rarely seek medical attention.

All data assessed showed the very poor oral health status of children in Kosovo. Interviews with children and teachers indicated poor knowledge regarding oral health. Significant measures must be taken to improve this situation. Education of the dental practitioners, with well designed programs (caries management and prevention), economy increase and its effects in the society would make a significant contribution to reducing the prevalence of Periodontitis associated with endodontic treatment in the population of Kosovo. Also studies of dental health involving larger samples that cover more regions of Kosovo will help to identify public dental health problems, an essential step in improving the general health status of the citizens of this country (97,98).
Purposes of the thesis

The purpose of this study was to evaluate glycemic levels and periodontal parameters of non-diabetic and type 2 diabetic Kosovo patients after non-surgical periodontal therapy in combination with extraction of periodontally compromised teeth in the patients with chronic periodontitis.

The aim of the thesis

1. Non-surgical periodontal therapy and combined extraction of periodontally compromised teeth effect in periodontal parameters in the patients with chronic periodontitis.

2. Non-surgical periodontal therapy and combined extraction of periodontally compromised teeth effect in glycemic and inflammation levels in the patients with chronic periodontitis.
**Study Hypothesis**

1. Non-surgical periodontal treatment and extraction of periodontally compromised teeth may reduce tissue glycemic levels in type 2 diabetic patients and non diabetic patients.

2. Non-surgical periodontal treatment and extraction of periodontally compromised teeth may reduce tissue systemic inflammation in diabetic patients that might reflect in better glycemic control in type 2 diabetic patients and non diabetic patients.
Methods

Participants

This study was designed as a cluster-randomized trial of parallel-group design conducted at endocrinology department of Peja’s Regional Hospital and the Dental Polyclinic in the city of Peja, between December 2015 and February 2017. Surgical procedures were performed by one expert clinician (DB). Some patients diagnosed with periodontal disease from our study are shown in the (Figure 4).

Figure 4. The sample from the group of patient diagnosed with chronic periodontal disease and analyzed for the study
Participation of every candidate was voluntary according to the principles embodied in the Declaration of Helsinki of 1975 for biomedical research involving human subjects, as revised in 2013. All of the patients were informed about the nature of the treatment and their written consent was obtained. The study was approved by Ethical-Professional Board at University Clinical Centre of Kosovo based on Administrative Instruction Nr.05/2012 for Supervision of Professional Ethics, decision dated October 21st, 2014 Org.Unit.01, Nr. Prot., 4212/2. With further additional approval of the Ethical-Professional Board at University Clinical Centre of Ljubljana, decision dated May 31st, 2016; (KME 73/01/16).

The present study was undertaken according to the CONSORT statement to improve the quality of reports of parallel-group, randomized trials (http://www.consort-statement.org/), and it was registered on Clinical.Trials.gov (NCT02874963).

**Study inclusion and exclusion criteria**

A priori sample size calculation was performed given Effect size $d=0.5$, alfa error probability 0.08 and power 0.8 resulting in 26 patients for the group. Any partially edentulous patient (had at least 10 teeth in the functional dentition excluding third molars, aged 18 years or older, able to sign an informed consent form, with a clinical diagnosis of chronic periodontitis, as determined by the presence of at least 1 site with a periodontal probing depth (PPD) $\geq 5$ mm, two teeth with attachment loss $\geq 6$ mm, positive bleeding on probing (BoP) (99), and at least 1 periodontally compromised tooth, was considered eligible for this study. A periodontally compromised tooth was noted when two or more of the following characteristics were present: loss of more than 75% of supporting bone, probing pocket depths $\geq 8$ mm, class III furcation, hypermobility, and non-treatable endodontic issues (100).

Hemoglobin (HbA1c) levels and of high-sensitivity C-reactive protein (hs-CRP) were collected from clustered patients with type 2 diabetes (diabetes mellitus) and non-diabetic patients. The cut-off value used to clustered patients with diabetes was HbA1c $\geq 6.5\%$ and hsCRP $\geq 1.5\%$ in both groups. Information about diabetes including duration, type of treatment, diabetes self-care management, blood glucose testing, patient's adherence to their current medications, diet therapy, and any physical activities was also collected. In addition, body mass index (BMI) changes, medications, smoking status and weight were noted.
**Study Design, subjects, and procedures**

Personal interviews were performed to collect baseline data from each participant using a pre-structured questionnaire. Basing on the questionnaire, patients were not admitted to the study if any of the following exclusion criteria were present: general medical contraindication to oral surgery (American Society of Anesthesiologists [ASA] Physical Status Class III or IV), irradiation of the head and neck area less than 1 year before research, alcohol or drug abuse, pregnant or nursing, severe bruxism or clenching, and history of antibiotic therapy or non-steroidal anti-inflammatory drug therapy 4 months before the first visit.

Detailed medical history, socio-demographic data (age, sex, level of education and income), preoperative photographs, periapical radiographs, and model casts were obtained for initial screening and evaluation. The periodontal clinical examination was performed according to the periodontal chart, School of Dental Medicine (ZMK), University of Bern, Department of Periodontology (http://www.periodontalchart-online.com/uk/index.asp).

A total of 200 consecutive patients were screened for eligibility. After clinical examination, 160 patients aged from 30 to 70 years old were selected for this study.

All the patients underwent professional oral hygiene prior to the surgeries and received prophylactic antiseptic (chlorhexidine mouthwash 0.2%, Listerine, Johnson & Johnson, UK). Patients were treated under local anesthesia using articaine hydrochloride with adrenaline 1:100000 (Orabloc, Pierrel, Milan, Italy).

**Non-surgical periodontal treatment and extraction of periodontally compromised teeth**

Fifty patients with type 2 diabetes and 30 non-diabetic patients received non-surgical periodontal therapy before extraction of periodontally compromised teeth (test groups). Non-surgical periodontal therapy consists in instrumentation of all pockets (full mouth scaling and root planing [FMSRP]) without local antiseptics.

Ultrasonic device (UDS-J Ultrasonic Scaler, Guilin Woodpecker Medical Instrument) and periodontal curettes (1/2 Gracey Curette, SGR 1/24; 1/2 Mini Fie Graey Curette SAS1/2C8; 1/2 After Five Gracey Curette; CL866, Hu-Friedy) were used for the mechanical debridement of supra- and subgingival plaque and calculus. The additional instruments and the antiseptic solution for the mouthwash are shown in the additional (Figure 5), and a patient sample after non-surgical treatment (Figure 6).
**Figure 5.** A) Woodpecker dental ultrasonic scaler technique for full mouth scaling and root planning; B) Instruments for full mouth scaling and root planning; C) Prophylactic antiseptic for mouthwash (Listerine)
Figure 6. Non-surgical periodontal treatment in patients with periodontal disease. A) Before the treatment and B) After the treatment with full mouth scaling and root planing.
The others 50 and 30 patients in each cluster (diabetic and non-diabetic) received periodontally compromised teeth extraction alone (control groups).

Afterwards, in both groups, periodontally compromised teeth extractions were performed as atraumatically as possible, with the aid of a periotome and atraumatic elevators (PT1 and EPTSMS, Hu-Friedy, Milan, Italy). Multiple-rooted teeth were sectioned at the furcation and the roots were individually extracted. Then, the residual extraction socket was washed with physiological solution and debrided thoroughly from granulation tissue with a curette. The periodontally compromised tooth orthopan images and additional extraction procedures are shown in additional (Figure 7 and 8).

Figure 7. Periodontally compromised tooth diagnostic procedures with orthopan images (samples from four patients A-D)
Painkillers were administered as needed. Post-operative rinsing was followed by the use of the antiseptic solution Listerine (Johnson & Johnson, Berkshire, UK) as a mouthwash thrice a day 3 weeks. Follow-up visits were scheduled every 3 months up to 1 year after treatment.

**Outcomes measure were:**

Periodontal clinical parameters plaque index [PI], bleeding on probing [BOP], probing depth [PPD] and clinical attachment level [CAL] were collected into the online periodontal chart (Department of Periodontology, School of Dental Medicine (ZMK), University of Bern) at baseline and 3 months after the periodontal treatment. All the parameters were recorded for six measurement points (mesial buccal, buccal, distal buccal, mesial lingual, lingual, distal lingual) on all teeth (excluding 3rd molars) during each of two visits, using a periodontal probe (PCP UNC-15, Hu-Friedy).

The periodontal clinical parameters measurement were shown in the additional (Figure 9).
Figure 9. Measurement of clinical periodontal parameters after each treatment A) Plaque; B) Bleeding on Probing; C) Mean probing depth; D) Clinical Attachment level. Which were proceed further in the periodontal chart online for calculation (http://www.periodontalchart-online.com/uk/index.asp).

Biochemical analysis

The levels of HbA1c and hs-CRP were measured using venous blood collected from patients at baseline and 3 months after the study procedures. All biochemical analyses were conducted in a biochemical laboratory in Peja (Laboratory Diagnostic Center, Peja, Kosovo) using a biochemistry analyzer (Select Pro XS, ELITech Clinical Systems, Paris, France) and enzyme-linked immunoassay kits (ELITech Clinical Systems, Paris, France). All the biochemical analysis steps, from blood, withdrawal up to result preparation are shown in the (Figure 10).
**Figure 10.** Biochemical analysis steps. A) Venous blood withdrawal in the baseline and after 3 months after periodontal treatment B) The technique of measurement of the biochemical analysis (Select Pro XS, ELITech Clinical Systems) C) The result sample overview from a patient (HbA1c & hs-CRP)
**Statistical analyses**

All data were reported as means±standard deviation (SD); 95% confidence interval (CI). Before the statistical analysis was performed, the normal distribution and homogeneity of the variances were tested. Associations between the experimental parameters were investigated over time for using paired t-tests. Differences of means at patient level for continuous outcomes between groups were compared by unpaired t-tests. The results were considered significant when the P value was P<0.05 (GraphPad Prism 5.0 software, San Diego, CA, USA).
Thesis Results

A total of 200 consecutive patients were screened for eligibility. After clinical examination, 160 patients aged from 30 to 70 years old (59.49±10.82) were selected for this cluster-randomized trial. A consort flow diagram with reasons for exclusion is shown in (Fig. 11).

Figure 11. Study population flowchart.
**Characteristics of Participants**

Patients were clustered in type 2 diabetic (n=100) and non-diabetic (n=60) patients and then randomized in two parallel groups. Patients with type 2 diabetes received non-surgical periodontal therapy and extraction of periodontally compromised teeth (n=50; 87 extracted teeth; test group), or extraction of periodontally compromised teeth alone (n=50; 88 extracted teeth; control group). Non-diabetic patients received non-surgical periodontal therapy and extraction of periodontally compromised teeth (n=30; 54 extracted teeth; test group), or periodontally compromised teeth extraction alone (n=30; 49 extracted teeth; control group). At the end of the study, no drop-out occurred and no deviation from the original protocol occurred.

In addition to this, the patient characteristics in the type 2 diabetes and the control group in our study were shown below in (Table 1). There were not any differences between the selected groups and the gender and gender, weight, height, and BMI. However only type 2 diabetes patients were under anti-diabetic treatment. The baseline characteristics of biochemical and clinical data are from the patients were shown in additional in the (Table 2). There were not any statistical differences between the selected groups in the baseline.
**Table 1.** Patients Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>T2DM</th>
<th>Non-Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients (n)</td>
<td>100</td>
<td>60</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>50/50</td>
<td>33/27</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59.49±10.82</td>
<td>56.66±12.22</td>
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<tr>
<td>Weight (Kg)</td>
<td>76.03±9.76</td>
<td>78.3±9.76</td>
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<tr>
<td>Height (cm)</td>
<td>174.64±13.96</td>
<td>171.86±6.81</td>
</tr>
<tr>
<td>BMI</td>
<td>26.01±3.64</td>
<td>26.49±2.20</td>
</tr>
<tr>
<td>No. of teeth extracted</td>
<td>175 (1.75)</td>
<td>103 (1.72)</td>
</tr>
<tr>
<td>Oral Antidiabetic Therapy</td>
<td>48</td>
<td>-</td>
</tr>
<tr>
<td>Insulin</td>
<td>52</td>
<td>-</td>
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</table>
Table 2. Baseline characteristics of biochemical and clinical data's from the patients.

<table>
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<th>Parameters</th>
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<th>Non-Diabetic Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tooth Extraction</td>
<td>Tooth Extraction</td>
</tr>
<tr>
<td></td>
<td>&amp; FM-SRP</td>
<td>&amp; FM-SRP</td>
</tr>
<tr>
<td>No. of teeth extracted</td>
<td>87</td>
<td>88</td>
</tr>
<tr>
<td>PI (%)</td>
<td>95.07±7.14</td>
<td>96.57±8.28</td>
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<tr>
<td>BOP (%)</td>
<td>70.36±22.58</td>
<td>73.31±32.26</td>
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<tr>
<td>PD (mm)</td>
<td>5.92±1.06</td>
<td>6.37±0.93</td>
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<tr>
<td>CAL (-mm)</td>
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<td>6.8±1.68</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.82±3.01</td>
<td>9.59±2.57</td>
</tr>
<tr>
<td>hs-CRP (mg/L)</td>
<td>4.05±2.20</td>
<td>4.44±2.55</td>
</tr>
</tbody>
</table>
**Glycemic control and inflammation in the Diabetic type 2 patients**

The diabetic type 2 patients have shown a significant improvement in the HbA1c plasma serum levels compared to the baseline which was founded in both groups.

- In the test group *(with non-surgical periodontal therapy-test)*, non-surgical periodontal therapy before periodontally compromised teeth extraction improves HbA1c plasma serum levels.

- In the control group *(without non-surgical periodontal therapy-control)*, periodontally compromised teeth extraction alone improves HbA1c plasma serum levels, with a tendency for more improvement in the test group, however, the difference between test and control group was not statistically significant.

- Significantly reductions of hs-CRP were founded in both groups and also the difference between test and control group was statistically significant with better value for the test group.

**a) Glycemic Control**

Significantly improvements in the HbA1c plasma serum levels compared to the baseline were found in both groups. In the test group, non-surgical periodontal therapy before periodontally compromised teeth extraction improves HbA1c plasma serum levels from 9.59±2.57% (95% CI 7.94 to 9.36) to 8.05±1.67% (95% CI 6.96 to 7.89). The mean difference was 1.55±1.67% (95% CI 0.89 to 1.81; P = 0.000) (Figure 12A) (Table 3).
Figure 12A. Graphical representation (box plot) of HbA1c values (%) in diabetic type 2 patients with periodontal disease at baseline and 3 months after non-surgical periodontal therapy and periodontally compromised teeth extraction. *p<0.05; **p<0.01; ***p<0.001; NS = Not Significant
In the control group, periodontally compromised teeth extraction alone improves HbA1c plasma serum levels from $8.89 \pm 2.94\%$ (95% CI 6.72 to 8.38) to $8.08 \pm 2.53\%$ (95% CI 6.53 to 7.97). The mean difference was $0.8 \pm 2.35\%$ (95% CI -0.27 to 1.07; $P = 0.022$) (Figure 12B) (Table 3). Difference between test and control group was not statistically significant ($0.78 \pm 3.08$; 95% CI 0.13 to 1.87; $P = 0.076$) (Table 3).

**Figure 12B.** Graphical representation (box plot) of HbA1c values (%) in diabetic type 2 patients with periodontal disease at baseline and 3 months after periodontally compromised teeth extraction alone. *$p<0.05$; **$p<0.01$; ***$p<0.001$; NS = Not Significant
b) Inflammation

Significantly reductions of hs-CRP were founded in both groups. In the test group, hs-CRP was 4.42±2.58% (95% CI 3.18 to 4.62) at baseline and 2.87±1.96% (95% CI 1.91 to 2.99) 3 months later. The difference was 1.55±1.46% (95% CI 0.89 to 1.71; P = 0.000) (Figure 13A) (Table 3).

Figure 13A. Graphical representation (box plot) of hs-CRP values (mg/L) in diabetic type 2 patients with periodontal disease at baseline and 3 months after non-surgical periodontal therapy and periodontally compromised teeth extraction. *p<0.05; **p<0.01; ***p<0.001; NS = Not Significant
In the control group, hs-CRP was 4.05±2.2% (95% CI 2.69 to 3.91) at baseline and 3.24±1.67% (95% CI 2.54 to 3.46) 3 months later. The difference was 0.81±1.46% (95% CI -0.10 to 0.70; P = 0.000) (Figure 13B) (Table 3). Difference between test and control group was statistically significant with better value for the test group (0.74±2.06%; 95% CI 0-22 to 1.38; P = 0.013). The data are summarized in (Table 3).

Figure 13B. Graphical representation (box plot) of hs-CRP values (mg/L) in diabetic type 2 patients with periodontal disease at baseline and 3 months after periodontally compromised teeth extraction alone.
*p<0.05; **p<0.01; ***p<0.00; NS = Not Significant
**Periodontal conditions in Type 2 Diabetic Patients**

The periodontal parameters in the diabetic type 2 patients including:

- The mean PI (mPI) values statistically decreased in both groups and the difference between test and control group was statistically significant with better value for the test group.

- The mean BoP (mBoP) values statistically decreased in both groups and the difference between test and control group was statistically significant with better value for the testing group.

- The mean mPPD (mPPD) values statistically decreased in both groups and the differences between test and control group were not statistically significant.

- The mean CAL (mCAL) values statistically decreased in the test group but not in control the group, however, the differences between test and control group were not statistically significant.
a) mPI

The mean PI (mPI) values statistically decreased in both groups. The mean PI (mPI) was 98.06±5.92% (95% CI 98.36 to 101.64) at baseline and 57.80±22.76% (95% CI 58.81 to 46.19) 3 months later, in the test group. The difference was 40.26±23.14% (95% CI 37.59 to 50.41; P = 0.000) (Figure 14A) (Table 3).

**Figure 14A.** Comparison of mean PI (%) among groups at baseline and 3 months after allocated interventions in diabetic patients after non-surgical periodontal therapy and periodontally compromised teeth extraction. *p<0.05; **p<0.01; ***p<0.001; NS-not significant
In the control group, mPI was 91.26±20.54% (95% CI 94.31 to 105.69) at baseline and 77.88±23.79% (95% CI 75.41 to 88.59) 3 months later, in the control group. The difference was 13.38±15.02% (95% CI 6.34 to 14.66; \( P = 0.000 \)) (Figure 14B) (Table 3). Difference between test and control group was statistically significant with better value for there test group (26.88±25.44%; 95% CI 19.80 to 34.20; \( P = 0.000 \)) (Table 3).

**Figure 14B.** Comparison of mean PI (%) among groups at baseline and 3 months after allocated interventions in diabetic patients after periodontally compromised teeth extraction alone. *\( p<0.05 \); **\( p<0.01 \); ***\( p<0.001 \); NS-not significant
b) mBoP

The mean BoP (mBoP) values statistically decreased in both groups. The mBoP was 87.76±23.89% (95% CI 93.38 to 106.62) at baseline and 28.94±21.65% (95% CI 21.0 to 33.0) 3 months later, in the test group. The difference was 58.82±28.61% (95% CI 58.07 to 73.93; P = 0.000) (Figure 15A).

![Figure 15A. Comparison of mean BoP (%) among groups at baseline and 3 months after allocated interventions in diabetic patients after non-surgical periodontal therapy and periodontally compromised teeth extraction. *p<0.05; **p<0.01; ***p<0.001; NS-not significant](image-url)
In the control group, mBoP was 72.98±33.44% (95% CI 90.73 to 109.27) at baseline and 52.04±33.57% (95% CI 45.70 to 64.30) 3 months later, in the control group. The difference was 20.94±22.46% (95% CI 11.27 to 23.73; P = 0.000) (Figure 15B).

Difference between test and control group was statistically significant with better value for the test group (37.88±35.27%; 95% CI 36.02 to 55.98; P = 0.000). The data are summarized in (Table 3).

**Figure 15B.** Comparison of mean BoP (%) among groups at baseline and 3 months after allocated interventions in diabetic patients after periodontally compromised teeth extraction alone. *p<0.05; **p<0.01; ***p<0.001; NS-not significant
c) mPPD

In the test group, mPPD was 6.52±0.82 mm (95% CI 6.17 to 6.63) at baseline and 5.08±1.10 mm (95% CI 4.82 to 5.42) 3 months later. The difference was 1.44±0.96 mm (95% CI 1.01 to 1.55; P = 0.000) (Figure 16A).

Figure 16A. Comparison of mean PPD (mm) among groups at baseline and 3 months after allocated interventions in diabetic patients after non-surgical periodontal therapy and periodontally compromised teeth extraction. *p<0.05; **p<0.01; ***p<0.001; NS-not significant
In the control group, mPPD was 6.60±1.47 mm (95% CI 6.17 to 6.63) at baseline and 5.24±2.17 mm (95% CI 4.84 to 6.04) 3 months later. The difference was 1.36±1.81 mm (95% CI 0.46 to 1.56; P = 0.000 (Figure 16B) (Table 3). Difference between test and control group was not statistically significant (0.08±2.11%; 95% CI -0.28 to 0.92; P = 0.792) (Table 3).

Figure 16B. Comparison of mean PPD (mm) among groups at baseline and 3 months after allocated interventions in diabetic patients after periodontally compromised teeth extraction alone. *p<0.05; **p<0.01; ***p<0.001; NS-not significant
d) mCAL

The mean CAL (mCAL) values statistically decreased in the test group but not in control the group. In the test group, the mean CAL (mCAL) was -8.51±1.56 mm (95% CI -8.85 to -7.98) at baseline and -7.32±1.32 mm (95% CI -7.67 to -6.95) 3 months later. The difference was -1.19±0.84 mm (95% CI -1.25 to -0.79; P = 0.000) (Figure 17A) (Table 3).

**Figure 17A.** Comparison of mean CAL (mm) among groups at baseline and 3 months after allocated interventions in diabetic patients after non-surgical periodontal therapy and periodontally compromised teeth extraction. *p<0.05; **p<0.01; ***p<0.001; NS-not significant
In the control group, mCAL was -6.87±2.78 mm (95% CI -7.57 to -6.03) at baseline and -6.03±2.68 mm (95% CI -6.86 to -5.38) 3 months later. The difference was -0.84±3.11 mm (95% CI -1.37 to 0.35; P = 0.061) (Figure 17B) (Table 3). Differences between test and control group was not statistically significant (-0.34±3.29%; 95% CI -1.36 to 0.51; P = 0.455) (Table 3).

Figure 17B. Comparison of mean CAL (mm) among groups at baseline and 3 months after allocated interventions in diabetic patients after periodontally compromised teeth extraction alone. *p<0.05; **p<0.01; ***p<0.001; NS-not significant
Table 3. Diabetic type 2 patients: differences in glycemic control and periodontal condi-
tions between test (A) and control groups (B), reported as mean±SD (95%CI).

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 months later</th>
<th>Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test HbA1c (%)</strong></td>
<td>9.59±2.57 (7.94 to 9.36)</td>
<td>8.05±1.67 (6.96 to 7.89)</td>
<td>1.55±1.67 (0.89 to 1.81)</td>
<td>0.000*</td>
</tr>
<tr>
<td><strong>Control HbA1c (%)</strong></td>
<td>8.89±2.24 (6.72 to 8.38)</td>
<td>8.08±2.53 (6.53 to 7.97)</td>
<td>0.8±2.35 (-0.27 to 1.07)</td>
<td>0.022*</td>
</tr>
<tr>
<td><strong>Difference</strong></td>
<td></td>
<td></td>
<td>0.78±3.08 (0.13 to 1.87)</td>
<td>0.076</td>
</tr>
<tr>
<td><strong>Test hs-CRP (mg/L)</strong></td>
<td>4.42±2.58 (3.18 to 4.62)</td>
<td>2.87±1.96 (1.91 to 2.99)</td>
<td>1.55±1.46 (0.89 to 1.71)</td>
<td>0.000*</td>
</tr>
<tr>
<td><strong>Control hs-CRP (mg/L)</strong></td>
<td>4.05±2.2 (2.69 to 3.91)</td>
<td>3.24±1.67 (2.54 to 3.46)</td>
<td>0.81±1.46 (-0.10 to 0.70)</td>
<td>0.000*</td>
</tr>
<tr>
<td><strong>Difference</strong></td>
<td></td>
<td></td>
<td>0.74±2.06 (0-22 to 1.38)</td>
<td>0.013**</td>
</tr>
<tr>
<td><strong>Test mPI (%)</strong></td>
<td>98.06±5.92 (98.36 to 101.64)</td>
<td>57.80±22.76 (58.81 to 46.19)</td>
<td>40.26±23.14 (37.59 to 50.41)</td>
<td>0.000*</td>
</tr>
<tr>
<td><strong>Control mPI (%)</strong></td>
<td>91.26±20.54 (94.31 to 105.69)</td>
<td>77.88±23.79 (75.41 to 88.59)</td>
<td>13.38±15.02 (6.34 to 14.66)</td>
<td>0.0028*</td>
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<tr>
<td><strong>Difference</strong></td>
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<td></td>
<td>26.88±25.44 (19.80 to 34.20)</td>
<td>0.000**</td>
</tr>
<tr>
<td><strong>Test mBOP (%)</strong></td>
<td>87.76±23.89 (93.38 to 106.62)</td>
<td>28.94±21.65 (21.0 to 33.0)</td>
<td>58.82±28.61 (58.07 to 73.93)</td>
<td>0.000*</td>
</tr>
<tr>
<td><strong>Control mBOP (%)</strong></td>
<td>72.98±33.44 (90.73 to 109.27)</td>
<td>52.04±33.57 (45.70 to 64.30)</td>
<td>24.94±22.46 (11.27 to 23.73)</td>
<td>0.0023*</td>
</tr>
<tr>
<td><strong>Difference</strong></td>
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<td></td>
<td>37.88±35.27 (36.02 to 55.98)</td>
<td>0.000**</td>
</tr>
<tr>
<td><strong>Test mPPD (mm)</strong></td>
<td>6.52±0.82 (6.17 to 6.63)</td>
<td>5.08±1.10 (4.82 to 5.42)</td>
<td>1.44±0.96 (1.01 to 1.55)</td>
<td>0.000*</td>
</tr>
<tr>
<td><strong>Control mPPD (mm)</strong></td>
<td>6.60±1.47 (6.17 to 6.63)</td>
<td>5.24±2.17 (4.84 to 6.04)</td>
<td>1.36±1.81 (0.46 to 1.56)</td>
<td>0.000*</td>
</tr>
<tr>
<td><strong>Difference</strong></td>
<td></td>
<td></td>
<td>0.08±2.11 (-0.28 to 0.92)</td>
<td>0.792</td>
</tr>
<tr>
<td><strong>Test mCAL (mm)</strong></td>
<td>-8.51±1.56 (-8.85 to -7.98)</td>
<td>-7.32±1.32 (-7.67 to -6.95)</td>
<td>-1.19±0.84 (-1.25 to -0.79)</td>
<td>0.000*</td>
</tr>
<tr>
<td><strong>Control mCAL (mm)</strong></td>
<td>-6.87±2.78 (-7.57 to -6.03)</td>
<td>-6.03±2.68 (6.86 to -5.38)</td>
<td>-0.84±0.31 (-1.37 to 0.35)</td>
<td>0.061</td>
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<tr>
<td><strong>Difference</strong></td>
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<td>0.34±3.29 (-1.36 to 0.51)</td>
<td>0.455</td>
</tr>
</tbody>
</table>
**Glycemic Control and Inflammation in the Non-Diabetic patients**

Non-Diabetic patients have shown a statistically significant reduction in the HbA1c plasma serum levels which was found during the study period in the test group but not in the control group, however, the differences between test and control group were not statistically significant. The variation in the serum levels of hs-CRP in non-diabetic patients during the study period was statistically significant in the test group, while in the control group it was sustained the same and the differences between test and control group were statistically significant with better value for the testing group.

*a) Glycemic control*

Statistically significant reduction in the HbA1c plasma serum levels of non-diabetic patients was found during the study period in the test group but not in the control group. The HbA1c plasma serum levels was 5.79±0.63% (95% CI 5.63 to 5.97) at baseline and 5.58±0.75% (95% CI 5.24 to 5.66) 3 months after treatment, in the test group; difference was 0.21±0.51% (95% CI 0.01 to 0.29; P=0.034) (Figure 18A) (Table 3).
Figure 18A. Graphical representation (box plot) of HbA1c values (%) in non diabetic patients with periodontal disease at baseline and 3 months after non-surgical periodontal therapy and periodontally compromised teeth extraction. *p<0.05; **p<0.01; ***p<0.001 NS = Not Significant
In the control group, HbA1c plasma serum levels was 5.56±0.62% (95% CI 5.33 to 5.67) at baseline and 5.45±0.63% (95% CI 5.22 to 5.58) 3 months later; difference was 0.11±0.35% (95% CI 0.1 to 0.3; P = 0.099) (Figure 18B) (Table 4). Differences between test and control group was not statistically significant (0.1±0.59%; 95% CI -0.11 to 0.21; P = 0.396) (Table 4).

Figure 18B. Graphical representation (box plot) of HbA1c values (%) in non diabetic patients with periodontal disease at baseline and 3 months after periodontally compromised teeth extraction alone. *p<0.05; **p<0.01; ***p<0.001; NS = Not Significant
b) Inflammation

The variation in the serum levels of hs-CRP in non-diabetic patients during the study period was statistically significant in the test group, while in the control group it was sustained the same. In the test group, it was 3.63±2.19% (95% CI 2.49 to 3.71) at baseline and 3.11±1.95% (95% CI 2.41 to 3.49) 3 months later; difference was 0.52±0.74% (95% CI 0.25 to 0.65; P = 0.001) (Figure 19A) (Table 4).

Figure 19A. Graphical representation (box plot) of hs-CRP values (mg/L) in non diabetic patients with periodontal disease at baseline and 3 months after non-surgical periodontal therapy and periodontally compromised teeth extraction surgical periodontal therapy and periodontally compromised teeth extraction *p<0.05; **p<0.01; ***p<0.001; NS = Not Significant
In the control group, the serum levels of hs-CRP was 1.63±1.05 (95% CI 0.91 to 1.49) at baseline and 1.64±0.97% (95% CI 0.83 to 1.379) 3 months later; difference was 0.01±0.33% (95% CI -0.19 to -0.01; P = 0.913) (Figure 19B) (Table 4).

Differences between test and control group was statistically significant with better value for there test group (0.52±0.80%; 95% CI 0.13 to 0.57; P = 0.001). The data are summarized in (Table 4).

**Figure 19B.** Graphical representation (box plot) of hs-CRP values (mg/L) in non diabetic patients with periodontal disease at baseline and 3 months after periodontally compromised teeth extraction alone.

*p<0.05; **p<0.01; ***p<0.00; NS = Not Significant*
Periodontal conditions in the Non-Diabetic Patients

The periodontal parameters in the non-diabetic patients including:

- The mPI values statistically decreased in both groups and differences between test and control group was statistically significant with better value for there test group.

- The mBoP values statistically decreased in both groups and differences between test and control group was statistically significant with better value for there test group.

- mPPD values statistically decreased in both groups and the differences between test and control group was statistically significant with better value for there test group.

- The mCAL values was not statistically significant in both groups and the differences between test and control group was statistically significant with better value for there test group.
a) mPI

The mPI values statistically decreased in both groups. The mPI was 96.57±8.29% (95% CI 97.70 to 102.30) at baseline and 61.07±25.28% (95% CI 45.49 to 59.51) 3 months later, in the test group. The difference was 35.50±25.26% (95% CI 29.50 to 43.50; P = 0.000) (Figure 20A) (Table 4).

**Figure 20A.** Comparison of mean PI (%) among groups at baseline and 3 months after allocated interventions in non diabetic patients after non-surgical periodontal therapy and periodontally compromised teeth extraction. *p<0.05; **p<0.01; ***p<0.001; NS-not significant
In the control group, mPI was 95.07±7.14% (95% CI 98.02 to 101.98) at baseline and 86.23±12.52% (95% CI 85.53 to 92.47) 3 months later. The difference was 8.83±11.64% (95% CI 2.77 to 9.23; P = 0.0014) (Figure 20B) (Table 4). Differences between test and control group was statistically significant with better value for there test group (26.67±27.61%; 95% CI 22.85 to 38.15; P = 0.000) (Table 4).

**Figure 20B.** Comparison of mean PI (%) among groups at baseline and 3 months after allocated interventions in non diabetic patients after periodontally compromised teeth extraction alone. *p<0.05; **p<0.01; ***p<0.001; NS-not significant
b) mBoP

The mBoP values statistically decreased in both groups. The mBoP was 73.31±33.26% (95% CI 56.42 to 82.58) at baseline and 48.57±29.71% (95% CI 39.48 to 53.52) 3 months later, in the test group. The difference was 33.75±21.26% (95% CI 27.51 to 39.51; P = 0.000) (Figure 21A) (Table 4).

![Figure 21A. Comparison of mean BoP (%) among groups at baseline and 3 months after allocated interventions in non diabetic patients after non-surgical periodontal therapy and periodontally compromised teeth extraction. *p<0.05; **p<0.01; ***p<0.001; NS-not significant](image-url)
In the control group, mBoP was 70.37±22.58% (95% CI 61.24 to 73.76) at baseline and 55.70±20.57% (95% CI 52.30 to 63.70) 3 months later. The difference was 14.67±19.27% (95% CI 2.16 to 12.84; \( P = 0.003 \)) (Figure 21B) (Table 4). Differences between test and control group were statistically significant with better value for there test group (19.17±14.77%; 95% CI 22.85 to 38.15; \( P = 0.011 \)). The data are summarized in (Table 4).

**Figure 21B.** Comparison of mean BoP (%) among groups at baseline and 3 months after allocated interventions in non diabetic patients after periodontally compromised teeth extraction alone. *p<0.05; **p<0.01; ***p<0.001; NS-not significant
c) mPPD

The mPPD values statistically decreased only in the test group. The mPPD was 6.37±0.92 mm (95% CI 6.14 to 6.66) at baseline and 5.43±1.08 mm (95% CI 5.14 to 5.74) 3 months later, in the test group (difference was 0.94±0.62 mm (95% CI 0.79 to 1.13; P = 0.031) (Figure 22A) (Table 4).

Figure 22A. Comparison of mean PPD (mm) among groups at baseline and 3 months after allocated interventions in non diabetic patients after non-surgical periodontal therapy and periodontally compromised teeth extraction. *p<0.05; **p<0.01; ***p<0.001; NS-not significant
In the control group, mPPD was 5.93±1.04 mm (95% CI 5.47 to 6.05) at baseline and 5.53±0.97 mm (95% CI 5.17 to 5.71) 3 months later. The difference was 0.41±0.40 mm (95% CI 0.21 to 0.43; P = 0.124) (Figure 22B) (Table 4). Differences between test and control group was statistically significant with better value for there test group (0.53±0.76 mm; 95% CI 0.43 to 0.85; P = 0.000) (Table 4).

**Figure 22B.** Comparison of mean PPD (mm) among groups at baseline and 3 months after allocated interventions in non diabetic patients after periodontally compromised teeth extraction alone. *p<0.05; **p<0.01; ***p<0.001; NS-not significant
The mCAL value was not statistically significant in both groups. The mCAL was $-8.31\pm1.70$ mm (95% CI -9.05 to -8.12) at baseline and $-7.71\pm1.75$ mm (95% CI -8.39 to -7.42) 3 months later, in the test group. The difference was $-0.60\pm0.42$ mm (95% CI -0.71 to -0.48; $P = 0.187$) (Figure 23A) (Table 4).

**Figure 23A.** Comparison of mean CAL (mm) among groups at baseline and 3 months after allocated interventions in non diabetic patients after non-surgical periodontal therapy and periodontally compromised teeth extraction. *p<0.05; **p<0.01; ***p<0.001; NS-not significant
In the control group, mCAL was -7.37±1.30 mm (95% CI -7.76 to -7.03) at baseline and -7.05±1.22 mm (95% CI -7.31 to -6.63) 3 months later. The difference was -0.32±0.35 mm (95% CI -0.27 to -0.07; P = 0.325) (Figure 23B) (Table 4). Differences between test and control group was statistically significant with better value for there test group (0.27±0.57 mm; 95% CI 0.01 to 0.33; P = 0.009) (Table 4).

**Figure 23B.** Comparison of mean CAL (mm) among groups at baseline and 3 months after allocated interventions in non diabetic patients after periodontally compromised teeth extraction alone. *p<0.05; **p<0.01; ***p<0.001; NS-not significant
Table 4. Non-Diabetic patients: differences in glycemic control and periodontal conditions between test (A) and control groups (B), reported as mean±SD (95%CI)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 months later</th>
<th>Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test HbA1c (%)</strong></td>
<td>5.79±0.63 (5.63 to 5.97)</td>
<td>5.58±0.75 (5.24 to 5.66)</td>
<td>0.21±0.51 (0.01 to 0.29)</td>
<td>0.034*</td>
</tr>
<tr>
<td><strong>Control HbA1c (%)</strong></td>
<td>5.56±0.62 (5.33 to 5.67)</td>
<td>5.45±0.63 (5.22 to 5.58)</td>
<td>0.11±0.35 (0.1 to 0.3)</td>
<td>0.099</td>
</tr>
<tr>
<td><strong>Difference</strong></td>
<td></td>
<td></td>
<td>0.1±0.59 (-0.11 to 0.21)</td>
<td>0.396</td>
</tr>
<tr>
<td><strong>Test hs-CRP (mg/L)</strong></td>
<td>3.63±2.19 (2.49 to 3.71)</td>
<td>3.11±1.95 (2.41 to 3.49)</td>
<td>0.52±0.74% (0.25 to 0.65)</td>
<td>0.001*</td>
</tr>
<tr>
<td><strong>Control hs-CRP (mg/L)</strong></td>
<td>1.63±1.05 (0.91 to 1.49)</td>
<td>1.64±0.97 (0.83 to 1.37)</td>
<td>0.01±0.33 (-0.19 to -0.01)</td>
<td>0.913</td>
</tr>
<tr>
<td><strong>Difference</strong></td>
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<td></td>
<td>0.52±0.80 (0.13 to 0.57)</td>
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</tr>
<tr>
<td><strong>Test mPl (%)</strong></td>
<td>96.57±8.29 (97.70 to 102.30)</td>
<td>61.07±25.28 (45.49 to 59.51)</td>
<td>35.50±25.26 (29.50 to 43.50)</td>
<td>0.000*</td>
</tr>
<tr>
<td><strong>Control mPl (%)</strong></td>
<td>95.07±7.14 (98.02 to 101.98)</td>
<td>86.23±12.52 (85.53 to 92.47)</td>
<td>8.83±11.64 (2.77 to 9.23)</td>
<td>0.0014*</td>
</tr>
<tr>
<td><strong>Difference</strong></td>
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<td>26.67±27.61 (22.85 to 38.15)</td>
<td>0.000**</td>
</tr>
<tr>
<td><strong>Test BOP (%)</strong></td>
<td>73.31±33.26 (56.42 to 82.58)</td>
<td>48.57±29.71 (39.48 to 53.52)</td>
<td>33.75±21.26 (27.51 to 39.51)</td>
<td>0.0031*</td>
</tr>
<tr>
<td><strong>Control mBOP (%)</strong></td>
<td>70.37±22.58 (61.24 to 73.76)</td>
<td>55.70±20.57 (52.30 to 63.70)</td>
<td>14.67±19.27 (2.16 to 12.84)</td>
<td>0.0109*</td>
</tr>
<tr>
<td><strong>Difference</strong></td>
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<td></td>
<td>19.17±14.77 (22.85 to 38.15)</td>
<td>0.000*</td>
</tr>
<tr>
<td><strong>Test mPD (mm)</strong></td>
<td>6.37±0.92 (6.14 to 6.66)</td>
<td>5.43±1.08 (5.14 to 5.74)</td>
<td>0.94±0.62 (0.79 to 1.13)</td>
<td>0.031*</td>
</tr>
<tr>
<td><strong>Control mPD (mm)</strong></td>
<td>5.93±1.04 (5.47 to 6.05)</td>
<td>5.53±0.97 (5.17 to 5.71)</td>
<td>0.41±0.40 (0.21 to 0.43)</td>
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<tr>
<td><strong>Difference</strong></td>
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<td></td>
<td>0.53±0.76 (0.43 to 0.85)</td>
<td>0.000**</td>
</tr>
<tr>
<td><strong>Test mCAL (mm)</strong></td>
<td>-8.31±1.70 (-9.05 to -8.12)</td>
<td>-7.71±1.75 (-8.39 to -7.42)</td>
<td>-0.60±0.42 (-0.71 to -0.48)</td>
<td>0.187</td>
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<tr>
<td><strong>Control mCAL (mm)</strong></td>
<td>-7.37±1.30 (-7.76 to -7.03)</td>
<td>-7.05±1.22 (7.31 to 6.63)</td>
<td>-0.32±0.35 (-0.27 to -0.07)</td>
<td>0.325</td>
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<td><strong>Difference</strong></td>
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<td></td>
<td>0.27±0.57 (0.01 to 0.33)</td>
<td>0.009**</td>
</tr>
</tbody>
</table>
Impact of the number of teeth extraction in Glycemic Control and Inflammation

Significantly improvements in the HbA1c plasma and hs-CRP serum levels compared to the baseline were found in patients with non-surgical periodontal therapy (test) and without non-surgical periodontal therapy (control) after one tooth extraction or more than one. However the only one tooth extraction were not significantly different when compared with more than one tooth extraction in all the groups (Table 5AB and 6AB).

**Table 5A.** Diabetic type 2 patients: differences in glycemic control and inflammation in periodontal conditions in baseline and after 3 months in test group, reported as mean±SD (95%CI). (at least one tooth extraction, n=20; 2-5 teeth extraction, n=30)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 months later</th>
<th>Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(1 tooth extraction)</td>
<td>9.70±2.58</td>
<td>7.89±1.80</td>
<td>1.82±0.70</td>
<td>0.0137*</td>
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<td></td>
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<td>(0.39 to 3.24)</td>
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</tr>
<tr>
<td>(2-5 tooth extraction)</td>
<td>9.52±2.61</td>
<td>8.16±1.60</td>
<td>1.37±0.56</td>
<td>0.0175*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.25 to 2.49)</td>
<td></td>
</tr>
<tr>
<td><strong>Difference</strong></td>
<td></td>
<td></td>
<td>0.45±0.48</td>
<td>0.3534</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>(-0.52 to 0.48)</td>
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</tr>
<tr>
<td><strong>hs-CRP (mg/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1 tooth extraction)</td>
<td>4.39±2.47</td>
<td>2.76±1.64</td>
<td>1.69±0.66</td>
<td>0.0151*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.35 to 3.03)</td>
<td></td>
</tr>
<tr>
<td>(2-5 tooth extraction)</td>
<td>4.44±2.70</td>
<td>2.99±2.17</td>
<td>1.45±0.63</td>
<td>0.0254*</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>(0.19 to 2.72)</td>
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</tr>
<tr>
<td><strong>Difference</strong></td>
<td></td>
<td></td>
<td>0.24±0.43</td>
<td>0.5752</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(-0.62 to 1.1)</td>
<td></td>
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Table 5B. Diabetic type 2 patients: differences in glycemic control and inflammation in periodontal conditions in baseline and after 3 months in control group, reported as mean±SD (95%CI). (at least one tooth extraction, n=21; 2-5 teeth extraction, n=29)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
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<th>Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>8.93±3.49</td>
<td>7.99±2.88</td>
<td>0.94±0.98</td>
<td>0.3458</td>
</tr>
<tr>
<td>(1 tooth extraction)</td>
<td></td>
<td></td>
<td>(-1.05 to 2.94)</td>
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<tr>
<td>HbA1c (%)</td>
<td>8.69±2.49</td>
<td>7.99±2.27</td>
<td>0.70±0.63</td>
<td>0.2682</td>
</tr>
<tr>
<td>(2-5 tooth extraction)</td>
<td></td>
<td></td>
<td>(-0.56 to 1.96)</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td></td>
<td>0.24±0.66</td>
<td>0.7176</td>
</tr>
<tr>
<td>(1 tooth extraction)</td>
<td></td>
<td></td>
<td>(-1.09 to 1.58)</td>
<td></td>
</tr>
<tr>
<td>hs-CRP (mg/L)</td>
<td>4.10±2.20</td>
<td>3.11±1.58</td>
<td>0.90±0.59</td>
<td>0.1354</td>
</tr>
<tr>
<td>(1 tooth extraction)</td>
<td></td>
<td></td>
<td>(-0.29 to 2.01)</td>
<td></td>
</tr>
<tr>
<td>hs-CRP (mg/L)</td>
<td>4.07±2.23</td>
<td>3.31±1.75</td>
<td>0.75±0.53</td>
<td>0.1631</td>
</tr>
<tr>
<td>(2-5 tooth extraction)</td>
<td></td>
<td></td>
<td>(-0.31 to 1.80)</td>
<td></td>
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<tr>
<td>Difference</td>
<td></td>
<td></td>
<td>0.16±0.41</td>
<td>0.7074</td>
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<td>(-0.67 to 0.98)</td>
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</table>
Table 6A. Non-Diabetic patients: differences in glycemic control and inflammation in periodontal conditions in baseline and after 3 months in test group, reported as mean±SD (95%CI). (at least one tooth extraction, n=14; 2-5 teeth extraction, n=16)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
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<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>(1 tooth extraction)</td>
<td>5.35±0.65</td>
<td>5.24±0.63</td>
<td>0.11±0.25 (-0.38 to 0.61)</td>
<td>0.6402</td>
</tr>
<tr>
<td>(2-5 tooth extraction)</td>
<td>5.74±0.55</td>
<td>5.64±0.59</td>
<td>0.11±0.20 (-0.31 to 0.52)</td>
<td>0.6039</td>
</tr>
<tr>
<td><strong>Difference</strong></td>
<td></td>
<td></td>
<td>0.007±0.13 (-0.26 to 0.28)</td>
<td>0.9518</td>
</tr>
<tr>
<td><strong>hs-CRP (mg/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1 tooth extraction)</td>
<td>1.87±1.06</td>
<td>1.86±1.03</td>
<td>0.007±0.39 (-0.80 to 0.82)</td>
<td>0.9857</td>
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<tr>
<td>(2-5 tooth extraction)</td>
<td>1.43±1.04</td>
<td>1.44±0.90</td>
<td>-0.02±0.34 (-0.72 to 0.68)</td>
<td>0.9568</td>
</tr>
<tr>
<td><strong>Difference</strong></td>
<td>0.02±0.12 (-0.23 to 0.28)</td>
<td>0.8351</td>
<td></td>
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</tr>
</tbody>
</table>
Table 6B. Non-Diabetic patients: differences in glycemic control and inflammation in periodontal conditions in baseline and after 3 months in control group, reported as mean±SD (95%CI). (at least one tooth extraction, n=14; 2-5 teeth extraction, n=16)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 months later</th>
<th>Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1 tooth extraction)</td>
<td>5.84±0.56</td>
<td>5.43±0.79</td>
<td>0.40±0.27</td>
<td>0.1369</td>
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<tr>
<td></td>
<td></td>
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<td>(-0.14 to 0.94)</td>
<td></td>
</tr>
<tr>
<td>(2-5 tooth extraction)</td>
<td>5.75±0.70</td>
<td>5.71±0.70</td>
<td>0.04±0.25</td>
<td>0.8804</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(-0.47 to 0.54)</td>
<td></td>
</tr>
<tr>
<td><strong>Difference</strong></td>
<td></td>
<td></td>
<td>0.37±0.18</td>
<td>0.0512</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.002 to 0.723)</td>
<td></td>
</tr>
<tr>
<td><strong>hs-CRP (mg/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1 tooth extraction)</td>
<td>3.06±1.81</td>
<td>2.63±1.78</td>
<td>0.44±0.68</td>
<td>0.5254</td>
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<tr>
<td></td>
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<td>(-0.96 to 1.83)</td>
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<tr>
<td>(2-5 tooth extraction)</td>
<td>4.13±2.42</td>
<td>3.54±2.05</td>
<td>0.59±0.79</td>
<td>0.4649</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(-1.03 to 2.21)</td>
<td></td>
</tr>
<tr>
<td><strong>Difference</strong></td>
<td></td>
<td></td>
<td>-0.15±0.27</td>
<td>0.582</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(-0.70 to 0.41)</td>
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</table>
Discussion

Contribution to science

The Scientific rationale for study: The prevalence of diabetes has drastically increased over the past decade especially in the Balkans. Glycemic control is generally affected by oral complications such as periodontal infection, otherwise, poorly controlled type 2 diabetes affects periodontal health, and the loss of teeth was considered to be higher as compared to individuals without diabetes. Hence, dentists play an important role in the diagnosis and treatment of diabetes.

Principal findings: HbA1c and hs-CRP levels decreased significantly in the diabetic groups and decreased more markedly when non-surgical periodontal therapy was performed in combination with the extraction of periodontally compromised teeth.

Practical implications: The clinician should inform the patient that there is a relationship between glycemic control and periodontal health. Among different periodontal treatment approaches, non-surgical periodontal therapy resulted in improvement of glycemic levels and periodontal parameters of healthy and type 2 diabetic Kosovo patients with chronic periodontitis. Thus, this information should be taken into consideration for correct treatment planning.
This doctoral thesis study was designed to evaluate the glycemic levels and periodontal parameters of both healthy and type 2 diabetic Kosovo patients after non-surgical periodontal therapy and extraction of periodontally compromised teeth or teeth extraction alone.

This study was conducted to investigate the beneficial properties of full-mouth tooth cleaning as a non-surgical treatment after tooth extraction in ND subjects and DT2 patients with moderate to severe periodontitis.

This study investigated the effects of surgical and full-mouth tooth cleaning as a non-surgical treatment after tooth extraction in the glycemic control (HbA1c) and systemic inflammation (hs-CRP) of T2M and ND subjects with periodontal diseases.

The critical analysis of different periodontal parameters in the T2DM group and the ND group enabled us to find valuable evidence that indicates that the study interventions are effective in reducing oral complications, particularly in T2DM patients.

Therefore, the null hypothesis that non-surgical periodontal treatment and extraction of periodontally compromised teeth may not reduce tissue inflammation in diabetic patients was rejected in favor of the hypothesis of reduction. Despite a lack of strong evidence, non-surgical periodontal therapy before extraction of the periodontally compromised teeth (test groups) showed a trend of improved values for all the outcomes measured, in both healthy and type 2 diabetic Kosovo patients, compared to periodontally compromised teeth extraction alone (control group).
**Periodontal Status, Glucose and Inflammatory Control**

In diabetic patients, statistically, significance was reached for reduction of hs-CRP levels, mPI, and mBoP, with the higher reduction in the test group. In nondiabetic patients, statistically significant reduction in the HbA1c and hs-CRP levels were found in the test group but not in the control group, during the study period and between them.

All the periodontal parameters (mPI, mBoP, mPPD and mCAL) statistically decreased in both groups with statistically significant higher reductions in the test group (p<0.05). Furthermore, a critical analysis of differences found in the periodontal parameters between test and control group allowed us to seen as for as a valuable evidence that indicates that non-surgical periodontal therapy before extraction of periodontally compromised teeth is effective in reducing oral complications, particularly in type 2 diabetic patients.

The main limitation of the present study was the short follow-up period. Nevertheless, there are some studies that confirm 3 months could be considered as a sufficient time period to evaluate the glycemic levels and periodontal parameters after non-surgical interventions (101,102). Moreover, this limitation could be overcome continuing to follow the patients in the long-term period, as planned in the original design of this randomized controlled trial.

It is known that inflammation takes part in the insulin resistance in type 2 diabetes (103). However, there are studies that periodontal treatment with topical and systemic antibiotics and surgery that demonstrate improvement of HbA1c through reduction of CRP levels and other inflammatory markers (99,104). Which was further confirmed in type 2 diabetes group of periodontal intervention also with the improvement of lipid profile and inflammatory cytokines also (105).

Furthermore, Kahder et al. 2010 also confirmed that full-mouth extraction of periodontally compromise teeth raised the importance of improvement in glycemic control among patients with type 2 diabetes (106).
The results of the present doctoral thesis study designed as a randomized controlled trial are consistent with those from previous studies in which surgical and non-surgical periodontal treatment can effectively improve the periodontal inflammatory conditions with a decrease in HbA1c levels in a period of three and 6 months (107–110). Schara et al. 2006 demonstrated that a full-mouth disinfection in type 1 diabetes patients produced a positive effect on metabolic control (94). A meta-analysis of Kiran et al. 2005 concluded that non-surgical periodontal treatment improved metabolic control in patients with periodontitis and diabetes.

These results are confirmed by recent studies evaluated HbA1c and hs-CRP levels as indicators of glycemic control after periodontal treatments, such as topical and systemic antibiotics and surgical procedures, significant improvements in HbA1c level through the reduction of hs-CRP levels were found (96,99,104,105). Similarly, following extraction of periodontally compromised teeth alone, patients tended to have improved of HbA1c and hs-CRP values, but of a minor entity (90,104).

The progression of periodontal disease, as a chronic infection, may be a risk factor for the development of diabetes, and this was also observed in a previous studies (111). It is well known that oral hygiene plays an important factor in the control of periodontal status and in the metabolic control (112). Although dental prophylaxis and oral hygiene maintenance alone play a role in periodontal health, there is limited evidence regarding the possible improvement of HbA1c levels (93).

A recent study concluded that improved oral hygiene may improve periodontal health and metabolic control (113), implying glycemic control with HbA1c and insulin resistance and sensitivity (114).

According to the aforementioned prospective studies, these randomized controlled trial confirmed a beneficial effect of non-surgical periodontal treatment before extraction of periodontally compromised teeth, on control of glycemic levels and periodontal parameters, highlighting their importance in dental oral practice.
**Thesis Conclusion**

Our study has shown the critical effects of non-surgical periodontal therapy accompanied by extraction in the response to and efficacy of treatment for periodontal disease in diabetic (type 2) and non-diabetic Kosovar Albanians population.

The results of the present doctoral thesis study designed as randomized controlled trial demonstrated that non-surgical periodontal therapy and extraction of periodontally compromised teeth may improve glycemic levels and periodontal parameters of both healthy and type 2 diabetic patients with chronic periodontitis. Our work may set the stage for larger investigational studies and further follow-ups, as well as larger investigational studies aimed at evaluating the impact of non-surgical and surgical approaches to the clinical management of periodontal disease and diabetic patients, need to confirm these results.
Answers to thesis research hypothesis

1. Non-surgical periodontal therapy reduced significantly glycemic levels in type 2 diabetic patients and non-diabetic patients with the extraction of periodontally compromised teeth which were associated also improvement of periodontal status.

2. Non-surgical periodontal therapy reduced significantly systemic inflammation in diabetic patients which were accompanied with the better glycemic control in type 2 diabetic patients and non-diabetic patients with the extraction of periodontally compromised teeth which were associated also improvement of periodontal status.
Acknowledgments

For this thesis, there are some people, whom I am feeling very grateful and I wish to thank them all of their contribution, motivation, and support.

First of all, I would like to thank the Slovenian Human Resources Development and Scholarship Fund (SHRDSF) and Slovenia Country for the providing me this opportunity to get enrolled in the study program and the scholarship for me in all the period of my Ph.D. studies.

Moreover, this thesis won't be realized if the patients and their voluntary participation in the study, whom I feel very thankful for them and their collaboration.

A special thank is dedicated to my supervisor/mentor Doc. Rok Schara, dr.dent.med, for his support in my Ph.D. studies, especially his worm support during my stay in Slovenia and for his motivation and also advice for the essential work.

Next, I would like to thank and express my sincere gratitude to my colleague and also as supervisor Dr.Sci.Armond Daci, for his support in study design, clinical trial registration and English proofreading, and also prof.dr. Erika Cvetko and assist.dr. Aleš Skvarča dr.med for Slovenian proofreading.

I would like to thank all the staff of the Department of Oral Surgery in the Policlinic of Peja, Kosovo, including nurses, clinicians, specializing students, for their help support during this work.

A significant contribution was made also by the Department of the Endocrinology in Regional Hospital in city of Peja.

I would like to thank my thesis evaluation Commission for their review and the comments which have increased the value of this thesis, the president prof.dr. Tadej Battelino dr.med, and members prof.dr. Zlatko Pavlica dr.vet.med and Doc. Boris Gaspirc dr.dent.med.

In the end, my special thanks go to my family including my wife Dr. Manushaqe Bukleta for her support and motivation during all this long period, with my son Art and daughter Puhiza, and also my mother and father for their encouragement during my entire academic career.
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Supplementary files:

ClinicalTrials.gov Identifier: NCT02874963

FM-SRP and Tooth Extraction Improve Type 2 Diabetes Mellitus in Periodontitis

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

Sponsor:
University Clinical Centre of Kosovo

Collaborator:
University of Ljubljana, Faculty of Medicine

Information provided by (Responsible Party):
Dashor Bukleta, University Clinical Centre of Kosovo
Evaluation of metabolic control of type II diabetic patients after tooth extraction
Vpliv ekstrakcije zobi na urejeno z glikemijo HbA1c

Protokoll

Broj protokola

Ime

Prebivalisce

Profesija

Datum 23.10.2015

Prezime

Tel. 045/661116 AA

Prvi osnovni podaci

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<td>rural / urban područje</td>
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ANAMNEZA

Anamneza bolesti

Anamneza bolesti:
Pacijent ima diabetes

Diabetes tip I

Diabetes tip II

Kontrolirani diabetes:

- Vrsta lekova koje upotrebljava pacijent

- Vrsta antibiotika koje upotrebljava pacijent

Nekontrolirani diabetes:

Da Ne

Konsupiranje cigarete

(koliko cigarete na dan)
Doc. dr. Rok Schara, dr. dent. med.
Stomatološka klinika
Univerzitetni klinični center Ljubljana
Hrvatski trg 6
1000 Ljubljana

Številka: 0120-699/2015-4
KME 71/06/16
Datum: 31. avgust 2016

Zadeva: Ocena etičnosti predložene raziskave

Spoštovani gospod docent dr. Schara,
Komisiji za medicinsko etiko (KME) ste z datumom 13. 5. 2016 poslali nov dokument k vlogi za oceno etičnosti predloga raziskave z naslovom
"Ocena uraženosti glikemije pri sladkornih bolnikih tipa 2 po izdržu zob", ang. "Evaluation of glycemic control of type 2 diabetic patients after tooth extraction".
Gre za kopijo dokumenta, ki ga je izdala Komisija za etiko in strokovnost UKC Kosova vašemu študentu Dashnorju Bukleti, dr. dent. med., ki bo tudi odgovoren za varnost oseb v predloženi raziskavi.

KME se je na seji 14. junija 2016 zadovoljila z vašim odgovorom na svoj dopis (KME 73/01/16) in vam s tem izdaja svoje soglasje za izvedbo raziskave.

Lepo pozdravljam,

[Signature]

Anton Zakelj

P.S.: Pri morebitnih nadaljnjih dopisih v zvezi z raziskavo se obvezno sklicujejo na številki tega dopisa.

1 KME je vlogo uradno prejela 17. 5. 2016.
Date: 13.10.2014

The University of Ljubljana, Faculty of Medicine

From: Prof. Hilmi Dauti, DDS, PhD, Ethical and Professional Commission of UCCK

The Ethical and Professional Commission of UCCK analyzed the request of Dr. Dashnor Haklieta in order to realize her study.

The project proposal fully complies with actual ethical and professional standards and criteria of University Clinical Center of Kosovo, therefore we fully support this study.

Head of Ethical and Professional Commission UCCK

Prof. Hilmi Dauti, DDS, PhD