Novel surface tailoring of innovative dental zirconia implants for improved osseointegration and soft-tissue attachment

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Project abstract:

In the recent years, development of dental implants is clearly shifting toward alternative metal-free implant systems, as a result of biocompatibility concerns and the unpleasing esthetic appearance of ‘gold-standard’ titanium (Ti) implants. Currently, 3 mol% yttria-stabilized tetragonal zirconia polycrystal (3Y-TZP) is the material of choice for metal-free dental implants because of their superior mechanical characteristics, excellent biocompatibility with low bacterial plaque affinity and natural aesthetics. However, 3Y-TZP zirconia suffers from hydrothermal aging or low-temperature degradation (LTD), which leads to slow tetragonal-to-monoclinic (t-m) phase transformation and material deterioration, in particular in a wet environment. Additionally, increased surface roughness due to changes in structural integrity (grain pull-out, micro-cracking) may affect 3Y-TZP’s interaction with the surrounding bone and soft tissues. For instance, there is growing concern over problematic osseointegration due to debris release during the implantation process, since high wear forces on the implant surface can cause shedding of surface particles. Even though this issue has only been addressed for Ti implants, there are strong indications that this scenario may also happen with 3Y-TZP implants. Various studies have focused on strategies to avoid LTD in 3Y-TZP and to develop new innovative zirconia grades with improved in-vivo stability. One of the most promising materials is based on CeO2-stabilized zirconia (e.g. Ce-TZP/Al2O3), which are nearly LTD-free and combine more stress-induced phase transformation with a significantly improved fracture toughness. A novel Ce-TZP zirconia formulation was developed at KU Leuven and uniquely combines high toughness and strength with damage-tolerant properties. Such metal-like characteristics assure this new zirconia formulation to be a perfect candidate for the production of dental (as well as orthopedic) zirconia-ceramic implants.

The long-term clinical success of dental implants largely depends on two major factors: osseointegration potential of the implant fixture and soft-tissue attachment to the abutment. While zirconia abutments are considered superior compared to Ti abutments thanks to their low microbiological affinity, implant fixtures (screw part) should on the other hand possess good osseointegration properties, as they are in direct contact with bone. Even though, many in-vitro and in-vivo studies have demonstrated that the osseointegration potential of zirconia is comparable to that of Ti, zirconia osseointegration remains controversial, as some clinical studies have reported a higher failure rate and peri-implant crestal bone loss for zirconia implants. Unfortunately, the exact reasons for this still remain speculative. The surface characteristics of a biomaterial play a crucial role in bone healing and the speed of osseointegration. Surface modification by acid etching, sandblasting and micromachining have been introduced to create nano-scale porosities that promote the biological response upon implantation. However, although these surface-modification techniques are suitable to create the targeted average surface roughness, they lack the capability to fine-tune different micro- and nano-topographical parameters crucial to stimulate different biological responses. Laser micro-patterning is another promising surface-modification technique that can generate extremely precise hierarchical (sub)surface structures with regular patterns. An alternative approach involves biofunctionalization of the implant surface that mimics the extracellular matrix; it revealed promising results in terms of enhanced osseointegration, improved soft-tissue attachment and increased biofilm resistance.

Traditionally, 2D monolayer cell-culture models have been used to evaluate biological responses to implant surfaces, but they do not fully represent the complex 3D micro-environment in tissues. Numerous researchers indicated that 2D models carry little scientific relevance and have no other reason of existence than purely for regulatory purposes. Thus, due to a lack of relevant 3D cell-culture models and long-term in-vivo studies, the nature of cell-zirconia surface interactions is insufficiently explored. We aim to address the knowledge gaps that exist between material design and manufacturing of zirconia and its final clinical application as dental implant. Using an interdisciplinary research approach, clinically relevant zirconia implant surfaces will be characterized in depth and subjected to assessment of particle debris release. To integrate the results obtained, the biological and microbial responses to modified zirconia implant surfaces will be investigated in vitro with novel 3D cell cultures simulating attachment of both soft (gingiva) and hard tissues (bone) to, respectively, the abutment and fixture part of a dental implant. Finally, soft-tissue attachment and osseointegration potential of these surfaces will be assessed by thoroughly characterizing the soft tissue-abutment and bone-implant interface in a clinically relevant in-vivo model.

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Research Data Summary

List and describe all datasets or research materials that you plan to generate/collect or reuse during your research project. For each dataset or data type (observational, experimental etc.), provide a short name & description (sufficient for yourself to know what data it is about), indicate whether the data are newly generated/collected or reused, digital or physical, also indicate the type of the data (the kind of content), its technical format (file extension), and an estimate of the upper limit of the volume of the data.

Dataset name / ID	Description	New or reuse	Digital or Physical data	Data Type	File format	Data volume	Physical volume
		*Indicate: **N**(ew data) or **E**(xisting data)*	Indicate: **D**(igital) or **P**(hysical)	Indicate: **A**udiovisual **I**mages **S**ound **N**umerical **T**extual **M**odel **SO**ftware Other (specify)		Indicate: <1GB <100GB <1TB <5TB >5TB NA	
SEM images	Scanning microscopy images	Generate new data	Digital	Experimental	.TIF of .JPEG	<100GB	
XRD data	X-ray diffraction	Generate new data	Digital	Experimental	.njc, raw, csv	<1GB	
µRaman data	Micro-Raman spectroscopy	Generate new data	Digital	Experimental	.OPUS, jpg	<1GB	
TEM images	Transmissional electronic microscopy images	Generate new data	Digital	Experimental	.TIF of .JPEG	<100GB	
TEM grids	TEM grids for imaging	Generate new data	Digital	Experimental			8 grid boxes
Micro-CT data	Micro-computer tomography	Generate new data	Digital	Experimental	,TIF	<5TB	
Hardness and toughness data	Hardness and toughness testing	Generate new data	Digital	Experimental	.txt	<100MB	
P3B, 4-point bending data	Fracture strength	Generate new data	Digital	Experimental	.txt	<100MB	
3D optical and laser profilometry data	3D optical and laser profilometry measurements of materials surface	Generate new data	Digital	Experimental	.stl	<100GB	
Histology and immunohistochemistry data	Histology sections and immunohistochemistry slides	Generate new data	Physical	Experimental			15 small boxes for glass slides (can be stored on the shelf)
PCR data	Real time qPCR files	Generate new data	Digital	Experimental	.txt	<5TB	
Light microscopy data	Light microscopy images	Generate new data	Digital	Experimental	.TIF	<5TB	

If you reuse existing data, please specify the source, preferably by using a persistent identifier (e.g. DOI, Handle, URL etc.) per dataset or data type:

Only new data will be used.

Are there any ethical issues concerning the creation and/or use of the data (e.g. experiments on humans or animals, dual use)? If so, refer to specific datasets or data types when appropriate and provide the relevant ethical approval number.

- Yes, dual use (Provide approval number below)

Use of human cells as approved by the Ethics Committee Research UZ/KU Leuven under the file number S54254.
Ethical approval of the animal study will be requested in due time when all project details of the planned animal research are known.

Will you process personal data? If so, please refer to specific datasets or data types when appropriate and provide the KU Leuven or UZ Leuven privacy register number (G or S number).

- No

Does your work have potential for commercial valorization (e.g. tech transfer, for example spin-offs, commercial exploitation, …)? If so, please comment per dataset or data type where appropriate.

- Yes

Commercial valorization is not a a direct goal of this project. However, if such an opportunity presents itself, it will be discussed among the staff and collaborators involved
in the project.

Do existing 3rd party agreements restrict exploitation or dissemination of the data you (re)use (e.g. Material or Data transfer agreements, Research collaboration agreements)? If so, please explain in the comment section to what data they relate and what restrictions are in place.

- No

Are there any other legal issues, such as intellectual property rights and ownership, to be managed related to the data you (re)use? If so, please explain in the comment section to what data they relate and which restrictions will be asserted.

- Yes

A PATENT application (ref. Zl921151) was submitted on 28-11-2021 to KU Leuven LRD (IP officers: Ivo Roelants, Ivo De Baere) for an European PATENT for the
invention of a zirconia ceramic-based material with very good mechanical (toughness – hardness - strength) properties: “Cation grain-boundary stabilized transformation
induced plasticity in Ce-TZP ceramics” (F. Zhang, M. Li, B. Van Meerbeek, J. Vleugels) (EP22176376). The search report and written opinion of the European Patent Office
(EPO) attorney confirmed the primary novelty of our invention, upon which the inventors will amend claims and create clarity before 31-05-2023.
This new zirconia-ceramics formulation will be used in the current project (patent pending; one of the patent holders is co-promoter of the current FWO project).

Documentation and Metadata

Clearly describe what approach will be followed to capture the accompanying information necessary to keep data understandable and usable, for yourself and others, now and in the future (e.g. in terms of documentation levels and types required, procedures used, Electronic Lab Notebooks, README.txt files, codebook.tsv etc. where this information is recorded).

1. Internal:
Raw data (temporary data, digital notebooks) will be stored on the UZ Leuven cumulus server with automatic back-up. All data will be stored in folders with the names

clearly indicating the folder content.
Research-project Protocols will be saved in the form of MsWord or pdf files.
In addition, regular reports based on the data will be generated using Microsoft Word. PowerPoint files will be used for presentation at regular internal meetings.
In both the Word reports and Powerpoint presentations, the file names of the raw data files will be included.
2. External:
Publications of results in scientific international (and national) peer-reviewed papers. Data in publication format will be published.
The last manuscript version, based on which the paper was accepted for publication, will be uploaded in the KU Leuven Lirias bibliography system. In case of publication in
an open-access journal, the journal pdf of the paper will be uploaded.

Will a metadata standard be used to make it easier to find and reuse the data?
If so, please specify which metadata standard will be used.

If not, please specify which metadata will be created to make the data easier to find and reuse.

- Yes

During each experiment, a detailed logbook will be used (different logbooks for the different experimental setups). Logbooks will contain the date, a brief description of
the performed experiment, the parameters used for each measurement, as well as the names of all the saved files. The names of the files will be structured in a
comprehensible way: system studied/date/main parameters used. In addition, data will be stored in a folder per experimental setup, the type of investigated system and
the corresponding date. In this way, by tracking the corresponding logbook notes, each file can be easily found on the local computers controlling the setup and on the
server of the laboratory. The analysis files will contain notes describing the analysis procedure and mention which original data files are included. A readme file describing
the goal of the experiment and the analysis procedure will be stored in the folder where the data is saved.

Data Storage & Back-up during the Research Project

Where will the data be stored?

- Other (specify below)

The data will be stored via a password-protected cloud storage solution (UZ Leuven cumulus google drive) that allows sharing with the researchers involved in the project.
Copies can be made and kept on personal devices.

How will the data be backed up?

- Other (specify below)

Data in the home directory of the users is backed up periodically. Snapshots of the home directories are also taken. The important data will be stored on the KU/UZ
Leuven central servers with automatic daily back-up procedures.

Is there currently sufficient storage & backup capacity during the project?

If no or insufficient storage or backup capacities are available, explain how this will be taken care of.

- Yes

Unlimited.

How will you ensure that the data are securely stored and not accessed or modified by unauthorized persons?

Password protected user accounts ensure that only the persons of the account can access the working data. The data generated during the project will be systematically
transferred to the cloud storage server. Only the researcher and (co)-promotors will have access to the shared folders where the data, reports and presentations will be
stored.

What are the expected costs for data storage and backup during the research project? How will these costs be covered?

The expected costs for data storage will not exceed a few hundred euro for external hard disks. This will be covered by the bench fee of the project.
There is no cost for the UZ Leuven cumulus drive.

Data Preservation after the end of the Research Project

Which data will be retained for 10 years (or longer, in agreement with other retention policies that are applicable) after the end of the project?

In case some data cannot be preserved, clearly state the reasons for this (e.g. legal or contractual restrictions, storage/budget issues, institutional policies...).

- All data will be preserved for 10 years according to KU Leuven RDM policy

All the generated data will be stored on the cloud storage server for a period of 10 years
after the end of the project.

Where will these data be archived (stored and curated for the long-term)?

- Large Volume Storage (longterm for large volumes)
- Other (specify below)

All the generated data will be stored on the cloud storage server (UZ Leuven cumulus google drive) for a period of 5 years after the end of the project.
Beyond 5 years after the end of the project, one of the following options will be picked
(1) continuation of storing the data on the cloud storage server or (2) transferring the
data to the KU Leuven central servers for archiving.

What are the expected costs for data preservation during the expected retention period? How will these costs be covered?

No additional costs are expected at this moment.

Data Sharing and Reuse

Will the data (or part of the data) be made available for reuse after/during the project?
Please explain per dataset or data type which data will be made available.

- Yes, as restricted data (upon approval, or institutional access only)

The written reports and Powerpoint presentations summarizing the results obtained can be made available. The (raw) data used in publications can be made available on
a repository, if e.g. requested by the Editors or Publisher of a scientific journal, or individual researchers.

If access is restricted, please specify who will be able to access the data and under what conditions.

If access is restricted, promoter and co-promoters will be able to access the data. Upon request or within research group, access to the samples and data can be granted.

Are there any factors that restrict or prevent the sharing of (some of) the data (e.g. as defined in an agreement with a 3rd party, legal restrictions)?

Please explain per dataset or data type where appropriate.

- No

Where will the data be made available?

If already known, please provide a repository per dataset or data type.

- Other (specify below)

Upon request by mail.

When will the data be made available?

- Other (specify below)
- Upon publication of research results

Upon publication of the research results. Description of the full scientific method and results will be made available with journal publications (and upon request).

Which data usage licenses are you going to provide?

If none, please explain why.

- Other (specify below)

We will consult the License selector tool in order to choose the best license that fits our data.

Do you intend to add a persistent identifier (PID) to your dataset(s), e.g. a DOI or accession number? If already available, please provide it here.

- Yes, a PID will be added upon deposit in a data repository

We will use DIO that is commonly used in KU Leuven RDR repository.

What are the expected costs for data sharing? How will these costs be covered?

No costs associated with data sharing.

Responsibilities

Who will manage data documentation and metadata during the research project?

The promoter and co-promotors will be jointly responsible for data documentation during the research project.

Who will manage data storage and backup during the research project?

The promoter and co-promoters involved in this project.

Who will manage data preservation and sharing?

The promoter and the FWO PostDoctoral researcher involved in this project.

Who will update and implement this DMP?

The promoter and co-promoters of this project.