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A review of modified DLC coatings for biological applications

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Abstract

Diamond-like carbon (DLC), also known as amorphous hydrogenated carbon (a-C:H), is a class of materials with excellent mechanical, tribological and biological properties. By the addition of other elements into the DLC all of these properties can be changed within a certain range. It will be shown that the ratios of the different proteins adsorbed on the surface can be influenced by the addition of different elements into the DLC film. These proteins will then subsequently influence cell attachment, cell proliferation and cell differentiation. Certain toxic elements such as Cu, Ag, V, embedded in the DLC will, when exposed to a biological media, be released and cause toxic reactions. This allows the preparation of surfaces with a tunable antibacterial effect. DLC has proven its outstanding tribological properties in many technical applications due to the transformation of DLC into graphite (a solid lubricant) and the build up of a transfer layer on the counterpart. However, it is questionable if this effect takes place in artificial joints. Contradicting results on DLC coated hip joints are found in the literature, some indicating an improvement and some a change for the worse. DLC coatings have an excellent haemocompatibility, which is expressed in a decreased thrombus formation. When exposed to blood, an increased ratio of albumin to fibrinogen adsorption as well as decreased platelet activation is observed on coated surfaces. DLC coated cardiovascular implants such as artificial heart valves and stents are already commercially available.

Keywords: Amorphous hydrogenated carbon; Diamond-like carbon; Biomaterials; Biomedical applications

1. Introduction

The implantation of biomaterials into the human body allows it to re-establish biological and mechanical functions and therefore to increase the quality of life. Depending on the biomedical application, the implant has to withstand dynamical mechanical loads and has also to perform a desired long-term biological interaction with the surrounding biological tissue. The load bearing properties of the implants are mainly controlled by the bulk properties of the implant whereas the interaction with the surrounding tissue is governed by the implant surface. The implant surface influences in particular the interaction and adsorption of different proteins which, in turn, control the cell adhesion and behavior. However, the overall reaction of the body on an implant is a system property that includes many different aspects, such as surface chemistry and texture, implant movement, biodegradation and surgical aspects. The highly corrosive environment and the low tolerance of the body to some dissolution products restrict the materials to be used for implants. These are alloys based on titanium, iron (surgical steel), cobalt, chromium, nickel (may cause allergies), zirconium, tantalum, the noble metals and carbon in its different forms, as well as ceramics such as alumina and zirconia. Additionally different polymers such as PTFE (Teflon), PEEK (polyetheretherketone) and polyethylene are also used for implants.

When coating an implant, the bioreactions at the implant surface and the functional properties (load bearing capacity, wear, corrosion, etc.), can be optimized separately for the workpiece and for the surface. To create a surface for desired bioreactions, a promising approach is to start from an existing biocompatible coating (to prevent inflammatory reaction or repulsion) and to alloy it with adequate elements. Additionally, it has to be considered that the bioreactions and the in-vivo behavior of an implant are influenced also by the surface texture as described by Boyan [1]. Due to its bio- and haemocompatible nature [2,3], there is a growing interest in the application of DLC on orthopedic and other implants [4]. Additionally, DLC is an excellent

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base coating to be alloyed with different elements. The amorphous nature of DLC opens the possibility to introduce certain amounts of additional elements, such as Si, F, N, O, W, V, Co, Mo, Ti and their combinations, into the film and still maintain the amorphous phase of the coating. By this technique, different film properties such as tribological properties, electrical conductivity, surface energy and biological reactions of cells in contact with the surface can be continuously adapted to a desired value. Today, two main fields of biological applications of DLC can be seen: the application of DLC in blood contacting implants such as heart valves and stents; and the use of DLC to reduce wear in load bearing joints. However, whereas DLC coated heart valves and stents are already commercially available, the situation for DLC coated load bearing implants is contradicting. For an introduction to DLC see the review articles by Robertson [5–7] and Butter and Lettington [8,9].

2. Cells in contact with DLC and alloyed DLC

Several different research groups confirmed the biocompatibility of DLC by growing different cell types in-vitro on DLC and studying the cell response. Macrophages, fibroblasts, human myeloblastic ML-1, human embryo kidney 293 cells and other cell types have been grown on DLC under different conditions and cell responses such as proliferation rate, viability, cell adhesion, differentiation, cell morphology and cytoskeletal architecture have been monitored [10–12]. In-vitro experiments as well as the in-vivo reaction of DLC coated CoCr cylinders, implanted for 90 days in the lateral femoral cortex of sheep, showed that the DLC coated surfaces are well tolerated by the body [13]. Mohanty et al. [14] confirmed the biocompatibility on DLC coated Ti samples which stayed in the skeletal muscle of rabbits for up to 1 year. An overview on the reaction of different cells on DLC can be found in review articles [8,15,16].

The biological behavior of an implant is strongly influenced by the chemical situation present at the implant surface. Therefore, bioreactions can be tuned by tuning the surface chemistry of an implant, especially the elemental composition, to create a specific surface yielding a defined biological response. This can be done by alloying or by surface treatments, for example plasma exposure, ion implantation, or chemical attachment of specific molecules. DLC as a biocompatible base material can be easily alloyed with other biocompatible materials such as titanium as well as with toxic materials such as silver, copper and vanadium. By varying alloy element concentration, it should be possible to tailor the bioreactions to any desired point between the bioproperties of DLC and those of the added element. In the last years, only a few papers present experiments where bioreactions on DLC have been changed by alloying [17–23].

In [17], the addition of SiO_x to DLC reduced the induction of inflammatory reactions, as described below in Section 3. Similarly, some companies (Sulzer CarboMedics and St Jude Medical) use silicon-alloyed pyrolytic carbons (Pyrolite®), a material that proved to be resistant to clotting, also indicating an improved biocompatibility by the addition of Si. Dorner-Reisel et al. [18] demonstrated that the addition of Ca-O to DLC decreased the film hardness, the wetting angle and the fraction of sp^3/sp^2 bonded carbon. Cell tests with mouse fibroblast showed, with respect to the pure DLC, an increased number of cells and an improved cell viability for the Ca-O-DLC films. Which one of the changed film properties had the main contribution for the improved cell behavior was not determined. A correlation of the number of adhering blood platelets, which influences the blood compatibility of a surface, with the ratio of the Raman D/G band signals, which depends on the fraction of sp^3/sp^2 bonded carbon, is shown in Ref. [24].

For applications where no cells or bacteria should attach to a surface, such as catheters, sensors and temporary implants, surfaces that inhibit cell proliferation and differentiation are required. DLC films containing different amounts of the cytotoxic elements silver, copper, or vanadium can be made by standard DLC deposition and simultaneously magnetron sputtering of copper, silver or vanadium. When such films are exposed to biological media, the metallic element is, within days or weeks, slowly released out of the film causing adverse reactions in the cells attached to the surface. By this approach, cytotoxic reaction as well as cell differentiation can be continuously tuned between the bioreactions on the pure metals and the biocompatible behavior of DLC. Above the surface a sufficient concentration of the toxic element has to be obtained to prevent cell growth. The toxic elements will then usually be distributed in the body and the total amount of the toxic element released has to be well tolerated by the body. As an example, the total number of cells, taking the total amount of DNA in BMC (bone marrow cells) cultures after 14 days in-vitro as an index, is displayed in Fig. 1a [23]. With increasing silver content, an increasing tendency of BMC cells to differentiate into osteoclast (bone resorbing cells) cells was determined by the TRAP (tartrate resistant acid phosphatase)/DNA ratio as can be seen in Fig. 1b. Similar effects were also obtained by copper containing DLC [23] and vanadium containing DLC [20].

DLC samples containing different amounts of titanium have been examined in vitro to obtain a biocompatible surface which is in addition hard in order to prevent abrasion and scratching and which is additionally enhancing bone in-growth. When Ti-DLC is exposed to

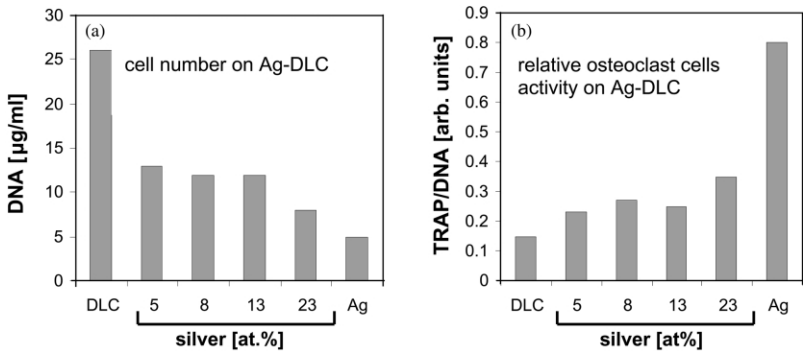

Fig. 1. (a) Number of BMC cells monitored by the total amount of DNA and (b) relative osteoclast activity after 14 days in vitro for Ag-DLC films containing different amounts of silver.

a biological environment, the adsorption of different proteins was altered as a function of the Ti content in the DLC film [21,23]. The adsorbed proteins will subsequently influence cell attachment, cell proliferation and cell differentiation. Bone marrow cells culture experiments on these Ti-DLC coatings demonstrated that the differentiation of bone marrow cells into bone resorbing cells, i.e. osteoclasts, is inhibited by the addition of Ti into the DLC, making Ti-DLC a valuable hard coating for implants requiring improved fixation by improved osseointegration [19,20].

When introducing a coating into the body, the beneficial properties of the coating have to be weighted in against the unknown long-term behavior and danger of delamination. Materials that are well tolerated in bulk form are able to induce toxic reactions if present in particulate form. To investigate the bioreactions induced by DLC particles, bone marrow cell cultures have been incubated in vitro with particles from a deliberately delaminated approximately 500-nm thick DLC film. The cells were able to internalize most of the particles within a few days and the appearance of the cells after 7 days was not different from the control cultures with no particles. Furthermore, the addition of particles did not have any effect on the lysosomal activity of the cells nor on the proliferation or differentiation, indicating that no toxic or inflammatory reaction of the body to delaminated DLC particles may be expected [23,25].

3. Blood contacting applications

For implants in direct contact with blood, a key issue is the ability of the implant surface to prevent thrombus formation. The reactions of the body to a blood contacting implant crucially depends on the surface of the implant, especially the chemical situation present at the surface, the surface texture, the local flow conditions as well as other factors. It is generally known, that increased platelet adhesion, activation and aggregation on implant surfaces exposed to blood precede the formation of a thrombus. Therefore, in vitro analysis of these properties is usually performed as a first test of the haemocompatibility of a surface. Additionally, the platelet morphology (circularity and area) can be taken as an indication of the ability of the surface to support thrombus formation. A high ratio of the proteins albumin/fibrinogen, adsorbed on a implant surface prior to cell or platelet attachment, can be correlated with a low number of adhering platelets and therefore with low tendency of thrombus formation. However, some materials may show contradicting results between the in vitro experiments described above and the in vivo behavior, as shown in Weisenberg and Mooradian [26] for polyurethane and parylene. Several papers of in vitro essays on DLC surfaces indicate that this material may have the ability to suppress thrombus formation similar or even better than glassy carbon, a material widely used for heart valves. An introduction to DLC coatings and plasma surface treatment of mechanical heart valves is given in the review article by Tran et al. [27].

Using whole human blood and a parallel plate flow chamber, Krishnan et al. [28] showed that the adherence of platelets depends on the shear rates that the material is exposed to. Compared to a Ti surface, the platelet adhesion is reduced on DLC. In vitro experiments by Jones et al. [29,30] showed that the DLC surfaces expressed a decreased area coverage of platelets compared to titanium, TiN and TiC. Whereas on the Ti containing surface platelet activation, clotting of platelets and thrombus formation was observed, no such reaction took place on the DLC surface.

A higher ratio of albumin/fibrinogen adsorption was observed on the DLC surfaces, compared to Ti, TiN and TiC which is an indication of the ability of DLC to prevent thrombus formation [29]. A higher albumin/fibrinogen ratio was also observed on DLC compared to silicone (a polymer widely used for implants) by Dion et al. [31]. Cui and Li state in their review article [15] a good tissue- and blood-compatibility for DLC and amorphous CN films from in vitro experiments,

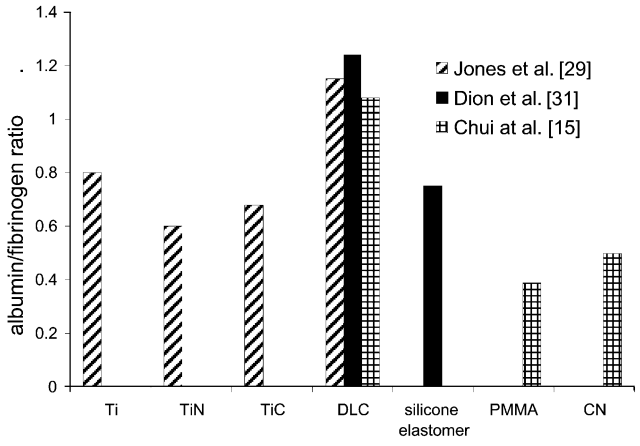

Fig. 2. Albumin/fibrinogen ratio for different surfaces. Data from Cui and Li [15], Jones et al. [29] and Dion et al. [31].

with DLC also showing a high albumin/fibrinogen ratio. The albumin/fibrinogen ratios from the different research groups are summarized in Fig. 2. It can be seen that DLC has the best albumin/fibrinogen ratio among all the materials tested.

Gutensohn et al. [32] analyzed the intensity of the platelet activation antigens CD62p and CD63. In their in vitro experiment they showed that the DLC coating of a 316L stainless steel coronary artery stents resulted in a decrease of the CD62p and CD63 antigens indicating a low platelet activation on DLC and, therefore, a low tendency for thrombus formation. Additionally, they showed the metal ion release from the stainless steel stents, which may negatively influence the haemocompatibility of a surface, could be suppressed by the DLC coating. Similarly, the ability of DLC to have a low percentage of platelets adhering to the surface was shown by Alanazi et al. [33] in an in vitro experiment using a flow chamber and whole human blood. However, the results obtained varied with the deposition conditions used for the DLC production. Analogous results can be found in many other papers, confirming that DLC and also ta-C have a good biocompatibility and lower number of adhering platelets compared to pyrolytic carbon, Ti, 316L stainless steel and other implant materials [8,34–36].

Only a few papers present in vivo results of DLC coated implants. Scheerder et al. [17] report on DLC and DLN or Dylyn™ (diamond like nanocomposite) coated stainless steel stents, which were implanted into pigs for 6 weeks. The DLN or Dylyn™ coatings were produced by Bekeart, Belgium from siloxane precursors. In Neerinck et al. [37], Dylyn™ is described as a Si:O containing DLC where the Si atoms are present as SiO_x in different oxidation states and also as SiC. Their histopathologycal observation on the explanted stents showed a decreased thrombus formation for the DLC and the DLN coated stents compared to the uncoated stents. However, the inflammatory reactions, monitored by the number of inflammatory cells on the stent surface, were significantly higher on DLC than on DLN [17]. If the addition of Si:O to DLC generally results in a reduced inflammatory reaction and therefore an increased biocompatibility of DLC should be further investigated. In his Ph.D thesis [38] Yang studied the haemocompatibility of different surfaces implanted for 2 h into the intrathoracic venae cavae of Swedish native sheep. The results showed that there was significantly more thrombus on pyrolytic carbon and methylated titanium than on titanium, cobalt-chromium [39] and DLC [38]. The lowest coverage of thrombus was obtained for a TiN coated sample [38]. The diamond like coating center in UK reports on their home page on DLC coatings in a blood flow accelerator. They showed, by in vivo experiments, that on an uncoated device significant thrombus deposits occur, both on the accelerator device and artery wall, whereas an inhibition of thrombus formation and platelet deposition was observed in the DLC coated device. A DLC coated centrifugal ventricular blood pump device (made by SunMedical Technology Research Corporation, Nagano, Japan) coated with DLC was implanted in calves and, even without post-operative anticoagulation, only minor evidence of thrombosis was found on the DLC coated surfaces after explantation [40,41].

Due to the good haemocompatibility of DLC, a few companies have DLC coated implants already commercially available or in the state of development. The Cardio Carbon Company Limited states that it has the following two DLC coated titanium implants under development or in clinical trials. An ‘Angelini Laminaflo’ mechanical heart valve and an ‘Angelini Valvuloplasty’ ring which is used for heart valve repairs. The ring is sutured round the valve orifice to reshape it and to retain the natural functions and structure of the valve. The company Sorin Biomedica produces heart valves and stents which are coated by approximately 0.5-μm thick Carbofilm™. This coating is produced by PVD from a carbon target and the company states that Carbofilm™ has a turbostratic structure equivalent to that of pyrolytic carbon. A clinical study on coated stents, implanted in 122 patients, resulted in a low restenosis rate of 11% after 6 months [42]. The company PHYTIS sells DLC coated stents on which they report a reduced rate of restenosis due to the DLC coating and that target revascularisation has been necessary in only 3.27% of the lesions treated. Probably, none of the worldwide key players in commercial production of heart valves and stents is selling DLC coated implants up to now. However, in recent years, drug-eluting stents have become the main area of interest and showed a large potential in preventing restenosis, see for example the overview article by Garas et al. [43].

4. Hip Joints and load bearing implants

In prosthetic hip replacements, polyethylene wear debris is identified as the main factor limiting the lifetime of the implants. Especially debris from the joint can induce tissue reactions and bone resorption that may lead to the implant loosening. An overview of different materials and surface-treatments used in bearing surfaces in human joint replacements was published in 1999 by Dearnley [44].

It is known that DLC shows a low wear and also low friction coefficients between 0.05 and 0.2 in atmosphere against most materials except some polymers. DLC, in some cases also modified by alloying with different elements, has, due to its outstanding properties, been studied extensively as a tribological coating as described in the review articles by Grill [45,48], Donnet [46] and Gangopadhyay [47] and is also established in several industrial applications [49–52]. Under tribological conditions, usually the softer of the two materials will be worn. In the case of DLC, the situation may be different since the wear of DLC, which has a graphitic nature, can be deposited onto the partner surface forming the so-called transfer layer. Then DLC slides against its own transfer layer and, although it is the harder surface, only DLC is worn at a very low wear rate, whereas the softer partner surface will not be worn. However, it is questionable if this situation is also present in an in vivo joint where body fluids are capable of removing the wear products out of the tribological contact area. Due to its excellent biocompatibility and it's low wear and friction, DLC was a promising candidate, tested as a coating in orthopedic applications by several research groups.

There are many papers reporting on experiments using a hip simulator to determine friction and wear of DLC coated hip joint balls sliding against UHMWPE (ultra high molecular weight polyethylene) or of metal/metal joints with both sides coated with DLC. Tiainen [53] as well as Lappalainen et al. [54] reports that hydrogen free DLC, also named tetrahedral amorphous carbon (ta-C), coated metal hip joint balls tested in 1 wt.% NaCl water by pin-on-disk and in a hip joint simulator reduce the wear of the UHMWPE cup by a factor of 10–100. In the case of a metal/metal joint with both sides coated, the wear could be reduced by a factor of 10^5. Additionally, an increase in the corrosion resistance of the metallic material was obtained by the coating [53]. Tested in a knee wear simulator using distilled water as a lubricant, Oñate et al. [55] obtained a decrease of a factor of five in wear of the UHMWPE by coating the cobalt chromium counter face with DLC. Dong et al. [56] tested different coatings in a pin-on-disk tester, also using distilled water as a lubricant, and obtained a large decrease in UHMWPE wear with all the coatings. However, the thermally oxidized Ti6Al4V coating still performed approximately eight times better than the DLC coating. Analogously, Dowling et al. [4] coated a stainless steel femoral head with DLC and determined the wear of the UHMWPE cups in a hip joint simulator using distilled water. They obtained a decrease of wear by a factor of six due to the DLC coating. The same low wear of the UHMWPE was also obtained when using a zirconia femoral head under the same test conditions. Sheeja et al. [57] prepared multilayer ta-C films by the filtered cathodic arc method from pure C targets. The wear tests of the CoCrMo/UHMWPE and DLC/UHMWPE sliding pairs have been made in water and simulated body fluid on a pin-on-disk apparatus and, in contradiction to the results presented above, no significant difference in wear could be measured between the coated and the uncoated samples [58]. Saikko et al. [59] compared the wear of UHMWPE cups operated against CoCr, alumina and DLC coated CoCr hip joint balls in a biaxial hip wear simulator in the presence of diluted calf serum. They found no significant difference in the wear of the UHMWPE for all three pairs tested. The same results have been obtained also by Affatato et al. [60].

From the results shown above it can be seen that apparently contradicting results on the wear of DLC coated joints are obtained. There are several issues presented below which may explain these differences found in the literature. The liquid lubricant used in a tribological test has a crucial influence on the friction and wear values obtained as well as on the type of wear particles produced [61–63]. It was suggested that when bovine serum or synovial fluid was used as a lubricant, the different proteins, especially phospholipids, adsorbed on the surfaces, strongly influences the tribological behavior in the joints [61,63]. Also, the surface texture has a decisive influence on the wear behavior of a joint. It was shown that even single scratches, which may not be detected by an average surface roughness measurement, are capable of increasing the wear rate of UHMWPE by a factor of 30–70 [64]. As a summary, it can be stated that wear tests on load bearing implants should be made in an adequate implant joint simulator. As a lubricant, a supply of synovial fluid (or any other fluid containing an adequate distribution of proteins) has to be maintained to compensate for the proteins decomposed due to high pressures between contact spots of the bearing [65]. Additionally, the surface texture of the areas involved in the tribological process must be characterized carefully.

From the literature presented above, it can be said that the superior properties, which DLC shows in air or vacuum, can probably not be easily transferred to hip joints and other load bearing implants. The build up of a transfer layer does not seem to take place, and the UHMWPE counterpart still shows wear. Perhaps DLC coated load bearing implants sliding against ceramics or

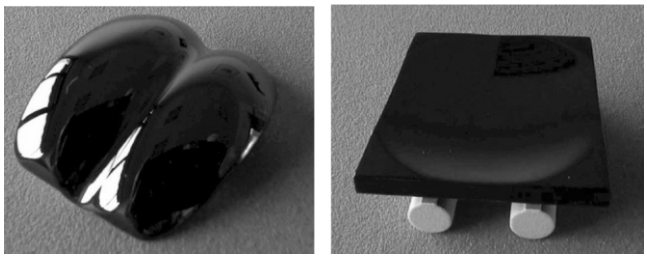

Fig. 3. Ankle joint with both parts coated with DLC (talar component left picture, tibial component right picture). Pictures from M.I.L.SA.

against DLC coated counterparts may show good 'ceramic like' tribological properties, but it is questionable if a real improvement in wear against the existing ceramic/ceramic or metal/ceramic bearings can be obtained.

Dearnley [44] states in his review article, published in 1999, that he is unaware of any commercially available DLC coated bearing surfaces for joint replacements. To my knowledge, to date, only the French company 'M.I.L. SA (Matériels Implants du Limousin SA)' commercially offers DLC coated titanium shoulder-joint balls and ankle-joints with both parts (the tibial and the talar component, see Fig. 3) made from a nitrided AISI Z5 CNMD 21 steel and coated with DLC.

In 2001, the company Implant Design AG sold knee-joints under the trade name 'Diamond Rota Gliding' with the sliding area of the femur component coated with DLN which was sliding against UHMWPE. However, the company did not make the tests required prior to commercialization, nor did they have the necessary permission to sell the 'Diamond Rota Gliding' knee joint implant. Within a short time, some of the approximately 190 implanted joints showed increased wear and partial coating delamination and had to be replaced. Additionally, residual coating on the upper side of the implant was held responsible for the inadequate bone ingrowth. In July 2001, the implantation of this knee joint was forbidden by the Swiss Federal Office of Public Health (SFOPH).

5. Conclusions

Two main fields of biological applications of DLC can be found in the literature. The application of DLC in blood contacting implants such as heart valves and stents and the use of DLC to reduce wear in load bearing joints. Additionally, it is possible to tune the biological properties of DLC by alloying with different elements. DLC coatings can also be used to reduce the release of metal ions (especially nickel, which is the most common contact allergen) from metallic implants.

For blood contacting applications of DLC, the different in vitro and in vivo experiments showed a high albumin/fibrinogen ratio, a low number of platelets adhering to the surface, a decreased platelet activation and a decreased tendency of thrombus formation for DLC surfaces confirming the excellent haemocompatibility of DLC. Additionally, the reported decrease in inflammatory reactions by the addition of Si:O into the DLC matrix [17,37] has to be further examined. Since it is possible to add different elements into the DLC matrix and to continuously adjust the different biological properties, it should be possible to improve the excellent blood compatibility of DLC even further.

For DLC coated load bearing implants, the different in vitro experiments showed contradicting results, due to the different experimental setups (pin-on-disk, hip or knee simulator, different surface roughness) and the different liquids used as lubricants. The low wear properties known from the tribological behavior of DLC in air could not be adapted to load bearing joints operated in a biological fluid. No in vivo experiments on DLC coated load bearing implants could be found in the literature and only one company offers DLC coated shoulder-joint balls and ankle-joints.

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