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Protein-material interactions in human body fluids

Literary Review

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Biofouling is a phenomenon where proteins attach to the surfaces of materials, which happens inside a living system like the human body. Protein adsorption is a significantly limiting factor for the use of sensors, as it reduces their accuracy and the duration of use. Proteins gather at the surface of the material, and the distance between the sensor and analyte grows. The process of biofouling is generally quite well understood, but unfortunately, there are many blind spots in the available research. Not all the proteins, especially the smaller ones, and their roles are known. There are currently no universal solutions to prevent biofouling.

This study aims to investigate the primary proteins causing biofouling in biomedical devices and study their properties. The available literature on the topic was gone through in a quasisystematic manner. Separate search strings were used to identify proteins involved in biofouling for blood, sweat, lacrimal fluid, and urine.

19 papers were chosen for this study, 15 of which were focused on blood. Albumin is the most numerous protein causing biofouling in both blood and lacrimal fluid. Other main proteins involved are of similar size to albumin, about 50 to 100 kDa. There is also a complex system of smaller proteins that quickly adsorb and then desorb from the surface, which partly regulates the behavior of the bigger proteins. Sweat and urine do not seem to have biofouling caused by proteins, because of their low concentration.

Biofouling is an intricate process where the parts involved influence each other in many ways, many of which are still not very well understood. The smaller proteins look particularly promising as a potential target of future research, as it seems that their behavior might also contribute to the ability of the larger proteins to attach properly.

Key words: Protein, Biofouling, Material, Human, Sensor, Blood, Urine, Sweat, Lacrimal fluid, Tears

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Biolikaantuminen on ilmiö, missä proteiinit kiinnittyvät materiaalien pinnoille. Sitä tapahtuu biologisissa järjestelmissä, kuten ihmiskehossa. Proteiinien adsorboituminen on merkittävä rajoittava tekijä sensoreiden käytölle, sillä se vähentää niiden tarkkuutta ja käyttöikää. Tämä johtuu siitä, että proteiinit kertyvät materiaalin pinnalle ja etäisyys anturin ja analyytin välillä kasvaa. Biolikaantumisprosessi on melko hyvin ymmärretty, mutta harmillisesti on vielä paljon alueita missä tutkimustietoa on vähemmän tai ei juuri ollenkaan. Kaikki osallisena olevat proteiinit, erityisesti pienikokoisemmat, ja niiden roolit eivät ole tunnettuja. Tällä hetkellä ei ole tapaa ehkäistä biolikaantumista universaalisti.

Tutkimuksen tavoite on tutkia tärkeimpiä proteiineja, jotka aiheuttavat biolikaantumista lääketieteellisissä laitteissa ja näiden proteiinien ominaisuuksia. Saatavilla olevat tutkimukset aiheesta käytiin läpi kvasisystemaattisesti. Erilliset hakulausekkeet muodostettiin tunnistamaan proteiinit, jotka aiheuttavat biolikaantumista veressä, hiessä, kyynelnesteessä ja virtsassa.

19 tutkimusta valittiin tarkempaan tarkasteluun, 15 niistä keskittyi vereen. Albumiini on yleisin biolikaantumisen aiheuttaja sekä veressä että kyynelnesteessä. Muut keskeiset proteiinit ovat samaa kokoluokkaa kuin albumiini, noin 50–100 kDa. Pienet proteiinit myös nopeasti adsorboituvat ja irtoavat pinnalta, muodostaen monimutkaisen kokonaisuuden, jossa ne vaikuttavat isompien proteiinien adsorbtioon. Hiki ja virtsa sisältävät vähäisen pitoisuuden proteiinia, minkä takia niissä ei juuri esiinny proteiinien aiheuttamaa biolikaantumista.

Biolikaantuminen on monimutkainen prosessi, jossa eri osat vaikuttavat toisiinsa monilla tavoilla ja monet näistä tavoista eivät olet kovin hyvin ymmärrettyjä. Erityisesti pienikokoisemmat proteiinit vaikuttavat lupaavilta kohteilta tutkimukselle, sillä näyttää että niiden toiminta voi myös vaikuttaa isompien proteiinien kykyyn kiinnittyä.

Avainsanat: proteiini, biolikaantuminen, materiaali, ihminen, anturi, veri, virtsa, hikoilu, hiki, kyynelneste, kyyneleet

Table of contents

1 Introduction

Biofouling is a major factor in reducing the lifetime of sensors used in biological environments. This phenomenon is characterized by the adsorption of biological molecules like proteins and lipids to the sensor surface. This creates distance between the sensor and the analyte, the component being detected. It also affects the results by changing measurable properties, like conductivity, and by causing background noise. In time, these effects multiply, and the sensors become less accurate. In certain non-medical applications, this is not a problem, since those sensors can be cleaned. In medical applications, this is usually not possible [1–3]. For this reason, devices used in monitoring blood sugar for type 2 diabetes, which are installed on the surface of the arm, need to be changed periodically, like every two weeks [4]. The impact of the problem is emphasized if one wants to develop sensors that are implanted inside the body.

Biomedical sensors typically measure the electrochemical properties of body fluid. Examples of these fluids are blood, sweat, lacrimal fluid, and urine. All these fluids have their own features that affect biofouling. Blood has several factors related to clotting and the immune system, that cause biofouling. Sweat and lacrimal fluid carry with them many bacteria living on the surface of the skin and the membranes. So, there are many different causes for biofouling, and it happens on basically all biomedical devices that use sensors. [1–3]

Molecules adsorb to the sensors by different mechanisms, and these can be prevented by different antifouling mechanisms, of which four are significant. These are the hydration layer, electrostatic repulsion, static repulsion, and surface topography. [1]

Material choices and treatment can be used to slow down and prevent biofouling, thus increasing the lifetime and accuracy of biomedical sensors [2]. The beginning of biofouling is typically characterized by protein adsorption, so in this literary review, the main proteins and their characteristics are examined.

2 Background

Materials and biomaterials are engineered in medical applications to take a form that works alone or as a part of a system in combination with the components of a living system [5]. Implantation of biomaterials leads to a series of host reactions that include blood-material interactions, provisional matrix formation, inflammation (acute and chronic), granulation tissue development, foreign body reactions, fibrosis, and fibrous capsule development [5,6].

Materials science and engineering are used to adjust material properties to fulfil the needs for these specific applications. This can usually be achieved in regular scenarios, but this is often very difficult when materials are needed to function at the boundary layer with a biological system, called the interface. Dental and breast implants, artificial kidneys, pacemakers, and artificial heart valves are some examples of current successful applications [7]. Use of sensors inside the biological system like the human body comes with additional problems, because the sensor has to interact directly with the system, so it cannot be covered with an extra layer of biomaterial, that has minimal biofouling, since that extra layer would also impact the performance of the sensor. So there is a need to find a balance between preventing biofouling while still having a functioning sensor [7]. Immunological response from the host, often hinders the usage of biomaterials, especially in applications like sensors or drug delivery systems [8].

When the implant is added to the body, it causes an injury, after which the blood starts interacting with the biomaterial, followed by the provisional matrix formation. This first leads to acute inflammation that later becomes chronic. After this, granulation tissue starts forming, followed by the foreign body reaction, and finally, the fibrous capsule develops. [5]

Blood and material interactions start simultaneously with the implantation of materials, with protein adsorption to the surface of the material and the formation of blood-based transient provisional matrix forming on the surface and around the material [5]. The first proteins that attach to the materials are ones present in the serum, and they are only adsorbed very lightly. Then, they are desorbed and replaced by more surface-active proteins. This is a dynamic system where proteins are adsorbed and desorbed from the surface of the materials, and this is called the Vroman effect. The effect continues, so the composition of proteins on the surface is always changing [6–8]. The material or biomaterial immediately acquires a host of these quickly adsorbing surface materials, it is thus highly likely that the properties of these

proteins also affect the reaction of the body to the materials [6]. This also starts the development of granulation tissue, where cells of more permanent nature start forming at the implantation site to heal the injury [5].

In the first stage of the foreign body reaction, innate immune cells identify the material as foreign. They then start an immune response by producing cells like cytokines and chemokines that then recruit more immune cells to the site of implantation. The cytokines and chemokines also activate a protein set called the complement system, which works together to remove the foreign material. The effects of the complement system range from inflammation and stimulating phagocytosis to attracting extra immune cells to the site of the implantation. [8]

After the first stage, the adaptive immune system starts a response when T-cells and B-cells belonging to the innate immune system start recognizing specific antigens that are on the implanted biomaterial. The system identifies those antigens as foreign, and this leads to the immunological response. This reaction also leads to tissue regeneration at the site of implantation, starting the fibrosis and fibrous capsule development. [8]

Although the immune system's primary role is to protect the body from potentially harmful foreign entities such as bacteria, it is important to assess its response to different materials used, especially when considering the long-term functionality of biomedical devices [8].

3 Methodology

3.1 Research question, aim and objectives

Research questions are

1) What are the main proteins that cause biofouling in medical devices?

2) What are the typical characteristics of proteins involved in biofouling? and

3) How does the protein composition differ in blood, sweat, lacrimal fluid, and urine?

This thesis aims to identify the primary proteins causing biofouling in biomedical devices and study their properties.

More specifically, the objectives of this study are to find the most significant proteins involved in biofouling and identify the main characteristics of these proteins so that the information can be used to help prevent biofouling in the future

3.2 Literary review

A literary review is a systematic examination and overview of scholarly information about a specific topic. Here, the information is analysed, evaluated and synthesized. Furthermore, a comprehensive, critical and accurate understanding of the current state of knowledge should be presented. A stand-alone literary review is a self-contained document that provides a broad overview of a particular topic. It highlights the cumulative nature of knowledge creation. Generally, it consists of six major steps; choosing a topic, locating sources, analysing and evaluating the sources, organizing and synthesizing the literature, developing a writer voice and writing, editing and refining the review. [9]

3.3 Literary review process

PubMed was chosen as the search database. PubMed is a database maintained by the United States of America National Library of Medicine, centered on biomedical literature [10]. The inclusion criteria for the results were as follows: peer-review articles (both original research and review articles), written in English, with full text availability. In addition, the results were filtered to ones published in 2005 or later.

Due to the differences in the research focus on body fluids like desired analyte, material, and device type, a separate search was done for blood, sweat, lacrimal fluid, and urine. The search strings used for the searches were “protein AND "foreign body respons*"” for blood, “Sweat biofouling” for sweat, “tear biofouling” for lacrimal fluid, and “urine biofouling” for urine.

The number of studies chosen based on the different phases of the search process for the review are presented in Table 1. The number of studies done on blood is much higher than on the rest of the fluids. This was even more obvious when a single search string was used trying to find research for all the fluids, before fluid specific searches were conducted.

Table 1. Number of chosen studies.

Fluid	Number of studies from search	Number of studies chosen based on title	Number of studies chosen based on abstract	Number of studies chosen based on full text
Blood	384	148	38	15
Sweat	21	12	8	1
Lacrimal fluid	10	5	4	2
Urine	41	8	7	1
Total	456	173	57	19

3.4 Studies chosen

In total, 19 studies were chosen for this review. They are shortly introduced in Table 2. They are listed in in the order of the fluid they focus on, starting with the studies focused blood and in the year of publication from newest to oldest.

Table 2. A summary of the studies chosen.

Year, name of the study, author	Study type and methodology	Biological fluid	Biomaterial (s)	Focus of the study
2024, Surface Topography, Microbial Adhesion, and Immune Responses in Silicone Mammary Implant-Associated Capsular Fibrosis, Schoberleitner et al.	Mass spectrometry and profile analysis, in vivo and in vitro	Blood in the breast area	Silicones with different surface topography	How breast implant surface finish affects the FBR, proteome and microbiome.
2024, Osteointegration of Ti Bone Implants: A Study on How Surface	Literary review	Bone and blood in and near bone	Titanium and its alloys	Effect of the surface parameters of the implants on the protein adsorption and osteoimmunomodulation

Year, name of the study, author	Study type and methodology	Biological fluid	Biomaterial (s)	Focus of the study
Parameters Control the Foreign Body Response, Mesa-Restrepo et al.				
2023, Regulating Blood Clot Fibrin Films to Manipulate Biomaterial-Mediated Foreign Body Responses, Zou et al.	Histological and statistical analysis of the samples grown in vivo in rats	Human gingibval fibroblasts in a macropha ge-conditione d medium	Porcine bone-derived hydroxyapatit e	Role of the fibrinogen and clotting factors in the fibrin film formation and how the surface affects the adsorbtion of blood proteins
2023, Tuning foreign body response with tailor-engineered nanoscale surface modifications: fundamentals to clinical applications, Yadav and Bachhuka	Literary review	Blood and different compone nts of blood	Different materials with nano-modifications such as monifilament polypropylen e, cellulose, and titanium	Effects of controlled surface nanotopography and chemistry on FBR, protein adsorbtion and fibrous capsule formation
2023, Antibacterial Nanostructured Surfaces Modulate Protein Adsorption, Inflammatory Responses, and Fibrous Capsule Formation, Visalakshan et al.	Liquid chromatogra phy – mass spectrometry	Different fluids including human plasma and serum and bacterial cultures	Titanium alloy Ti6Al4V nanospikes	Proteins adsorbed on a nanostructured vs non-nanostructured surface and the effect they have on FBR and fibrous capsule formation
2023, An in vitro model that mimics the foreign body response in the peritoneum: Study of the bioadhesive properties of HA-based materials, Lehká et al.	Liquid chromatogra phy – mass spectrometry and Proteomic analysis	Serum combined with partially hepariniz ed fresh blood collected from humans	Hyaluronic acid based films grown in vivo in mice	Creating an in vitro model for assessing new materials based on their potential to induce a FBR
2022, IQGAP1-mediated mechanical signaling promotes the foreign body response to biomedical implants, Sivaraj et al.	Histological and immunohisto chemical analysis, proteomic analysis and RNA sequencing	Human blood and modified mice	Mechanically stimulated polydimethyl siloxane, surfaces of pacemakers and neurostimulat ors	Molecular mechanisms and the role of IQ motif containing GTPase activating protein 1 (IQGAP1) in FBR
2020, The Impact of Biomaterial Cell	Affinity chromatogra	Human acute	Stainless steel,	Creating a highly sensitive novel test system for examining the

Year, name of the study, author	Study type and methodology	Biological fluid	Biomaterial (s)	Focus of the study
Contact on the Immunopeptidome, Ghosh et al.	phy – mass spectrograph y	monocytic leukemia cell line THP-1 culture	aluminum, zinc, high-density polyethylene, polyurethane films	effects of biomaterials in immune system
2019, Biocompatibility of alumina-based biomaterials–A review, Rahmati and Mozafari	Literary review	Human blood and its compone nts	Alumina-based biomaterials	Protein adsorption and the FBR on the surface features of the materials
2019, Surface Area to Volume Ratio of Electrospun Polydioxanone Templates Regulates the Adsorption of Soluble Proteins from Human Serum, Fetz et al.	Infrared-based immunodete ction quantification and statistical analysis	8 human blood serum proteins	Fibers spun from polydioxanon e	Effect of protein adsorbtion on regulation on the release of Neutrophil extracellular traps (NETs)
2019, The Foreign Body Response Demystified, Chandorkar et al.	Literary review	Blood and it's compone nts	Many different surface finish coating materials	Overview of the FBR and analysis of challenges that need to be solved in the future
2015, Linking the foreign body response and protein adsorption to PEG-based hydrogels using proteomics, Swatzlander et al.	Proteomics and liquid chromatogra phy –mass spectrometry analysis	in vivo mice and in vitro bone marrow isolated monocyte s	Polyethylene glycol (PEG) hydrogels	FBR mechanisms and the role arginine-glycine-aspartic acid has in it.
2015, Macrophages, Foreign Body Giant Cells and Their Response to Implantable Biomaterials, Sheikh et al.	Literary review	Blood and it's compone nts	Many biomaterials such as different polyesters and bioceramics	Interaction of foreign body giant cells and macrophages with biomaterial surfaces
2014, Matricellular proteins and biomaterials, Morris and Kyriakides	Literary review	Blood and it's compone nts	Biomaterials, biomimetic materials	Interactions between implants and extracellular matrix and the expression of these proteins based on the FBR.
2008, Foreign body reaction to biomaterials, Anderson et al.	Literary review	Blood and it's compone nts	Implanted materials, devices and tissue-engineered constructs	Factors that modulate the way macrophages and foreign body giant cells interact on synthetic surfaces

Year, name of the study, author	Study type and methodology	Biological fluid	Biomaterial (s)	Focus of the study
2022, Uncovering the Sweat Biofouling Components and Distributions in Electrochemical Sensors, Wang et al.	Scanning electron microscope, optical microscope and an atomic force microscope analysis of surfaces	Human facial sweat	Gold film electrodes on glass and polyethylene terephthalate	Chemical composition of sweat and composition of biofouling components gathering on the material
2022, A Separation-Sensing Platform Performing Accurate Diagnosis of Jaundice in Complex Biological Tear Fluids, Zhao et al.	Surface-enhanced Raman Spectroscopy (SERS) and principal component-linear discriminant analysis (PC-LDA)	Human tears	SiO2 with Au nanoparticles	Creating a filter system for use with SERS to produce a platform that can be used to examine tears
2012, Quantification of protein deposits on silicone hydrogel materials using stable-isotopic labeling and multiple reaction monitoring, Omali et al.	Liquid chromatography – Mass spectrography, Multiple reaction monitoring quantification	Lacrimal fluid protein deposits, synthesized peptides	Contact lenses made of silicone hydrogels	Protein composition of deposits found on the lenses
2015, A survey of state-of-the-art surface chemistries to minimize fouling from human and animal biofluids, Blaszykowski et al.	Literary review	Human and animal urine	Oligoethylene glycol(OEG) Self-assembled monolayers(SAM), Poly OEG, Zwitterionic brush (Carboxybetaine) and poly (short hydroxyalkyl) brush	Biofouling in challenging biological media like urine

4 Results and Discussion

Based on the search results, blood is the most studied fluid of the four body fluids of interest. Lacrimal fluid, also called tears, seems to be another fluid with active biofouling caused by proteins. Urine and sweat seem to be mostly void of any significant protein biofouling, mainly because of their low protein concentration [11–14]. Because of this, blood is discussed in dedicated sections, while the other fluids are combined together and addressed in individual subsections.

4.1 Primary fouling proteins in the blood

Albumin is the most abundant protein in the blood, and it is also the main protein adsorbed during biofouling. It is also the only protein that has always been involved in biofouling studies [6,8,15–18]. Immunoglobulin G (IgG) is the second most abundant protein in blood and also usually always found adsorbed [6,8,15–19]. Other proteins often found adsorbed are vitronectin, globulins (the already mentioned IgG and also especially IgK), apolipoproteins A-I (especially E), fibrinogen, complements, and fibronectin [5,6,8,15,16,18,19].

In total, there are hundreds or thousands of different kinds of proteins found adsorbed to the materials [7,8,15–17]. The concentration and composition of proteins found adsorbed varies highly. It depends on numerous factors like the individual person, the method of implantation, if the study is done in vitro or in vivo, the material and its properties, and many others [5–8,15–25].

As mentioned previously, before the adsorption of the bigger and more permanent natured proteins, smaller and faster proteins are temporarily adsorbed to the surface. These proteins are then replaced by bigger and slower proteins. In addition, the proteins keep interchanging with each other. The proteins that adsorb to the material also change the properties of the material, so the situation is never static, and the composition keeps changing as time passes. Because of this, the proteins usually found adsorbed to materials, are not the only ones involved in biofouling. [6–8,18,19,21]

Their temporary nature and small size limits the possibilities to study the nature of the fast proteins involved in the first stages of biofouling [6,7,15,18,21,23]. One such protein is IQGAP1 that is involved in many signaling processes related to inflammation and has a big role in it. In IQGAP1 deficiency, foreign body response is greatly reduced in the areas of

inflammation, fibrosis and signaling. This is not the only one, but is perhaps one of the best studied proteins of its kind [22]. Many other smaller proteins are also known to play part, but their roles are not very well understood [6–8,18,19,21]. There are also proteins belonging to the extra cellular protein matrix, like matricellular proteins, that are involved the process even though they are not directly involved. They vary greatly in structure and form, so they are mostly grouped together through their function [23].

4.1.1 Possible variables

There were no studies that identified variables directly related to diet or other similar factors. Some studies encountered in the review involved diabetic mice and how it affected the biofouling process, there were no human studies found so they were not further considered. The process of implantation seems to have an effect in the protein variability however, as bacteria from the skin can be transferred through the implantation process and this affects the proteins found on the implant. It is also likely that some diseases like HIV can have an effect, since they directly affect the immune system [24].

4.2 Features of the proteins in the blood

The size of albumin is 66.5 kDa [16] and most of the proteins found adsorbed are around the same size or larger [17]. Biomaterial particles that are very small, around 10 to 100 μm, are generally eaten by macrophages. Particles around 100 μm and larger are immune to the phagocytic capability of macrophages and they are instead engulfed by multinucleated giant cells (MGCs). In particles of these sizes, proteins seem to not be involved [5].

Protein size is one of the factors affecting protein-material interactions. Fibrinogen, a larger protein may have more complex interactions with the surface compared to a smaller protein like albumin[18]. How well the pore size matches the protein size also affects the adsorption, most clotting factors like fibrinogen are between 10nm to 100nm, meaning that if the microporous surface structure is around that size, more clotting factors will also be adsorbed [20].

Material surface qualities also affects adsorption, with hydrophilic surfaces increasing the adsorption of fibronectin with other surface treatments resulting in a larger amount of albumin, fibronectin and fibrinogen being absorbed [18]. Macrophages can also sense the surface chemistry under the adsorbed proteins and can affect the behavior of the proteins [17].

Matricellular proteins influence many factors like protein adsorption and inhibiting angiogenesis or blood vessel formation [23].

Surface area to volume ratio (SAVR) changes the affinity of protein adsorption. This can permanently alter the composition of adsorbed proteins. On a material weaved from small diameter (SD) fibers (0.2-04 μm), vitronectin adsorption was much slower than in material weaved from large diameter (LD) fibers (1-3 μm), it was able to adsorb much more of vitronectin, however. Similar behavior was found from IgM. Albumin and IgG contrastingly adsorbed similarly on both templates. Large SAVR(one made from SD fibers) assumedly facilitated increased protein adsorption, with larger effect for smaller proteins. [19]

Proteins compete highly with each other for adsorption [21]. It is likely that some proteins also promote the adhesion of certain other proteins [15]. With time, the layer of proteins keeps growing, creating a more complex mixture of proteins that are adsorbed in different conformations and orientations [7]. It seems that the first layer of proteins has a significant impact on the larger layer, since it is involved in regulating the response of body to the material [8]. After the first stage of protein adsorption, fibrin films also start forming on the surface of the material. These films are ignored in most of the current studies for protein adsorption, which could cause unexpected results and lower the success rate of clinical use, as the fibrin films are a part of the FBR [20].

4.3 Proteins in fluids other than blood

4.3.1 Sweat

The major function of sweat is controlling the body temperature, and it does not actively take part in immune defense. In normal situations, sweat is mostly water and salt, and it has no cells and very limited amount of proteins. Because of this, the amount of biofouling in sweat should also be very limited. However, there is no study that has focused explicitly on the biofouling in sweat and what causes it. When sensors exposed to sweat have been studied, there have been no cells or proteins that have adsorbed to the sensors. There has been a large amount of lipids however, degrading the effectivity of the sensors and limiting the prolonged usage of sweat sensors. [11]

High-resolution mass spectrometry has been used to study sweat, and 95 different proteins were discovered. 92% of the total amount of proteins consisted of dermcidin, clusterin,

apolipoprotein D, prolactin-inducible protein, and albumin in the order of highest amount to the lowest. So dermcidin was the most abundant, with it representing 46% of the total proteins [11]. Dermcidin is processed after secretion into different peptides, of which DCD-1L is a common form that has a molecular mass of 4.8 kDa and a helical form [26]. It's important to emphasize that the amount of protein in sweat is extremely low [11].

4.3.2 Lacrimal fluid

The amount of protein in tears is lower than in blood, but still relatively high and the proteins in tears are also a main cause of biofouling in them [12]. The main proteins in tears are lysozyme, albumin, immunoglobulins A and G, peroxidase, lactoferrin, lipocalin and phospholipase [12,13]. The most common, lysozyme is present in many different forms, its size is around 14 kDa and it is a monomeric protein stabilized by 4 disulfide linkages [27]. Contact lenses have their own sets of proteins that depend on both the individual person and the material the lenses are made of. Lysozyme is the main protein found from contact lenses, with other common ones being lactoferrin, lipocalin, proline rich protein-4 and keratin. In contact lenses, the proteins, especially keratin, often form pockets where they gather in the same place [13]. In addition to proteins, tears also have impurities like bacteria that can cause biofouling in sensors, this is because tears are active part of human immune system [12].

4.3.3 Urine

In some studies, materials have been exposed to undiluted urine of healthy humans for 15 minutes, and after this time, the amount of proteins in the material was undetectable. Given that usually there is some protein adsorption almost immediately following the exposure, it can be expected that there should normally be no biofouling caused by proteins in urine. This is most likely because normally, the human urine contains almost no proteins, around 0.3 mg/mL, compared to 70 mg/mL in blood, 7 mg/mL [28] in tears and 0.06-0.12 mg/mL [29] in sweat. In a condition called proteinuria, often caused by kidney failure, there is a large amount of proteins in the urine, over 300 mg/mL. This is characterized by a foaming while urinating and can be detected with a simple urine test. [30]

4.4 General trends and common findings

Since the adsorbed proteins can compete and interchange with each other, a material created to resist albumin, for example, may still exhibit similar levels of biofouling, as albumin can

just be replaced by other proteins. It also seems very unlikely that a solution that prevents or greatly reduces biofouling in all situations is possible with the current knowledge, if at all. [6–8,18,19,21] This seems especially unlikely considering the many changes that things like illness or a state of health can have. For women, especially, more studies are needed, as things like menstruation and pregnancy can greatly affect how the body functions [31].

Many smaller proteins are temporarily adsorbed, and these proteins at least to some extents are involved in attracting the larger proteins, IQGAP1 is one such protein [22].

4.5 Research gaps and limitations

Studies on urine and sweat are limited. Especially they seem to not have many studies that consider the long-term term exposure to these fluids [11,30]. Because of this, sensors implanted in urine bladder for example, could run into unexpected problems. Studies on blood are also often quite specific, focusing on specific interactions, like a specific proteins adsorbed on a specific style of surface [19]. They also often use simplified models, where they ignore certain possibly important characteristics, like fibrin films that also form on the surface of implanted materials [20].

Previously mentioned smaller proteins and their role is not very well known, the effects they might have and if preventing their behaviour would be a way to limit adsorption of bigger proteins is not well understood[22]. Matricellular proteins are another area that is not well understood but they are being studied in an effort to create better biomimetic materials, as having a material with these proteins already attached can cause the body to respond in a more desired way to the implantation of the material [23].

4.6 Improvement of methodological approaches

Surface nanostructure is one way to possibly slow down the biofouling process, since the more permanent natured larger sized proteins might have trouble adsorbing to the smaller structures properly [19]. This might slow down the formation of the more complex protein layer on top of the lower layer. Surface with zwitterionic or other electrochemical qualities is another option worth exploring to prevent adsorption in a more universal manner [18]. If the surface can be modified to attract proteins that are more temporary in nature, the gathering of proteins can possibly be slowed down.

Because the main proteins found in biofouling are of a similar size, around 50 kDa or larger, if the size of the molecules being studied is much smaller than this, it might also be possible to use a filter [17]. This might be especially good if trying to make a sensor for lacrimal fluid, where the protein concentration is already lower and of smaller variability and there are other impurities that might be problematic [12].

Materials with the same surface finish still seem to attract very different proteins [25]. It is quite certain that a combination of correct materials with the correct surface finish is needed to achieve the optimal result of a biofouling resistant sensor.

5 Conclusions

This research aimed to explore the topic of proteins involved in biofouling that happens on materials implanted inside human bodies. There are many different proteins involved in biofouling, with the most numerous being albumin in blood, lysozyme in tears, dermcidin in sweat, and urine normally not having any proteins. Biofouling is not caused by proteins in the urine and sweat, because of the low concentration. In blood, most of the proteins are of similar size to albumin.

Biofouling is a complex process that happens in stages. First, the smaller proteins adsorb, and after that, the bigger proteins take their place. Biofouling is a dynamic process where the proteins that are adsorbed keep changing with each other. Biofouling is not easily prevented because of this complexity, and so, special care must be taken when considering the materials for a biomedical device.

The studies included consisted of reviews of more general nature and of more specific ones done in vivo or in vitro. Some also aimed to create new biotechnologies. The results found in this review demonstrate the current knowledge base but also highlight the topics that are not yet well-researched. Based on this, one topic worth exploring in the future is the more specific role the small proteins have in the biofouling process.

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