

Research article

Identification card and codification of the chemical and morphological characteristics of 62 dental implant surfaces. Part 1: description of the Implant Surface Identification Standard (ISIS) codification system

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Abstract

Dental implants are commonly used in dental therapeutics, but dental practitioners only have limited information about the characteristics of the implant materials they take the responsibility to place in their patients. Manufacturers, scientists and administrations are also lacking of a consensual and clear method and terminology to characterize and control implant surfaces. The objective of this series of 5 articles is to define and describe the Implant Surface Identification Standard (ISIS) system for the chemical and morphological characterization of dental implant surfaces, and to use it to characterize and establish the respective Identification (ID) Card and code of 62 implant surfaces available on the market. In this first part, the current version of the ISIS system and methodology is described and discussed. Using standardized protocols of analysis and terminology, each osseointegrated implant surface can be defined using a standardized characterization code. First the ISIS codification system describes the surface chemical composition: the core material (titanium grades, zirconia, hydroxy-apatite) and the chemical modification (impregnation, coating, pollution). The system then defines the surface morphology (topography, structures) at the microscale (microroughness, micropores, microparticles) and nanoscale (nanoroughness, nanopatterning, nanotubes, nanoparticles, nanosmooth), and its global architecture (homogeneity, cracks, fractal architecture). This standardized characterization, classification and codification system allows to clarify the identity of each surface and to easily sort out their differences, to control implant production and to facilitate communication. Therefore it

offers a global solution for the manufacturers, scientists, implant users, administrative authorities and the interactions of these 4 actors, and it could be suggested as the basis of an ISO standard in the future.

Keywords. Dental implant, nanostructure, osseointegration, surface properties, titanium.

1. Introduction

Dental implants are commonly used in daily dental therapeutics. Each implant system can be defined by several key characteristics that determine its biological behavior, particularly the chemical and morphological characteristics of each implant surface [1]. Implant users have however very limited information about these characteristics when they choose the implant system they will use in their patients. The surface characteristics are often advertised by the dental implant company in order to promote their products, but most data remain very commercial and without certified evaluation and disclosure of the surfaces characteristics [2,3]. Moreover, the scientific literature on the topic is not helpful for clinicians. It is a very wide and confusing literature [1], as no global consensual standard of terminology and characterization was widely accepted and developed, even if some publications characterized partially the main implant systems [4]. The customer remains therefore blind when buying the implantable materials he will place in his patients, while he is responsible of the implant he is using in most national legislations. Finally, this absence of standard of characterization has an industrial impact, as the companies do not have a clear and standardized industrial protocol to check and validate their own production [3]. Even if some national administrations can suggest some controls of the surfaces, there is no consensual and systematic method for checking the products, administrations, companies and clinicians are taking the responsibility to use in the population. Industrials, administrations and customers are lacking the standardized tools and terminology to define, understand and control in details the products available on the market and to communicate between each other [5].

In 2010, a first standard of characterization, terminology, classification and codification of dental implant surfaces was published [1], followed by the publication of a first series of 14 implant surfaces Identification (ID) cards [6,7]. This standard is based on the use of standardized tools of analysis widely and commonly used in other fields of surface science (semiconductor and chemical industry for example). Each osseointegrated implant surface can be defined using a characterization code. This code first describes the surface chemical composition: the core material (titanium grade, zirconia, hydroxyapatite) and the chemical or biochemical modification (impregnation, coating, pollution). This code then defines the surface morphological characteristics (topography, structures) at the micrometer (microtopography: microroughness, micropores) and nanometer scale (nanotopography: nanosmooth, nanoroughness, nanopatterning, nanotubes, nanoparticles). Finally, this code is completed with information about the general morphology of the implant surface, such as its homogeneity, the presence of cracks or large particle inclusions, and even the possibility of a fractal dimension between the 3 levels of investigation (micro, nano and atomic)[7]. This standardized codification system allows to clarify the identity of each surface and to easily sort their differences.

In this series of 5 articles, this classification was upgraded following the feedback of recent experience [1], and is now termed Implant Surface Identification Standard (ISIS). 62 different surfaces were analyzed following this characterization and codification system in order to give a clear overview of the situation of the market at this time. In this first part, the

final form of the ISIS system is described in details and discussed. All the terms and acronyms are regrouped in the standardized **ISIS Table**, and explained in the following sections of this article.

2. What is exactly an osseointegrated implant surface?

From a strict physical standpoint, a surface could be defined as the sudden interruption of the atomic arrangement of a material. The surface does not show the same properties as the bulk material. Each new surface is in fact a new biomaterial in itself. The best example is titanium itself: the bulk of a pure grade 4 titanium implant is mostly titanium, but the surface is a TiO₂ layer [1].

The problem is then to define what thickness of the peripheral part of the bulk material may be considered as the surface. From a strict physical standpoint, the surface may be defined by its first Angström-thick crystalline layer. However, in dental implants, the detailed chemical characteristics of all surfaces can be found in the first 100nm of the surface [4,6]. Moreover, the morphology of all implants must be characterized at the nanoscale [8], i.e. between 1 and 100nm, which means that an amplitude of 100nm is the minimum thickness to consider to define the surface features. Therefore, the ISIS system defines the surface as the 100nm-thick superficial layer of the implant.

Osseointegration is an experimental-revealed phenomenon assessable on histological sections using photonic microscopy, and is often defined as the close contact between bone and material [3]. Osseointegration is also a clinically defined concept based on implant stability. The original theory of osseointegration rested on the oxidation of implant titanium surface. The surgical trauma inherent to implantation induces a severe oxidative stress, and the production of free radicals and oxygenated derivatives against the implant induces the thickening of the titanium dioxide (TiO₂) layer of its surface. Calcium and phosphorus ions of the bone matrix are then incorporated within the TiO₂ porous layer. This dynamic bone/implant interface is the core principle of osseointegration, and of its pathological twin - peri-implantitis [9].

Nowadays, the osseointegration concept can be generalized to many forms of biocompatible surfaces and can be defined more accurately by 2 kinds of bone/implant interlocking [1,10]. First, the biochemical interlocking is based on the direct chemical interaction of bone tissue with the core material (in general titanium oxide layer, but not only); chemical modifications are frequent by incorporation of inorganic phases (like Calcium Phosphate CaP) on or within the core material [11,12], to stimulate bone regeneration and increase the biochemical interlocking between bone and surface. Second, the biomechanical interlocking is based on the direct mechanical interaction and lock of the bone tissue within the morphology of the core material (in general rough or porous at the microscale)[10,13]; the shape of the microtopography influences also directly the cell and tissue behavior. Finally, the presence of significant nanofeatures - still rare in dental implants - is a parameter influencing both biomechanical and biochemical interlocking processes [14], through proteins adsorptions, mineral chelation, direct cell and tissue interactions and induction.

Therefore two levels of characterization can be defined for an implant surface [1]. The first level is based on the chemical composition of the surface, i.e. the composition of the core material and its eventual chemical modifications. The second level is based on the surface morphological characteristics, i.e. its topography and structures at the micro- and nanometer

scale. These concepts allow us to define accurately the main families and characteristics of osseointegrated implant surfaces.

3. Main groups of dental implant surfaces

The surface production processes are numerous and the parameters defining each process (temperature, pressure, electrolytic solution, time, type and size of blasting particles, type and concentration of etching acids for example) can be modified significantly to reach a usable surface for dental implants. There is therefore an almost endless number of different surface aspects and compositions, even if they can be regrouped by their main specific patterns [6]. It is thus needed to define first each surface through its physical and chemical characteristics more than through its method of production [1]. Analyzed surfaces can then be regrouped by concept of production, in order to facilitate understanding of the main patterns of each technology and to compare easily their differences. There are actually only 3 main logical concepts of production of a surface: modification of the core material characteristics, carving of the core material by subtraction or chemical coating of the core material.

Four main groups of production concept were therefore defined in the ISIS final version, based on the feedback of this large study [6]. The Group 1 gathered all surfaces produced through modification of the core material characteristics, mostly the alteration of the titanium metallurgy through anodization or titanium-plasma spraying (TPS). The Group 2 gathered all surfaces produced through a subtractive processing to carve the surface morphology on the core material. Two subgroups can be defined, based on the techniques frequently observed on the market: the group 2A gathered all surfaces produced through a subtractive sand-blasting and acid-etching (SLA type); the group 2B gathered surfaces produced through all other subtractive methods such as Resorbable Blasting Media (RBM), Dual Acid-Etching (DAE) or Subtractive Impregnation Micro-Nanotexturization (SIMN). The Group 3 gathered all surfaces produced through chemical coating of the core material. Two subgroups can be defined, based on the techniques frequently observed on the market: the Group 3A regrouped titanium-based surfaces produced by subtraction and finally covered with a nanometric coating (often discontinuous) of Ca, CaP or Na-based nanocrystals; the Group 3B regrouped implants covered with a micrometric thick layer of hydroxyapatite (mostly Plasma-Sprayed Hydroxyapatite PSHA) or other forms of CaP (Ion-Beam Assisted Deposition IBAD, brushite coating, and others), therefore becoming the core material of the surface. Finally, the Group 4 gathered all surfaces designed specifically for the collar cervical area of the implant (to promote a better stability of the peri-implant bone and gingival attachment); this group is a bit artificial as it is not based on the concept of surface production, but on the specific use of these surfaces designed for the peri-implant cervical implant/bone/gingiva interface, and not strictly for the osseointegration itself.

The exact concept group of each surface is often disclosed by the companies (more or less clearly), but anyway it can be observed during the in-depth standardized characterization of each surface, following the ISIS system.

Level of characterization			Characteristics and their definitions	
Type	Code	Definition	Code	Definition
Chemical	Core	Core material	G2Ti Commercially Pure Grade 2 Titanium G4Ti Commercially Pure Grade 4 Titanium G5Ti Ti-6Al-4V Grade 5 Titanium G23Ti Ti-6Al-4V ELI (Extra Low Interstitials) Grade 23 Titanium TiZr Titanium-Zirconium alloy YTZP Ytria-stabilized Tetragonal Zirconia Polycrystals YPSZ Ytria-Partially Stabilized Zirconia PSHA Plasma-Sprayed Hydroxyapatite (thick coating) Brush Brushite CaP Calcium Phosphate (other forms)	
	Mod	Modification	X-RI Impregnation (elements X within the core material) <1% : Residual Impregnation X-LI 1 to 5% : Low Impregnation X-HI > 5% : High Impregnation X-CC Coating (elements X on the core material) Continuous Coating. On the whole surface X-DC Discontinuous Coating. >50% total surface X-SC Sprinkled Coating. <50% total surface OPol Pollution Organic Pollution X-IPol Inorganic Pollution. X = elemental composition	
Physical	Micro	Microtopography	R 1/ Morphology Type (number of dimensions D) Rough (1D) Pa/Po Patterned or Porous (2D) X-Pt Particle (3D): X = elemental composition	
			S 2/ Height Deviation Amplitude (Sa) Smooth: Sa = 0 to 0.5µm Mi Minimal: Sa = 0.5 to 1µm Mo Moderate: Sa = 1 to 2µm Ma Maximal: Sa > 2µm	
			Fl 3/ Spatial Density (developed area ratio, Sdr%) Flat: Sdr% = 0 to 50% Fo Flattened out: Sdr% = 50 to 100% Ru Rugged: Sdr% = 100 to 200% Re Rugged extra: Sdr% > 200%	
	Nano	Nanotopography (number of dimensions D)	S Smooth R Rough (1D) Pa/Po/T Patterned/Porous/Tubes (2D) X-Pt Particle (3D): X = elemental composition	
Archi	Global architecture	F/NF Fractal/Non Fractal Ho/He Homogeneous/Heterogeneous LC/EC Local Cracks/Extended Cracks along the surface X-RP Random Particle. X = elemental composition and associated characteristics		

Table. Standardized ISIS Table regrouping all the terms, acronyms and definitions used in the Implant Surface Identification Standard (ISIS) system. Details were given in the following sections of the article.

4. Characterization of the core materials and chemical modifications

Each surface can be defined by a core material, constituting the main component of the implant interface with the bone during the osseointegration process. This core material can be altered by chemical modifications that introduce specific ions, crystals or molecules on or within the core material [1].

4.1. Core material

For osseointegrated implants, 2 main core materials are currently used: predominantly titanium and, if still not very common, zirconia. Titanium is commonly used in the grades 2, 4, 5 or 23 forms, due to their chemical and mechanical properties. Grade 4 Titanium (G4Ti), called commercially pure titanium, shows only some residues (less than 1%) of iron and oxygen and is the most frequently used for its combination of strength, ductility and corrosion resistance. Some companies replaced it with Grade 2 Titanium (G2Ti), presenting higher corrosion resistance than Grade 4 but lower strength. Grade 5 Titanium (G5Ti), called Ti-6Al-4V, is a titanium alloy incorporating 6% of aluminium and 4% of vanadium, thus showing greater mechanical strength. Grade 23 Titanium (G23Ti), called Ti-6Al-4V ELI (Extra Low Interstitials), is a variation of the G5Ti alloy with similar chemical composition and lower interstitial elements content (particularly oxygen), what confers improved ductility and fracture toughness. Zirconia implants are currently made of yttria-stabilized tetragonal zirconia polycrystals (Y-TZP) or yttria-partially stabilized zirconia (Y-PSZ); their use remains however quite rare.

When a surface is coated with micrometric thick layers of another material (for example HA), then this coating material becomes *de facto* the core material of this surface. The most frequent example of thick coating is the Plasma-Sprayed Hydroxyapatite (PSHA). Thick micrometric coating with brushite was also used, even if it remained very rare. Other forms of Calcium Phosphate CaP relatively slim coating were also used.

4.2. Chemical modification: impregnation or coating

The chemical modification of the surface is considered as an alteration of the core material composition with different chemical elements. Chemical modifications can be integrated (impregnation) or superficial (coating)[6].

An impregnation (for example with Fluorine F or Calcium Ca) is integrated within the core material architecture and is therefore not observable during the morphological analysis with SEM (Scanning Electron Microscope). It can be residual (<1%), low (between 1 and 5%) or high (>5%) depending on the concentration of the impregnated element. The 1% and 5% thresholds are arbitrary, but appeared relevant considering the feedback of experience and the respective composition of G4Ti (1% residual elements) and G5Ti (6%Al-4%V).

A coating (for example with CaP or NaCl crystals) is a nanometric superficial layer covering the core material architecture. It can be continuous (on the whole surface), discontinuous (covering >50% of the total surface) or sprinkled (covering <50% of the total surface). Discontinuous and sprinkled coatings are easily detectable during the morphological analysis with SEM, while continuous coating is more clearly revealed using a chemical in-depth profiling.

The last types of chemical modifications are the many possible pollutions found on dental implant surfaces. Inorganic pollution is very frequent, particularly with various chemical residues of the surface processing or packaging such as Silicon (Si), Fluorine (F) or

Chlorine (Cl). Some very unexpected contaminant elements can also be found such as Barium Ba or Tungsten W, what raises some significant concerns about the security and control of implantable devices. Inorganic contaminants have the particularity to not be homogeneously distributed on the implant surface, to present unstable profiles and various concentrations [6].

Organic pollution is less frequent and is associated with the presence of heavy organic molecules on the surface (mostly dirt or residues from environment or the handling). All implants present normally some Carbon C in their superficial chemical composition, and it is mostly related to the adventitious Carbon (mostly CO₂ adsorbed from atmospheric exposure). However, carbohydrates and other complex C molecules can be identified and are always associated with much higher proportions of C in the superficial composition. This kind of pollution is often associated with early implant failures or peri-implantitis [9], and is therefore important to control.

4.3. Method of characterization

The evaluation of the chemical composition of a surface requires different kinds of spectroscopy techniques. Three methods of analysis can be combined for a standardized suitable and accurate chemical characterization of dental implant surfaces [1].

X-ray Photoelectron Spectroscopy (XPS)/Electron Spectroscopy for Chemical Analysis (ESCA) is based on the irradiation of a surface with monochromatic X-rays, resulting in the emission of photoelectrons showing the specific energies of the various material elements. XPS is used to determine accurately the superficial atomic composition (in %) and chemistry of a wide and thin surface area (typically 100-300µm in diameter, 5 to 10nm thin)[4]. XPS provides the chemical state of the detected elements, such as the binding forms of phosphorus in phosphates, and thus allows to characterize the impregnation of the core material after chemical modification. It also allows to clarify whether the C is related to adventitious carbon from atmosphere or to organic contaminants. For the ID cards, the XPS data are only provided in percentages of atomic composition, but the high resolution spectra must also be considered to validate the codification of the chemistry in each card [6].

Auger Electron Spectroscopy (AES) is based on the irradiation with a high-energy electron beam, resulting in surface atomic excitation and emission of Auger electrons, whose kinetic energies are characteristic of the surface elements. AES is less accurate than XPS, but it can analyze very small areas of less than 10nm in diameter: it is ideal for checking surface chemical homogeneity, using several repetitive analyses on a peak and in a valley within a rugged microtopography. Coupled with an ion sputter source, AES can perform a quick and accurate in-depth chemical composition profiling of the external surface layer, particularly the first 100nm [4]. It is thus particularly useful to characterize a nanometric coating or an impregnation on/in a core material, to identify specific core materials such as grade 5 Ti-6Al-4V titanium alloy (where the percentages of aluminium quickly reach almost 10% of the total composition), or to evaluate (in combination with XPS) the TiO₂ layer thickness (micrometric layer for anodized surfaces, around 5-10nm thin native layer for most other surfaces). Two in-depth profiles are often enough to check a sample. Due to the very small size of the AES analysis spot, the chemical composition observed in the AES profile may not be exactly the same than with XPS; some elements indeed presenting a heterogeneous distribution on the microtopography (for example alumina blasting residues or fluoride acid-etching residues) are detected through the wide XPS analysis but may be outside of the AES beam [6]. This is

part of the homogeneity check.

In the cases of implants coated with thick layers of calcium phosphates or hydroxyapatite, the use of AES analysis is not suitable, as the AES electron beam provokes a strong charging effect on these materials that alters significantly the results. In these cases, the in-depth analysis of the chemical composition of the external surface layer can be done through the use of XPS/ESCA, coupled with an ion sputter source to establish the in-depth chemical profile down to 100nm. This method allows a more accurate evaluation of the chemical composition than AES, but it is more time-consuming and does not allow an accurate homogeneity check (because of the large size of the analysis area with XPS, not less than 100µm in diameter).

Energy Dispersive X-ray Spectroscopy (EDX) is a simple elemental analysis coupled to the morphology evaluation by Scanning Electron Microscope (SEM). The irradiation by the SEM electron beam indeed results in X-Ray emission with characteristic energies of the surface elements. EDX allows to determine the elemental composition of specific points down to the nanometer scale and thus to identify particles or structures observed during the morphology evaluation. It is therefore a complementary instrument only [1].

A wide range of tools can be used to perform a chemical analysis of a surface, for example Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS), Raman Spectroscopy, or even Transmission Electron Microscopy (TEM) after Focused Ion Beam (FIB) cross sectioning of a sample. However, most of these techniques require a high degree of calibration to get relevant quantitative data, and do not truly fit to the requirements of osseointegrated surface standardized evaluation.

5. Characterization of the morphology at the micro- and nanoscale

The osseointegration performance of a surface is influenced by its topography on the micrometric and nanometric levels following two respective different biological mechanisms. Both levels should be characterized separately [1].

5.1. Microtopography

At the micrometer scale, the topography can increase the bone/implant contact surface and biomechanical interlocking. It has also a direct impact on the cell and tissue behavior in contact with the surface.

Microstructures can be differentiated by their number of dimensions. Microrough surfaces have one micrometric dimension (the peak heights). Micropatterns have two micrometric dimensions (dimensions of the repetitive pattern), like the micropores created by anodization. Microparticles have three micrometric dimensions [1].

A topography is characterized by a succession of peaks and valleys. In order to quantify the microtopography, several quantitative parameters have been used for 2D profile (Ra, Roughness average) or 3D area evaluation. Currently 3D area evaluation is considered to be more reliable than 2D profile evaluation, and the ISIS system selected particularly 2 parameters to quantify and classify the microtopography: Sa and Sdr%. Sa is an amplitude parameter, i.e. the Surface average height deviation amplitude of the microtopography, calculated on 2D standards extended to 3 dimensions (surface roughness average). Sdr% is a hybrid parameter integrating both the number and height of peaks of the microtopography on a determined surface, and expressing the spatial density. Sdr% is calculated as the developed interfacial area ratio and expresses the increment of the interfacial surface area

relative to a flat plane baseline. For a totally flat surface, $Sdr = 0\%$. When $Sdr = 100\%$, it means that the roughness of a surface doubled its developed area. The Sa is an important and frequent parameter for the comparison of surfaces and was already used in other classifications [13].

The Sa and $Sdr\%$ values allow to classify the microtopography, following the terminology developed in the ISIS system. The morphology mean height deviation amplitude (based on Sa) of a surface area can be defined as Smooth (Sa between 0 and $0.5\mu\text{m}$), Minimal (Sa between 0.5 and $1\mu\text{m}$), Moderate (Sa between 1 and $2\mu\text{m}$) or Maximal ($Sa > 2\mu\text{m}$).

The spatial density morphological aspect (based on the developed area ratio $Sdr\%$) of a surface area can be defined as Flat ($Sdr\%$ between 0 and 50%), Flattened out ($Sdr\%$ between 50 and 100%), Rugged ($Sdr\%$ between 100 and 200%), Rugged extra ($Sdr\% > 200\%$). The final terminology used in the **Table** and in this series of articles presents some minor updates in comparison to the 2 first articles that developed this system [1,6], due to the feedback of experience.

5.2. Nanotopography

At the nanometer scale, the topography influences the surface energy. A significant nanotexturization provides a strong surface energy that increases the wettability to blood and the spreading and binding of fibrin and matrix proteins on the surface. It favours cell attachment and tissue healing [15], particularly just after implantation at the critical moment of the osseointegration process. Specific nanotextures may even directly influence cell proliferation and differentiation [16], and the modulation of cell behavior by specific nanopatterning of surfaces is currently advocated [8,17,18].

Per definition, all surfaces have a nanotopography, i.e. a topography at the nanoscale; however only a few present repetitive and significant nanofeatures/nanostructures, while the majority are smooth on the nanoscale and have therefore no specific properties related to their nanotopography. Companies may therefore play on words with the term « nano » and the understanding of this clear terminology is important [14].

A nanostructure is an object of intermediate size between molecular and microscopic (micrometer-sized) structures, and defined between 1 Angström (0.1nm) and 100nm . In describing nanostructures, the number of dimensions on the nanoscale must be differentiated. Nanorough surfaces have one dimension on the nanoscale, i.e. the peak height of the repetitive and homogeneous texture is nanometric. Nanopatterns have two dimensions on the nanoscale, i.e. the diameter of the repetitive pattern is nanometric (for example, chemically-carved nanopatterns or nanotubes by anodization). Nanoparticles have three dimensions on the nanoscale, i.e. the particle is nanometric in each spatial dimension. When a surface presents no repetitive and significant nanostructures (insignificant texture, no pattern, no particle), it should be considered as nanosmooth [1].

The characterization of the nanotopography remains difficult to standardize in a quantitative way, due to the physical limits of instruments, and it is mostly based on the observation of the morphology [6].

5.3. Global architecture

To complete the characterization, some specific morphological characteristics must be considered. First, the fractal or non fractal nature of a surface can be determined following

the previously suggested definitions [7]. Natural fractals are repetitive patterns self-similar across a finite range of scales. When the same type of homogeneous modification is observed on the micro-, nano- and chemical scale, then a surface can be considered as a fractal ensemble. For example, a microrough (1 dimension), nanorough (1 dimension) and CaP impregnated (1 dimension) surface is a common example of fractal architecture.

Second, the homogeneity or heterogeneity of a surface can be evaluated through the synthesis of all the morphological and chemical analyses; a homogeneous surface must present a similar micro- and nanotopography and chemical composition/profile all over the surface. Finally, general microfeatures like cracks (local and extended) or random particles (like TiO₂ or Al₂O₃ particles) on the surface should be reported as well [6].

5.4. Method of characterization

The morphological characteristics of the surfaces can be evaluated using the combination of 2 techniques of investigation.

Scanning Electron Microscopy (SEM) performs a surface mapping using a focused electron beam reflecting across a surface. It is the gold standard for morphology characterization at the micrometer level (SEM with tungsten source)[4]. FE-SEM (Field Emission-SEM) is required to increase the analytical resolution, and to observe and characterize the nanotopography and nanostructures [14]. FE-SEM is also needed to analyze surfaces with strong CaP coating or impregnation, to avoid the risk of surface charging effect. Coupled to an auxiliary EDX detector, this technique also offers an efficient elemental identification of the observed structures. Coupled with a metrology stereologic software to produce 3D reconstructions of the surface (stereo SEM), this instrument allows to perform a quantitative morphology analysis, both at the micrometer and the nanometer level [5]. All the areas of the implants should be carefully examined with FE-SEM, from the macroscale to the nanoscale. This examination allows to highlight the various morphological characteristics of the surfaces at the microscale (rough, porous, particled, cracks, blasting residues, homogeneity) and to characterize the nanotopography of each sample (nanosmooth, nanorough, nanopatterned or nanoparticled)[6].

Optical Profilometer (OP) performs an accurate surface mapping using the interferences of light beams. It is an efficient tool for the evaluation of the microtopography quantitative parameters (particularly Sa and Sdr%) on wide areas, typically 230x230µm or 200x260µm [6]. OP is not suitable for a quantitative evaluation of the nanotopography (even with recent optimized devices), because in dental implant surfaces the nanotopography is hidden in the shadow of the microtopography (leading to uncontrollable artifacts). Several guidelines have been suggested to make an accurate quantification of the microtopography [13,19], particularly when implant surfaces are not homogeneous all along, such as mean values after evaluation of the top, valley and flank of 3 successive threads or mean values after repetitive measurements on 3 flat areas [6]. In the ISIS, three spots of analysis are selected on the flat cutting edge (or similar area in the lower part) of the implant and the corrected mean values calculated on these large areas are placed as reference values in each ID card. Another spot of analysis is selected in the middle of the implant between threads to serve as a control value for homogeneity check. Based on the feedback of experience and the comparison of the various methods [6], this protocol appeared easy and accurate enough to evaluate the Sa and Sdr% mean values and classify the various surfaces between each other within a standardized system.

6. Construction of an ISIS Identification ID card

Once all the previous analyses have been performed to characterize an implant surface, the exact ISIS profile and code can be defined through the filling of the ID card (**Figure 1**). The construction of an ID card is done in 6 experimental steps:

1/ Name of surface and sample, number of reference and batch are reported in the upper left part of the ID card. Each batch - and sometimes each sample - may present different chemical and morphological characteristics when the industrial processes are not fully controlled, and the detailed identification of the product is very important.

2/ The chemical composition of the superficial layer is evaluated through XPS/ESCA on a wide analysis area (100 μ m diameter) located between the second and third threads of each sample, and the percentages of atomic elements are reported in the table in the upper left part of the ID card. The elements and values that differ significantly from the classical chemical composition of a titanium-based implant are placed in bold font.

3/ The in-depth chemical profile of the surface is evaluated through AES down to 100nm on a very small analysis area (30nm in diameter) located in the middle of the cutting edge flat area (or an equivalent flat part, depending on the implant macrodesign) of each implant. Two in-depth profiles are established per sample, respectively on a peak and in a valley of the surface microtopography. One in-depth profile graph (peak) is reported in the upper right part of the ID card. In HA or CaP coated surfaces, the in-depth profile is evaluated through XPS/ESCA down to 100nm on a larger area (100 μ m diameter).

4/ The microtopography is evaluated with FE-SEM and OP. A first FE-SEM x1000 magnification picture is placed in the lower left part of the ID card, to illustrate the general aspect of the microtopography of each surface (it replaced the interferometer three-dimensional reconstruction picture used in the early version of the ISIS system)[6]. The Sa and Sdr% mean values (and standard deviation) are evaluated through 3 OP measurements (+ 1 for control homogeneity check) and placed as reference values in the corner of this first FE-SEM picture.

5/ A second FE-SEM x5000 magnification picture is placed in the lower right part of the ID card, to illustrate in more details the morphological characteristics of the surfaces (micropores, cracks, blasting residues for example). Finally, a FE-SEM x100,000 magnification picture is added to show the nanotopography of each surface, a small picture if nanosmooth and a wider picture if some nanopatterns or nanoroughness can be observed.

6/ Finally, the characterization codification table can be filled based on the gathered experimental data: identification of the name and company of the surface, definition of the core material, description of the various chemical modifications if available, description of the microtopographical characteristics, description of the nanotopography, description of the global architecture. A final ISIS characterization code can be spelled, and eventually serves as an identifier for a database comparison.

The various experiments can be doubled or tripled to ensure reproducibility, but the feedback of experience allows to consider that a limited quantity of analyses per sample is enough (1 XPS, 2AES in-depth profiles, 3+1 OP, 1 FE-SEM) in most cases.

Identification card of the surface, following the Implant Surface Identification Standard (ISIS) codification							
Name: (Ref: ; Batch:) XPS/ESCA Surface chemical composition (%)			AES AES (or XPS) in-depth profile graph				
Ti	%					%	
O	%					%	
C	%					%	
N	%		%				
OP: Sa: () Sdr%: ()			FESEM x1000				
FESEM general overview of the microtopography <div style="text-align: right;">50µm</div>			<div style="display: flex; justify-content: space-between;"> <div style="border: 1px solid black; padding: 5px;"> FESEM overview of the nanotopography 200nm x100000 </div> <div style="text-align: right;"> FESEM detailed overview of the microtopography 10µm </div> </div>				
Surface	Core Material (Core)	Modification (Mod)	Microtopography (Micro)	Nanotopography (Nano)	Global Architecture (Archi)		
	Core.	Mod.	Micro.	Nano.	Archi.		
ISIS () = Core. / Mod. / Micro. / Nano. / Archi.							

Figure 1. Construction of an ISIS Identification ID Card. Blank model. The card gathers the main information collected during surface analysis following the ISIS protocol and format: identification of the sample, XPS/ESCA superficial chemical composition (table in the upper left part), AES (or XPS) in-depth chemical profile (graph in the upper right part), FESEM general morphology overview and Optical Profilometry (OP) quantification of the microtopography (in the lower left part), FESEM detailed microtopography and nanotopography overview (in the lower right part). Finally, all data are synthesized in the table at the bottom, and a specific ISIS characterization code can be spelled.

7. Objectives and perspectives of the ISIS system

The ISIS protocol was developed to serve industrial, experimental, communication and health policy objectives [6].

The first objective of ISIS was to offer to manufacturers a simple a clear method to characterize the surface chemistry and topography of their products and check the homogeneity and quality of their production [3]. ISIS is therefore an industrial standard.

The second objective of ISIS was to offer to scientists a standardized terminology and method to characterize and isolate more clearly the chemical and morphological parameters of the implant surfaces they are developing and testing in their experiments [1]. Indeed, many studies are comparing the implant surfaces and their biological performances without the complete characterization of the tested samples; this frequent situation explains the lack

of coherence and clarity of the scientific literature on this topic, where many articles are difficult to sort, interpret and compare [20]. In fact, there is a lack of consensus on the terminology and some ignorance in the way to characterize the surfaces. The surface morphology on the microscale is commonly evaluated, but the methods of quantification of the microtopography remain largely debated, as the data are relatively dependent on the selected instruments and protocols [13]. Moreover, the characterization of surface chemistry (with well-known instruments like XPS/ESCA and AES) and of the nanotopography (with FE-SEM), for experimental surfaces or commercially available products, remains often neglected and even quite scarce in the literature, even if it started to change in the last years [4]. The ISIS protocol offers therefore a complete and homogeneous approach to fill these gaps. Finally, the ISIS terminology and codification offer another advantage, as the ISIS characterization code can serve as an identifier in a database, to allow easier comparison between studies. If the system of characterization code identifier was fully extended, it should be possible to make relevant correspondences within the large literature, for a better understanding and interpretation of the published results [6,12]. The ISIS system appears as a useful instrument to help scientists to clarify the link between surfaces characteristics and osseointegration performances. ISIS is therefore also an experimental standard.

The third objective of ISIS was to offer to implant users a reader-friendly document describing and certifying the main features of the implant surfaces they may take the responsibility to use in their patients [6], following a standardized protocol for the description and control of commercially available products. Indeed, implant users (the dental practitioners) have no clear independent information about the products they use: the scientific literature and the commercial document from the companies do not offer reader-friendly, accurate and controlled information. This contradictory situation of responsibility of the user towards his patients versus absence of information about the implant raises significant concerns, particularly as the surface design is a key of the biocompatibility of an implantable device. ISIS offers the possibility to deliver up to date information to the implant user, in a format that all professionals can easily learn to read. However, to guarantee the credibility and validity of the data, the surface analyses and the establishment of these ID cards following the ISIS protocol should always be organized by independent laboratories (to avoid conflict of interest), and repeated frequently within the various references and batches of a production. ISIS is therefore also a communication standard between implant manufacturers and users.

The fourth objective of ISIS was to offer to health administrations a standardized procedure for the description and control of commercial products. Each national administration uses nowadays different standards for the registration of implantable materials, and many of them may request specific analyses to grant access to a company to their national market. In the case of dental implant surfaces, there is actually a lack of control and most administrative steps are based on the demonstration that a new implant is « substantially equivalent » to previously registered similar implants [3]. The reason of this incomplete control is mostly related to the lack of standard method and consensus on the way to characterize and control the commercial products [20]. The ISIS therefore allows to national administrations to get clear, certified and understandable information about a product prior to granting the access to a market, but it also allows to all administrations worldwide to communicate between each other and reach similar high standards of control and quality [6]. The ISIS system is of particular interest nowadays, as the globalization of production and market created new unexpected challenges of health policy: many implants

are produced in unknown conditions in different countries with different regulations, and are often marketed without any serious control. This situation raises significant public health concerns, and requires to develop a simple procedure for an efficient and accurate control. The use of the ISIS system also implies to develop a network of certified independent laboratories equipped and trained to perform these analyses in proper conditions and establish the ID cards of the samples, particularly as these analyses should be repeated frequently on the various references and batches of a production, to offer the guaranty of a regular and efficient control to the responsible administrations. The ISIS system could therefore take the form of an ISO characterization standard, so that this format could be standardized and accepted by all administrations worldwide. ISIS is therefore also a health policy administrative standard.

The ISIS system offers thus solutions and perspectives for all actors of the field: manufacturers, scientists, users and administrations. It also highlights many transversal questions, significant for all actors, concerning the exact identification of products. First, even if dental implants are supposed to be carefully manufactured, many implants are not homogeneous [6]. This lack of homogeneity can be related to the nature of the production process itself or to the presence of many contaminants. When surfaces are very heterogeneous, they present different chemical and/or morphological characteristics and a different ISIS code depending on the area of analysis. Therefore an implant may present in fact different surfaces along, and implants of the same batch may also be very different. However, the administrative authorizations are given for one specific product, and the industrial production under an administrative approval is supposed to be homogeneous. Homogeneity is in fact expected by all actors of the field as a normal characteristic, while this is frequently not the case. Second, it is also frequent to observe evolutions of the surface characteristics of an implant reference year after year. The companies often change - voluntarily or not - their surface production, for example while trying to improve the surface cleaning or implant design. However, even if the surfaces may change significantly, the administrative authorizations are not reevaluated, and the administrative authorities are in fact never informed of the significant evolutions of the products during years. These problems of heterogeneity and undisclosed/uncontrolled evolution of surfaces are major concerns for all actors in the field (quality control of manufacturers, scientists testing the products, customers using the products in confidence, administrations in charge of the control for public health protection), and raise serious legal issues that should be considered in the future.

The ISIS system highlights another question about the exact identification of a surface: many surfaces are not clearly named (and trademarked) by the companies [6], as if the surfaces were not important and specific characteristics of the implant. This detail of form in fact reveals a much larger problem of identification, where surfaces process and characteristics are not clearly defined by the manufacturer, and therefore frequently evolving without notification [3]. For clarity and public health reasons, all surfaces should be clearly named. If different versions of the surface exist, the name could easily evolve like in most other industries (for example with a 1.0, 2.0, 2.1, etc. marking). From an industrial and legal standpoint, each surface should be ideally well defined and characterized, under a specific name referring to a specific surface. Evolutions of the regulations are unavoidable in the future, and the ISIS system may serve as a simple standard protocol and terminology to support it.

Finally, the ISIS system presents some limitations, like all systems of standardization and simplification. The ID card gathers all the key information and is enough to define and

compare surfaces, but the data in each card are obviously not exhaustive. For example, the chemical analysis methods and results (AES, XPS/ESCA) are accurate, but results are always difficult to interpret without the detailed spectrometric graphs and the ability to read them in details [4]. This is therefore the role of the scientist establishing the ID card to make a correct synthesis of the raw data. Moreover, the OP mean values are also dependent on the methodology (measuring equipment, filtering technique)[13], and the surface morphology evaluation is dependent on the instruments and terminology. Therefore, the use of the ISIS system implies to have well-equipped and trained independent laboratories and teams, able to develop their own practical reference database and experience, to perform the analyses in adequate conditions and also to translate the raw data and observations into the ISIS reader-friendly standardized format.

8. Conclusions

The ISIS system was developed to establish a complete and polyvalent standard for the characterization of implant surfaces, covering the industrial, experimental, communication and health policy administrative needs of all the actors of the field: manufacturers, scientists, users and administrations. The ISIS ID cards present a great practical interest, as it allows to gather the main characteristics of commercially available surfaces in a reader-friendly document. In this first article, the content of the system and terminology was defined and explained, and the following 4 articles of this series are the application and illustration of this system on a wide series of implant surfaces available on the market. This system remains flexible and adaptable to new technological evolutions. The ISIS system could be an interesting basis for the development of a clear and simple ISO standard for dental implant surfaces, but also for other implants such as orthopedic implantable devices.

Disclosure of interests

Like most specialists in the implant surface field of research, the authors of this article are currently involved in experimental studies with various dental implant companies. This codification article thus does not give qualitative opinions and is strictly founded on physical and chemical definitions, in order to avoid any subconscious conflict of interest. Moreover, the chemical values (XPS/AES) and the morphological data shown in the ID cards were double-checked by independent laboratories. This work has not been supported by grants from any commercial companies.

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