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Ronja Suokivi

AUGMENTATION MAMMOPLASTY: REACTIONS INDUCED BY SILICONE IMPLANTS

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Faculty of Medicine and Health Technology
Maiju Juusela
Minna Kellomäki
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ABSTRACT

Ronja Suokivi: Augmentation mammoplasty reactions induced by silicone implants
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The history of augmentation mammoplasty is eventful, and the earliest description of surgery on the breasts is from the 1890s. Back then the modern materials we nowadays utilize were not familiar to surgeons. In the 1930s, for example, glass balls and polyvinyl alcohol sponges were used as breast implants. It was later thought out that the sponges could be covered, and that is how silicone implants were discovered. From the 1960s onward, the popularity of silicone breast implants grew significantly. However, in the 1990s their safety was questioned. Breast implants were pulled off the market in the United States by FDA until sufficient research had been done on the safety of silicone breast implants. In 2006, the implants were returned to the market restrictively. Safety concerns arose from links between silicone implants and autoimmune diseases and cancer.

This thesis presents the reactions that occur in breast tissues during and after breast augmentation mammoplasty. The purpose is to carefully familiarize the reader to the stages of breast augmentation and the materials used in it. In addition, the aim is to distinguish normal tissue reactions from possible complications. This is achieved by spreading awareness on how silicone behaves as a material in the augmentation mammoplasty, especially in a soft tissue environment. The implantation causes multistage immune-provoking reactions in tissues with depending on the type of implant. Therefore, it is important to know how silicone implants could be manufactured so that they are protected from the evolved immune responses.

During the thesis, it is noted that there are multiple methods to control these reactions with expertise on foreign body reaction and silicone. At the same time, we learn how a prolonged foreign object reaction affects the durability of the implant, the immune system and the range of symptoms of the patient. This thesis is ultimately a literature review, which concludes that research on breast augmentation is still needed on a multidisciplinary basis, and that there is a particular need for expertise in tissue technology for breast augmentation surgery research.

Keywords: silicone, breast implant, tissue, augmentation mammoplasty, foreign body reaction, inflammation, regulation, FDA, plastic surgery

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TIIVISTELMÄ

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Naisten rintojen suurennusleikkausten historia on monivaiheinen ja värikäs. Jo 1890-luvulla oli kuvailtu ensimmäisestä rintoihin kohdistuneesta korjausleikkauksesta. Tällöin ei kuitenkaan vielä käytetty moderneja materiaaleja, vaan esimerkiksi 1930-luvulla rintaimplantteina oli käytetty lasipalloja ja myöhemmin polyvinyylialkoholista valmistettuja sieniä. Sienet keksittiin sittemmin päällystää silikonilla, josta silikoni-implantit saivatkin alkunsa. 1960-luvulta eteenpäin silikonisten rintaimplanttien suosio kasvoi merkittävästi. Kuitenkin 1990-luvulla niiden turvallisuutta alettiin epäilemään. Muun muassa Yhdysvalloissa rintaimplantit vedettiin pois markkinoilta, kunnes riittävää tutkimusta silikonisten rintaimplanttien turvallisuudesta oli tehty. Vuonna 2006 implantit palautettiin markkinoille rajoitetusti. Turvallisuuskysymyksiä herättivät epäilyt autoimmuunisairauksien ja syöpien kytköksistä silikoniin biolääketieteellisissä sovelluksissa.

Tässä työssä perehdyttiin reaktioihin, jotka syntyvät rintakudoksissa silikoni-implanttien aikaan saamina rintojen suurennosleikkauksen yhteydessä ja sen jälkeen. Tarkoituksena oli perehdyttää lukija huolellisesti rintojen suurennusleikkauksen vaiheisiin ja siinä käytettäviin materiaaleihin. Lisäksi pyrkimyksenä oli tuoda esille, millaiset kudosreaktiot ovat operaation jälkeen tavallisia ja mitkä mahdollisia komplikaatioita. Näiden asioiden ymmärtämiseen vaaditaan tietämystä siitä, miten silikoni käyttäytyy materiaalina rintojen suurennusleikkauksen tapauksessa erityisesti pehmytkudosympäristössä. Implanttien asennus aiheuttaa poikkeuksetta kudoksissa monivaiheisia immuunivasteen herättäviä reaktioita, joiden haastavuusaste vaihtelee implantin tyypistä riippuen. Siispä on tärkeää tietää, miten silikoni-implantteja voitaisiin valmistaa niin, että ne olisivat immuunivasteen kehittyneiltä reaktioilta suojassa.

Työn aikana huomattiin, että rintaimplantteihin liittyvien komplikaatioiden taustalla on monimutkaisia menetelmiä, joita voidaan hallita riittävällä asiantuntijuudella muun muassa vierasesinereaktiosta sekä silikonista. Samalla opittiin, miten pitkittynyt vierasesinereaktio vaikuttaa implantin kestävyyteen ja potilaan oirekuvaan. Kirjallisuuskatsauksesta tehtiin johtopäätöksiä; rintaimplantteihin liittyvää tutkimusta tarvitaan yhä edelleen monialaisesti ja kudosteknologian osaamiselle rintojen suurennusleikkauksen tutkimukseen on erityistä tarvetta.

Avainsanat: silikoni, rintaimplantti, kudos, suurennusleikkaus, vierasesinereaktio, inflammaatio, plastiikkakirurgia, säännökset, FDA

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1. INTRODUCTION

Breast augmentation is a popular cosmetic plastic surgery procedure, which enhances the structure and aesthetics of the breasts. It has always been controversial among society because of varying cultural perspectives on cosmetic plastic surgery. This has led to myths and taboos surrounding the issue. Moreover, the nature of the procedure has raised questions of safety and ethics all along the history of breast implant surgery (*augmentation mammoplasty*). Because of the complexity of breast tissues, augmentation mammoplasty is difficult to perform and often personalized. Due to individual variation of immune responses, it is important as a patient and a medical professional to fully acknowledge the steps in augmentation mammoplasty, the quality of the implants and the possible outcomes of the procedure. This bachelor's thesis is a literature review, which takes a look into the reactions in female's healthy breast tissue caused by silicone implantation known as breast augmentation.

The history of breast implants is rather eventful. The earliest breast implants were glass balls and polyvinyl alcohol sponges, which were meant to enhance the aesthetic of the breasts in the 1930's. Later, it was figured out that the implants should be encased to provide more durable results, and this is how the story of silicone implants started. In the early 1960's, breast augmentation gained popularity, when Dr. Cronin developed the very first silicone implant. (Ratner et al. 2013, 1110) Exact number of women, who had taken breast implants from that period of time is hard to find, but a study from 1989 by the Dow Corning Corporation gathered data, which states that 8.08 per 1000 women in the United States had taken breast implants. (Cook and Perkins 1996) Silicone implants faced backlash in the 1990's, when the United States Food and Drug Administration (FDA) noted that there was not enough evidence of the safety of silicone breast implants. Connections to breast cancer and autoimmune diseases were hypothesized. Thus, a nationwide ban of silicone implants was set until companies were able to prove the safety of their products. Silicone implants returned to the market restrictedly in 2006 after few companies provided results confirming the safety of their implants. (Santanelli di Pompeo et al. 2022)

In 2020 alone, approximately 1.15 per 1000 women in the US had had augmentation mammoplasty performed by ASPS member surgeons certified by The American Board

of Plastic Surgery® as well as other physicians certified by American Board of Medical Specialties-recognized boards. However, according to ASPS, the popularity of breast augmentation had decreased 33 % percent from the previous year. (American Society of Plastic Surgeons 2021; the World Bank 2022) Patients are nowadays more eager to evaluate the risks of the procedure and have information readily accessible, which could explain the decrease. In the recent years, more studies have emerged questioning the safety of silicone breast implants. The most common research questions are biofilm's effect on tissue reactions, chronic inflammation's role on breast implant associated anaplastic large cell lymphoma (BIA-ALCL) and the effect of topography on healing and capsular contracture.

According to 410 Allergan core study, which gathered data for ten years, 9.2% of 492 women suffered from capsular contracture after primary breast augmentation and 10.2% of the same cohort had confirmed implant rupture. The overall cohort included 941 women, of which one case of BIA-ALCL was reported. Other common complications were malposition and asymmetry of the breast implants in 9.1% and 6.9% of the overall cohort respectively. Moreover, some less common adverse events were seroma build-up (1.6% to 6.2%) and reoperations, which are a result of complications or a wish of the patient to reconstruct the aesthetic of the breast (3%). (Maxwell et al. 2015)

The numbers above give some direction on the prevalence of the adverse events of breast augmentation but are not entirely accurate representation of the mentioned complications. For example, as some studies have pointed out that capsular contracture can occur as often as 23% of primary breast augmentations (Peters 2012, chapter 6). In addition, BIA-ALCL recognition can be difficult and thus, left undetermined. All in all, it is best to know the possible complications comprehensively but at the same time to understand their varying relevance to the patient, surgeon and scientist, who all interpret this information in different ways.

The purpose of this thesis is to raise awareness of different reactions induced by breast augmentation, and to distinguish normal immune behavior from abnormalities resulted from implantation. The thesis also works as a guidance material for patients and for example, tissue engineering students, where they can learn of the immunology of silicone and foreign body reaction. My intention for the literature review was to provide answers to common questions regarding augmentation mammoplasty and to make those patients, who struggle with unrecognized symptoms, feel heard.

2. BREAST IMPLANTS

Some bizarre materials have been used as breast implants along the history of augmentation mammoplasty, such as, glass balls and polyvinyl alcohol (PVA) sponges, until silicone was thought out and tested. Silicone-gel filled breast implants gained popularity and from then on, other filling materials subsided. However, research on the consistency of the filling, the shell's material and topography have been changing and studied throughout the history of the first silicone-gel filled implants to the 21st century. (Ratner et al. 2013, 1110)

Currently, there are two types of breast implants allowed in the US market: silicone-gel and saline filled implants (FDA 2021). The European Parliament has not stated such straightforward regulations for breast implants and specific materials have not been indicated. The European Parliament has stated instead that the class III medical devices—a classification for breast implants—are to go through evaluation and clinical trials accordingly to get approval for manufacture. (Regulation (Eu) 2017/745 of the European Parliament and of the Council) With an inductive reasoning on the history of breast implants, one could assume the freer regulation in the European Union (EU) has led to the use of broader variety of materials, which has shown to be harmful on occasion. (Scientific Committee on Health Environmental and Emerging Risks 2017) It is therefore harder to review the materials' safety from a consumer's, or even a scientist's, point of view in the EU.

2.1 Breast tissues and augmentation mammoplasty

The tissues of breasts include all four tissue types: connective, epithelial, muscle and nervous tissue. The posterior outline of breasts is bordered by pectoralis muscles, proximal part by clavicles and anterior outline by epidermis and nipples (*areolas*). The interior of a breast includes adipose tissue, mammary nerves, veins, arteries and pectoral lymphatic vessels. There are also lymphatics and Cooper's ligaments□–connective tissue□–that hold the structure of the breast and lobules. (Shiffman 2009) The anatomy of breast from Gray's anatomy (Standring 2016) presents that the inside of the lobules is made of glandular tissue (*glands*), which produce milk and is regulated by hormones such as estrogen. The milk is conveyed via lactiferous ducts, which all connect to the areolas. The pectoralis muscles are divided by their locations: major, minor, deep and superficial fascia. There is also a space between deep and superficial muscles called

submammary space. The breast is visualized in Figure 1. (Shiffman 2009) Knowledge on the anatomy of breasts is essential in evaluation of implant insertion.

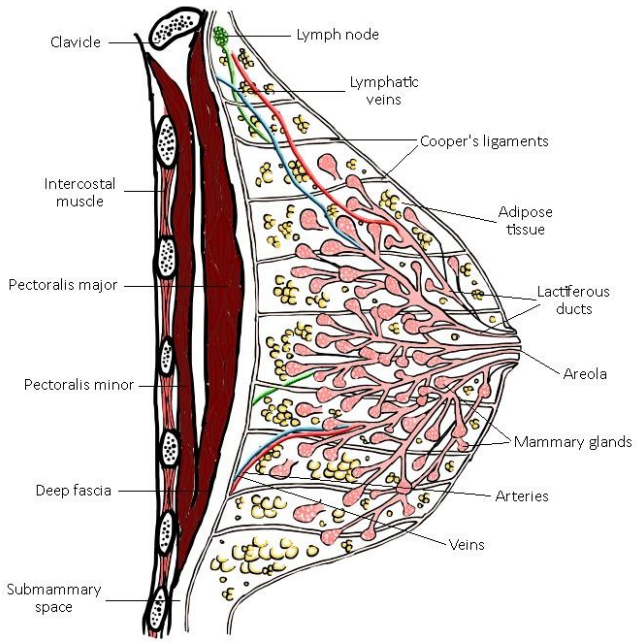

Figure 1: Illustration of the anatomy of a breast from a sagittal point of view

Augmentation mammoplasty is a multifactorial process, of which steps can be divided into those that mostly concern the patient and those that mostly concern the operating surgeon. The purpose of this thesis is to help the patients to understand the surgeons' point of view of the operation process and thus, biological processes and materials used in the procedure are presented thoroughly. Firstly, after anatomical assessments have been done, type of the implant must be chosen. The types are discussed shortly in chapters 1.2 and 2 in more detail with discussion of their effects.

Secondly, the implant insertion location is chosen. A silicone implant can be inserted into the breast in 4 ways. The implant can be opted to be inserted submuscularly, where it is implanted into the space between the pectoralis major pectoralis minor muscles. The location for the implant can also be in between the deep fascia and pectoralis major, although, this is not a common method. In addition, the implant can be inserted subglandularly, where it will be posterior to the mammary glands. Lastly, the implant can be

inserted in a dual plane fashion. Dual plane location or method means the implant placement is specifically controlled and because of this the operation can be personalized better accordingly with the needs of the patient. (Thorne et al. 2014, p. 576–578)

2.2 Silicone implants

Breast silicone implants were presented in 1960s to meet the need for those who wished for enhancement or reconstruction of their breasts. Their shell was made of a silicone elastomer, and they were filled with polydimethylsiloxane (PDMS), which is thick in consistency. The coating had Dacron patches, which were supposed to maintain the position of the implants. The structure of these implants was fragile with high capsular contracture rates and tears of the outer shell. They were also described as feeling artificial and dense. Therefore, new materials were researched and in 1964 scientists were able to create a softer implant accelerating the popularity of breast implants in 1970s. The popularity of breast implants kept rising and the research was on going to gain a durable and safe breast implant. However, in 1990s breast implants faced major backlash and silicone in breast implants was prohibited by Food and Drug Administration (FDA) in the US due to lack of studies of the safety of the implants. Breast implants were during the same time period linked to breast cancer and autoimmune diseases. Prohibition was partly lifted in 2006 due to studies assuring some silicone mixture's safety. Some silicone compounds still remain inadmissible. (Santanelli di Pompeo et al. 2022)

The size and materials used in implants vary affecting the properties of the implants. The implant's shell material, filling substance, shape and size must be selected accordingly to the specifics of a personalized augmentation mammoplasty because of this. (Thorne et al. 2014, p. 574–575) The size of an implant is usually from 80 to 800 cubic centimeters (*cc*), and sometimes they are made even bigger. The size is said to have a correlative effect with tissues: voluminous implants cause a stronger foreign body reaction (FBR). The shell of the implant is commonly made of a silicone rubber composition, of which substance proportions vary. It can also be, and is nowadays often made of, silicone elastomer. The shell's topography can be altered for better post-operation results. Filling of the implants is commonly made of saline (sterile saltwater) solution or silicone-gels, which both are approved for the US market by the FDA. (FDA 2011) (Bondurant et al. 2000) The European Commission on the other hand has merely given directives and guidelines for implant manufacture (European commission 1998) (European commission 2017). With this information, it is easier for us to take a deeper look into the causalities in augmentation mammoplasty.

2.3 Chemistry of silicone implants

Silicone is a polymer, which is composed of silicon (Si), hydrogen (H) and oxygen (O) atoms. Most common silicone polymer used in medical applications is polydimethylsiloxane (PDMS), which is also the most common material of silicone breast implants. The chemical structure of PDMS is pictured down below in Figure 2 (Bondurant et al. 2000).

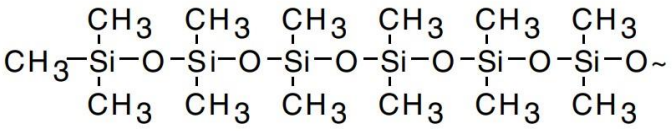

Figure 2: The chemical structure of polydimethylsiloxane (PDMS) (Bondurant et al. 2000)

Silicones are an extremely diverse polymer group, and they can be easily sterilized, modified and they are very resistant. For example, the more viscous silicone is, the thicker the filling is varying from water-like liquid to rubber consistency. They are basically chemically inert. Thus, silicones are preferred for biomedical applications and because a breast implant is supposed to imitate the soft tissue of a breast, silicone is often the most suitable material for the filling of a breast implant. Medical grade silicones can be produced by the hydrolysis of acetoxy silanes but sometimes chlorosilanes are used. However, the hydrolysis with chlorosilanes can leave toxic hydrogen chloride as a remnant. (Sastri 2013, 222-230)

Silicone oils are just long repeating units of dimethyl silicone (Me_2SiO), where a methyl group is CH_3. This is principally the same basic unit as is in PDMS as we can see from Figure 2. The viscosity of silicone can be changed with changing the length of silicone oils. The more repeating units a silicone oil has, the heavier its molecular weight is and thus, viscosity rises. Silicone oils can also be modified by adding other molecular units to the chain, and they can be made into silicone elastomers by radical chemistry, moisture cure and addition cure. Nowadays, silicone elastomers are the preferred choice of material for the shell of a breast implant. It is made by adding trichlorosilane to silicone

crosslinking polymers together, after which it resembles rubber. The properties of silicone elastomers can be modified to suit preferences with changing the amount of crosslinking. (Peters et al. 2012, chapter 3) In spite of this, silicone elastomers have shown unwelcome qualities such as lower abrasion resistance compared to silicone oil, which questions the biocompatibility of the material in breast implants (Sastri 2013, 222-230).

The filling material is usually picked from two popular options: silicone gel and saline. Silicone gel is composed of approximately 85 % of silicone oil and 15 % of silicone elastomers in breast implant fillings and the cohesiveness of the gel varies from more liquid to firmer depending on what kind of implant is wanted. Usually, silicone gel presents some diffusion, which is avoided with a barrier shell in addition to the silicone elastomer shell. The barrier is made of silicones like Me_2SiO and Ph_2SiO (diphenyl silicone), which are mixed so the silicone oils of the silicone gel would repel the barrier. Some implants use even three barrier layers, where the innermost layer has the highest Me_2SiO concentration, the second layer has a little less Me_2SiO and more Ph_2SiO, and the outermost is similar to the innermost layer. Silicone gel is normally cured with platinum. Saline (NaCl) filling is a little easier to manufacture and understand as it is simply an isotonic saltwater solution, of which ionic strength is the same as that of the body. (Peters et al. 2012, chapter 3)

2.4 Comparison between silicone gel and saline filled implants

Silicone gel and saline fillings have mostly different attributes but what is common for them, is the silicone elastomer shell. This gives a great ground for comparison between the two fillings. As pictured below in Figure 3, the silicone gel filling can be highly cohesive. These cohesive implants are named “gummy bear” implants and the purpose of the composition is to avoid leakage in a case of rupture, decrease diffusion and give a softer feel. Less viscous silicone gel fillings would leak more in case of a rupture. In addition, silicone gel filled implants are inserted as a whole into the breast, which requires a bigger incision compared to saline filled implants. Gummy bear implants also prevent gravity’s impact on the shape of the implant, whereas more viscous implants can droop over time as the filling flows to the bottom of the implant. The cohesiveness of an implant should be personalized and accustomed to the breast anatomy of the patient because these properties can affect for example, healing time. (Reiffel 2009, 165-174)

Figure 3: A cohesive high viscosity breast implant cut in half (Patrick Stanbro 2022)

Saline implants on the other hand usually feel harder depending on how much solution is added to the implant during the procedure. Because of the variability of the size of saline filled implant, they can be accustomed well for the needs of the patient. However, filling an implant incompletely causes rippling of the surface and scalloping of the edges, which can even be seen on the skin. Moreover, saline implants are also more prone to the effects of gravity because of their liquid state. Saline implants are also more prone to implant defects because they are filled during the implantation procedure making them susceptible to leaks and ruptures (Peters et al. 2012, chapter 1). The insertion requires a smaller incision compared to silicone gel implants because the shell is first implanted into the breast, which after the implant is filled. Saline implants are sealed by a self-sealing valve located on the anterior of the shell, of which defects can lead to deflation and leaks (Mentor 2004). Nonetheless, they both have their pros and cons. Saline implant rupture is said to be more symptomatic than silicone gel implant rupture. But sometimes saline filling is preferred over silicone gel filling because saline is believed to cause less harm to tissues in a case of rupture because the solution is nontoxic. Silicone gel filled implants are believed to be connected to long-term inflammation, but that connection has remained unsupported by scientists. (Reiffel 2009, 165-174)

2.5 Topography

Topography is an important factor of breast implantation because it has an effect on the foreign body reaction due its ability to affect adherence of cells. Nowadays, the topic is researched a lot and scientists have found out that with modifications of the silicone breast implant shell, the healing process can be controlled. Silicone is a highly modifiable

material, which gives a good base for studies. Also, PDMS is thought to be a well-tolerated biocompatible material, and it has been found that correlations between the material itself and complications are in a minority. However, PDMS implants (such as breast implants) intended for a permanent change in the body still cause complications, of which some are nowadays familiar to scientists.

In recent years, there have been researches on the effects of surface properties of an implant. Simply put, smooth surface implants cause less fibrotic encapsulation than rougher implants. Rougher surfaces (90 µm) activate innate immunity cells like macrophages and neutrophils, which then again accelerate inflammation. (Bondurant et al. 2000; Doloff et al. 2021) A study conducted by Doloff et al. in 2021 measured roughness levels (Ra) from 0 µm to 90 µm, which concluded in that the bigger the surface area and roughness for an implant is, the stronger the FBR is. Against hypotheses, Ra of 4 µm is the best for a shell of an implant as it is the most immunosuppressive. It is unclear, why 4 µm is better than 0 µm but the latter showed insignificant decrease in immunosuppression and capsulation compared to 4 µm. This could be because smoother implants possibly adhere less cells (a hypothesis with support from the study), but the topic needs further investigation, nonetheless.

It is interesting how these results adjust to real-life. Smoother implants are more utilized in the US market, where 88% of breast implants implanted are mainly smooth implants. On the contrary, the European market utilizes mainly texturized implants, where 95% of implants are texturized. The popularity of textured implants has increased in the US but remains a marginal group. (Jalalabadi et al. 2021) The US has been a leading example in breast implant regulation, which could once again explain the surface roughness utilization difference.

Capsulation on implants is also partly mediated by adaptive immunity, where helper and regulatory (CD4+CD25+ T_{reg}) T cells are activated. They express suppressive inflammatory proteins such as FOXP3 (Lu et al. 2017), and thus subdue macrophages and fibrotic capsulation. These cells have been shown to be impacted by the surface roughness of an implant: increasing in numbers when Ra rises. T_{regs} can suppress immunity in excessive amounts predisposing a patient to pathogens like microbes and preventing effective disposal of uncontrollably proliferating cells (possible cancer cells). Yet, too little number of T_{regs} predisposes a patient to autoimmune diseases because then adaptive immunity acts excessively. Thus, a balance must be found on the topography of an implant and therefore, it is important to evaluate the size of an implant and what type of surface will be used in augmentation mammoplasty. (Doloff et al. 2021)

Yet, some studies suggest that rougher implants are better for augmentation mammoplasty because they induce more tissue adhesion. Proper tissue adhesion minimizes the risk of implant dislocation and movement in the breast, which was for example, the initial purpose of the Dacron patches (Santanelli di Pompeo et al. 2022). On the contrary to the study of Doloff et al. (2021), a study conducted by Maxwell et al. (2013) states that macrotextured implants like Biocell with Ra 90 µm are most suitable for augmentation mammoplasty. They believe the benefits overweigh the risks of rougher implants. Although, it is acknowledged that these risks include double capsulation and seroma, the study recommends implants with macrotexture surfaces. (Maxwell et al. 2013) In spite of this, the statements are contradictory with other similar studies and the study may be caught up with bias. The contradictions could be covered by the fact that the study is almost 10 years old, but in 2011, FDA confirmed that breast implant associated anaplastic large-cell lymphoma exists, and the first ever reported case of BIA-ALCL is already from 1997 (Kricheldorff et al. 2018).

2.6 Adverse effects of silicone implants

In addition to complications caused by biological responses like the FBR, there are also complications that concern the implants themselves. For example, silicone breast implants can affect x-ray imaging, which is used for breast cancer screening known as mammogram. The silicone implants that are implanted submuscularly disturb mammogram pictures making pectoral muscles unclear because silicone and saline can alter the penetration of the x-rays. This can complicate breast cancer screening and thus, detection of cancer. (Sá dos Reis et al. 2020) However, magnetic resonance imaging (MRI) is best for diagnosing a rupture of an implant because its sequences are specific and sensitive in detecting differences between tissues and silicone (Juanpere et al. (2011).

During the procedure silicone gel filled breast implant can rupture due to mechanical defects and accidents like contact with sharp objects. This can lead to bleeding of the implant, which means silicone gel outflows. Obviously, more viscous gels do not flow similarly to less viscous gels. This can decrease complications and inflammation caused by the bleeding. However, it has been detected that silicone gel can break down to droplets that end up in in the lymphatic system and lymph nodes. Saline filling on the other hand can react with electrolytes in tissues. Furthermore, there have been cases, where saline has been infected for example by fungi prior to the procedure causing infections. (Giebler 2009)

2.6.1 Biofilm and breast implant associated large cell lymphoma

A biofilm is a colony of bacteria, which emerges on the surface of implants and into the tissues forming a slime-like matrix (EPS; extracellular polymeric substance) when an implant is contaminated with Gram-positive bacteria commonly from the *Staphylococcus* genus. Biofilm formation on the implant is a major complication of implantation because it is difficult to treat, and it is destructive to the tissues due to its antibiotic resistant and immune evasive properties. (Dapunt et al. 2016) The biofilm is adaptive to its environment in ways eukaryotic cells are not capable of. Because of their unique prokaryotic nature, they have evolved mechanisms against human-made eradication methods such as antibiotics. Another one of these methods is the EPS, which is capable of avoiding complement pathway activation and thus, the biofilm evades essential immune responses (Domenech et al. 2013). (Ratner et al. 2013, 567) There is also an increased risk of capsular contracture when a biofilm is present. Bacteria that are common on the skin are *S. epidermidis* and acne causing *Cutibacterium acnes*. They are linked to the genesis of a biofilm and thus, capsular contracture. To decrease the risk of biofilm formation, it is best to avoid skin contact with an implant. It is said that the areolas have the biggest number of bacteria and because of this, incision site plays a significant role in contamination and the preventive measures. (Mempin et al. 2018)

The research article by Dapunt et al. (2016) recognizes that neutrophils often try to opsonize the biofilm, but biofilms cannot completely evade immune responses. The same article states that when neutrophils and other immune responses cannot remove the biofilm, a prolonged infection persists leading to chronic inflammation, which then again leads to tissue damage. ESP is able to integrate into fibrin networks (potential interaction with capsulation), and cells embedded into the EPS grow slower than usually. When the cells associated with a biofilm are finally able to proliferate, they detach. These detached cells can cause systemic inflammation. (Donlan 2001) A biofilm essentially causes an infection, and it is important to recognize the formation of it early, as older biofilms are significantly harder to eradicate (Kostakioti et al. 2013). Thus, preventive measures should be taken to avoid the formation of a biofilm. Such actions could be careful sterilization of all used materials during the operation, possible antibiotic substances imbedded onto the implant, careful plan of incision and implantation, betadine treatment and post-operative care. (Rodríguez-Merchán et al. 2021)

Chronic inflammation has been connected to lymphomas, which is one of the biggest concerns of augmentation mammoplasty nowadays. Breast implant associated anaplastic large cell lymphoma (BIA-ALCL) is rare occurrence but important to understand, nonetheless. However, because of its rarity, it has been hard to study. BIA-ALCL is said to occur from as high as 1 per 3817 patients and as low as 1 per 50 000 patients, when the timeline is fitted to the most common time point of prevalence, which is approximately 10 years after implantation (Clemens et al. 2017; Loch-Wilkinson et al. 2017; De Boer et al. 2018). On the contrary to gram-positive bacteria, which cause biofilms and capsular contracture, gram-negative bacteria have been found in samples of BIA-ALCL. BIA-ALCL presents itself as seroma (fluid build-up) and malignant cells are found around the implant, and seldom in the local lymph nodes. T cell mediated immunity is a significant factor in BIA-ALCL, as a common markers for the disease are dysplastic and abnormally functioning T cells and activation of immune response suppressing cells such as T regulatory cells (T regs). Recognized cytokines in ALCL cases are interleukins 6 and 10, which stimulate T regs. Patients with genetic susceptibility are at increased risked for developing BIA-ALCL. Reported BIA-ALCL cases are highly linked to textured implants with greater surface area. An Australian study has found that approximately 85 % of BIA-ALCL cases are found in patients with textured implants. (Loch-Wilkinson et al. 2017) However, only 1 case of BIA-ALCL in 2,518 women was reported by an American breast implant company Mentor®, giving illustration of the rarity of the disease (Post-Approval Studies (PAS) Database).

The causality between bacteria and lymphoma has been researched before. Gram-negative bacteria *Helicobacter pylori* are recognized as a partial cause for gastric lymphoma, for which antibiotic treatments have been found to work. This indicates that ALCL could emerge from same mechanisms and even possibly be treated similarly. However, samples from capsular contracture breasts and BIA-ALCL breasts suggest that the pathogenesis of lymphoma caused by a biofilm is dependent on the type of bacteria, some being more triggering. (Mempin et al. 2018) Thus, more studies should be conducted of the types of biofilms and the topography's relation to ALCL.

2.6.2 Breast feeding

Breast augmentation carries a risk of tissue damage, which is why scientists have suspected alterations in milk production after breast implantation. So, silicone implants have raised concerns whether they affect the ability to breast feed. Some studies fortunately have researched the matter with somewhat consistent results. A couple of studies showed that there was no significant difference in breast feeding complications for breast

feeding women with and without breast implants. The most common complication was said to be insufficient lactation, which affects approximately 11 % of women with primary breast implantation. The likelihood of insufficiency is around 40 %. The studies have some inconclusiveness as the topography was not adequately considered. However, suggestions of the effects of implantation site were made. Both studies showed more adverse effects with subglandular positioning compared to submuscular. This is believed to be because the risk of damage to lactiferous ducts and milk glands is higher than in the case of submuscular positioning. Comparisons between silicone gel and saline implants were also made but the differences showed no clinical significance in lactation generally. (Jewell et al. 2019; Schiff et al. 2014)

2.7 Augmentation mammoplasty

Augmentation mammoplasty is a carefully planned procedure, where measurements of the implant and anatomy of the breast play significant roles. Therefore, it is important for the operating surgeon to personalize the oncoming procedure to meet the needs and specifics of a patient. There are many surgical techniques to how breast implantation can be performed. Beneath the breast there is an inframammary crease, to which an incision can be made. The crease covers the incision well and is aesthetically pleasing. Generally, an implant inserted through the crease will be implanted submuscularly. The incision can be as wide as 4.5 cm depending on the size of the implant, and the implant is irrigated before insertion. As has been stated in previous chapters, smaller incisions and implants cause weaker immune responses. This should be evaluated, when planning the augmentation mammoplasty. Dissection of muscles is a precise intervention and mistakes occurring during this step can lead to displacement of the implant and asymmetry of the breasts. Subglandular implants are placed in a similar fashion with similar steps and results. However, they can provide better symmetry and anterior protection. (Kreymerman and Rotemberg 2010)

Another surgical technique, which has evolved to meet the popularity level of the inframammary crease technique is transaxillary endoscopic approach. It is believed to be a nontraumatic technique, which decreases the strength of the FBR. The technique also dissects pectoralis muscles in a dual plane fashion with a sharp electrocautery, which provides better postoperation results for a patient due to alleviated pain. The initial incision is done into the crease of the armpit, and viscous gummy bear implants. The approach is almost ideal for augmentation mammoplasty, but it risks damaging nerves and lymphatic veins due to the approached direction. (Sim 2014)

In addition to the previous techniques, there is also another quite common but not that popular method for augmentation mammoplasty. The periareolar technique takes advantage of the areolar skin pigment because incision scar is barely visible there. The approach provides good vision to the breast tissues enabling great adjustment of the silicone breast implant and options for submammary or submuscular placement. However, areolas are generally small and thus, incision is left short. This can be quite challenging for surgeons and demands great skill in implantation. The periareolar approach however has a greater risk for contamination compared to the other techniques because the areolas contain more bacteria than the surrounding skin. Moreover, some patients have reported loss of sensation in areolas after the procedure done with this method. (Hammond 2008)

3. FOREIGN BODY RESPONSE

The implantation of silicone breast implants elicits an inflammatory reaction in the cells and tissues in the initial surgical site. An injury is created, which activates the inflammatory processes of blood. Extracellular matrix (ECM) rearranges, and connective tissues start healing at the place of injury. This leads to a formation of an interface between the implant and the tissues, where the implanted foreign material adsorbs proteins of blood such as fibrinogen. The adsorption of proteins in turn transmits immunological stimulus, which is why inflammatory systems activate. This is called the foreign body response or reaction (FBR), which is one of the essential aspects to be considered with implantation of biomaterials like breast implants because of its effect on the longevity of the implant. (Langer et al. 2014, 389)

Consequently, FBR starts already during the procedure of implantation: in seconds actually. Its timeline is illustrated in *Table 1*. This initiates blood-tissue interactions, of which characteristics are complement, thrombus formation and degradation systems' activation and blood coagulation. The incision required for implantation fractures the vasculature of the breast, and as can be seen from the *Figure 1*, there is plenty of fragile soft tissue and blood vessels susceptible to breakage. Therefore, the implant comes in contact with blood and its proteins during the operation. Albumin, fibrinogen and immunoglobulin G (IgG) are the most prominent proteins, which adsorb onto the breast implant. In addition, platelets—major factor in coagulation—are drawn to the site controlling blood clotting. These proteins induct inflammatory cells such as macrophages and neutrophils, which further contribute to inflammation at the site. Some of the proteins attach onto the implant, and their attachment is dependent on the affinity and other surface properties (i.e., topography) of the implant. This is known as the *Vroman effect* and thus, the shell of a breast implant is a critical factor in controlling the FBR. (Langer et al. 2014, 499)

Immediately	24 h	1 week	2 weeks
Protein adsorption	Granulomas	Granulocyte recruitment	Angiogenesis
Macrophage recruitment	Fibroblasts	Granulation tissue	Mononuclear cell recruitment
Coagulation	Neutrophil recruitment	Fibrotic capsulation	Connective tissue networking
Cytokine release	Lymphocyte recruitment	Scarring	Nerve sprouting
Provisional matrix	Inflammation	Acute inflammation	
	Reactive oxygen species	Leukocyte recruitment	
		Wound closure	

Table 1: The approximate timeline of FBR

The procedure also disturbs ECM networks and thus, new provisional matrix forms to aid structural integrity. The newly formed matrix also guides biochemical reactions and cellular interactions, which are important for wound healing and the FBR. This happens when the fibrinogens, fibronectin, proteoglycans and platelets establish a network for blood clotting functions, which later develops into a scaffold-like structure consisting of fibronectin, collagen, proteoglycans and fibroblasts. The development is led by the fibroblasts and other inflammatory cells. Inflammatory cells such as neutrophils are then able to continue inflammatory reactions because the scaffold provides growth factors like transforming growth factor beta (TGF-β), other cytokines and chemokines that stimulate these cells. (Barker and Engler 2017)

3.1 Immunology of silicone and saline

Implants elicit FBR when inserted into the breast. We are now looking into how silicone elastomer, silicone gel and saline effect FBR and later we take a further look into the biological mechanisms of the reaction. There are some differences in immune responses between implant types. Generally, the silicone implants do not elicit abnormal lymphocyte action, at least not because of the material itself. But some implants, such as Siltex®, has shown to induce cell attachment contrary to smoother implants due to its surface properties. (Cappellano et al. 2018) It is better known how the topography and shape of the implant affect immune responses than the materials themselves.

Nonetheless, recent studies have noted that breast implant rupture can cause drifting of silicone particles into tissues. The particles trigger FBRs, which turns into systemic inflammation due to infiltration of the particles into the lymphatic system. The droplets then promote the formation of autoantibodies (antibodies against own tissues), which can lead to the development of autoimmune conditions. Though these events are well recognized, it is still unclear whether the causation is due to silicone itself or just infiltration of immune response provoking particles. (Watad et al. 2018)

Studies have shown with *in vitro* models that silicone gel is not cytotoxic, but silicone can accelerate immune system by stimulating lymphocytes and thus, interleukin 1 (IL-1) secretion. IL-1 is linked to the formation of fibrosis because it activates fibroblasts indicating weak adjuvant immune reactions. This could mean that the silicone implant itself contributes to capsular contracture and the rupture of an implant, which is supported by studies on the effects of the surface of breast implants. (Tavazzani et al. 2005) In addition, the breakdown of implant shell due to i.e., capsular contracture can contribute to systemic inflammation as the silicone particles induce T cell responses and affect cytokine signaling (Cappellano et al. 2018) And as is written by a committee in *Safety of Silicone Breast Implants* "the committee finds that there is conclusive evidence that some silicones have adjuvant activity, but there is no evidence that this has any clinical significance." (Bondurant et al. 2000) This means that causality between silicone and abnormal lymphocyte action has not been efficiently proven.

Saline filled implants gained popularity in 1990's, when silicone gel filled implants were pulled off the market by FDA. However, one big concern for these implants is deflation, where the saline diffuses through the shell of the implant into tissues. This has raised questions of their safety. (Cunningham et al. 2000) In addition, some case studies have shown links between lymphomas and saline breast implants but there is a lack of further studies on the subject. (Keech Jr. and Creech 1997) However, some evidence can be found showing us connections between chronic inflammation, biofilms and lymphomas.

3.2 Inflammation

After the blood-tissue interactions like the Vroman effect and provisional matrix formation, inflammatory reactions take a step forward on the breast implant. Inflammation after implantation can be divided into two parts, acute and chronic inflammation. Acute

inflammation is a quick inflammatory reaction distinguished by neutrophils (polymorphonuclear leukocytes, PMNs) along mast cells and histamine distribution. Neutrophils phagocytize pathogens and foreign materials. On the contrary to histamine, cytokines interleukin 4 (IL-4) and interleukin 13 (IL-13) are anti-inflammatory, which means they suppress the stimulus for macrophages and monocytes. They are similar to histamine receptor antagonists, which decrease signaling for the mast cells. Acute inflammation commonly resolves quickly (lasting from hours to days) but the duration is dependent on the nature of the injury. Usually edema (swelling) occurs at the inflammation site. (Ratner et al. 2013, 505)

If acute inflammation does not resolve, it can turn into chronic inflammation. This is common for implanted biomaterials because like in the case of augmentation mammoplasty the implant is left in place and thus, the surgical site is dealing with foreign material continuously. Therefore, receding of the inflammation is delayed. Chronic inflammation is characterized by oncoming mononuclear cells, which in the FBR are monocytes and macrophages. Also, lymphocytes can appear on the interface between the tissue and the implant. Chronic inflammation is said to last for merely weeks, and if the inflammation is prolonged, it can be a sign of infection or toxic residue from the implant. These inflammatory reactions could be guided with the composition of the breast implant as we learned in *2.3 Immunological responses to silicone and saline*. (Anderson et al. 2007) However, when the monocytes and lymphocytes cannot break down the implant, they begin to layer. Then, fibroblasts and granulocytes are emerging to the site and angiogenesis (sprouting of new vessels) occurs. This can lead to formation of granulation tissue and a fibrous capsule. The layering and fusing of macrophages cause formation of foreign body giant cells (FBGCs). (Sheikh et al. 2015)

Granulation tissue begins to emerge when inflammation evolves. It is characterized by granularity with pinkish color due to angiogenesis. Sometimes granulation tissue can be seen as early as two days into the initial wound. The purpose of the granulation tissue is to continue the development of the provisional matrix and support healing. (Häkkinen et al. 2011) In addition to the signaling molecules assigned to the area during provisional matrix formation, reactive oxygen species (ROS) appear to help tissue formation. They are oxygen ions and other peroxides, which are highly effective signaling molecules in low amounts for tissue reformation. Higher amounts can cause tissue damage, but the ROS are fortunately carefully controlled by anti-oxidants. (Novo and Parola 2008)

The formation of granulation tissue initiates nerve sprouting to the site and wound closure. This is a proliferation phase, which slightly overlaps inflammatory phase (Fitridge

and Thompson 2011, 424). Wound closure starts with the employment of fibroblasts, which recruit fibronectins. Fibronectins are proteins that mediate cell adhesion and gather collagen to the site. Thence, wound closure accelerates. Furthermore, hyaluronan is present in granulation tissue. It prevents scar formation by stimulating expression of type I and III collagen in addition to TGF-β1 and - β3. Wound closure is advanced, when myofibroblasts form. They make a connective tissue network of collagen fibrils, which start to pull wound edges together. Unfortunately, disturbances during the granulation tissue development can lead to scarring, and on themselves—these strong inflammatory actions in adults—contribute to the formation of scars. (Häkkinen et al. 2011)

3.3 Healing after the procedure

The expected healing timeline is quite straight forward if everything goes as planned and no major complications appear. The healing timeline is illustrated in *Table 2*. The table is constructed of time stamps that appeared in 3. Foreign body response, NHS guidance material (2019) and multiple posts by plastic surgeons such as one blogpost written by Lee (2022).

Day 1	1 week	2 to 3 weeks	4 to 6 weeks	After
Anesthesia wears off	Granulation tissue	Granulation tissue	Inflammation should subside	Healing should complete
Seroma and edema	Connective tissue formation	Vascularization	Scarring completion	Observation for signs of infection
FBR begins	Bruising	Discomfort and pain subsides	Slight movement of the implants	Scar starts to fade
Blood coagulation	Increase in pain	Wound closing		Seroma subsides
Inflammatory reactions	Wound closure initiation	Stitches are removed or dissolved		Implants adhere to tissues
		Scarring		Life goes back to normal

Table 2: Healing timeline after augmentation mammoplasty

It is essential to understand that complications such as capsulation, hypertrophic scarring and chronic inflammation are common but are in a marginal group of results after breast augmentation. Therefore, healing normally is the expected outcome and this thesis just brings attention to the abnormalities to give comprehensive information on most of the tissue reactions resulting from augmentation mammoplasty.

3.4 Scarring

Wound finally closes when keratinocytes are activated at the site during epithelialization. This stage is a part of a remodeling phase, where wound closes and scar tissue forms while tissues strengthen. During wound closure (maturation) the angiogenesis declines via aggregation. Density of the site and activity of metabolism at the injury decrease. (Fitridge and Thompson 2011, chapter 23) Scarring occurs when collagen fibers begin to layer on the wound site parallel to normal collagen fiber composition in normal epidermis (skin). This can happen inside the surgical site and to the incision site. Scar tissue is defined by these changes in collagen structure and incomplete maturing formation of rete pegs and dermis. (Powers et al. 2017, 124-125) According to Fitridge and Thompson (2011, 431) “scar tissue is always weaker and will break apart before the surrounding normal tissue”, which is ultimately one of the main issues of scar tissue and aspects to consider, when performing implantation.

When the vasculature during remodeling does not decrease and tissue builds up, a scar becomes hypertrophic or a keloid. They have been thought to be caused by a lack of oxygen (hypoxia) and swelling of vessels and cells. Furthermore, an excess agglomeration of fibroblasts and collagen have been found to cause hypertrophy. Histologically, it is difficult to distinguish a hypertrophic scar from a keloid. However, a keloid is formed in a nodular fashion because of “keloid collagen” (disorderly collagen). Hypertrophic scars on the other hand reflect more a normal scar with increased amount of myofibroblasts and lack the nodules. Nevertheless, they both cause extra tension and extend over the initial wound, which can predispose to complications later. (Powers et al. 2017, 125-126) On the other hand, scars can also remain immature leading to atrophic scars. Atrophic scars are caused by insufficient inflammatory reactions, which in turn disturb the normal development of a scar. Thus, the forming scar is imbalanced in collagen composition and develops beneath the surface level of skin. This may cause sagging of skin and lost elasticity, which both can affect the healing process after an augmentation mammoplasty. (Bolton et al. 2017, 420)

Because the healing processes slightly overlap, we must take a little step back to observe what is happening inside the breast and on the implant prior wound closure. Before scar maturation finishes, macrophages layer and fuse into each other forming FBGCs as a result of complicated mechanisms like cytokine and molecule signaling. For example, a well-known molecule inducing this fusion is vitamin E (α-tocopherol). The fusion is believed to increase phagocytotic action, which is a desired reaction when an implanted foreign body is supposed to be removed. However, silicone implantation maintains the

reaction for a longer period of time risking material longevity of the breast implant because FBGCs release degradative enzymes and acids to achieve biodegradation. The acid (pH 4) environment inhibits antibacterial activities of cells and other immune systems at the implantation site increasing susceptibility to infections. In addition, FBGCs activate cells with fibrotic features accelerating formation of fibrous capsule and scarring. (Anderson 2009) These factors must be considered when deciding what kind of materials are suitable for a breast implant.

3.5 Capsulation

Along macrophages, fibroblasts emerge to the wound site. They differentiate into alpha smooth muscle actin expressing (α-SMA; a myofibroblast marker indicating smooth muscle formation) myofibroblasts, which aid in wound closure and connective tissue repair. Normally myofibroblasts are discarded through apoptosis after tissue integrity has been restored but in case of prolonged inflammation—like one caused by implantation—their presence is extended. (Wynn 2008) Chronic inflammation promotes fibrosis with stimulation of growth factors, cytokines, chemokines and enzymes such as matrix metalloproteinases 2 and 9 (MMP-2 and -9) and their inhibitors (TIMPs; tissue inhibitors of metalloproteinases). The ongoing presence of myofibroblasts cause accumulation of excessive collagen and loss of tissue function, which leads to immoderate scarring and hardening of tissues. (Rolfe 2011) Thus, fibrosis can endanger organ function of the breast and severely compromise the functionality of a silicone implant whilst upkeeping the inflammation by stimulating inflammatory cells.

The forming fibrous tissue surrounds the implant due to chronic inflammation after tissues have not been able to discard the foreign body material. This phenomenon is called fibrous capsulation or just capsulation for short, which is a general consequence of biomaterial implantation. (Jones 2015) The intensity of capsulation is dependent on the topography and material composition of the breast implant. The ultimate purpose of capsulation for body is to isolate the implant from the surrounding organs and tissues, which is often achieved with advanced fibrosis. Fibrotic tissue grows around the implant due to collagen synthesis induced by platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF) and TGF-β for example, which advance ECM remodeling and strengthen the fibrotic tissue by stimulating e.g., keratinocytes and fibroblasts. After complete isolation is achieved, encapsulating reaction stabilizes. If isolation is not accomplished properly, FBR keeps on going leading to thick fibrosis, scarring and capsular contracture. These consequences can lead to the rupture of an implant and be painful

for the patient. (Shin et al. 2018) Capsular contracture occurs as often as approximately 23 % of the cases (Peters 2012, chapter 6)

Capsular contracture is the most common cause of reoperation. It can cause the breast to feel stiff, may malposition the breast implant and can lead to additional adverse effects such as tissue trauma and pain. As we know, the cause of this is chronic inflammation. Furthermore, it has been shown that increased inflammation caused by an infection is a notable cause of capsular contracture. A biofilm that forms from an infection compromises the surface structure of the implant and accelerates inflammatory actions. Its genesis is linked to be dependent on where the implant was inserted from, with periareolar incision being the most concentrated in bacteria. In former capsular contracture studies Teitelbaum (2014, 566) stated that “saline (filled) implants had an advantage in reducing capsular contracture over older generation silicone gel implants”. This has since been disregarded because the shell properties of breast implants have developed so much that silicone diffusion and impurities within the materials are infinitesimal. (Teitelbaum 2014, 566) However, these problems must be considered when designing an implant and before the augmentation mammoplasty. Biofilms and their effects on the implant were discussed in more detail in *2.3 Immunological responses to silicone and saline*.

3.6 Connection to autoimmune diseases

Autoimmune diseases have often been speculated to have connections to various symptoms like fatigue and neurological symptoms after augmentation mammoplasty. Some studies associate these symptoms with silicone breast implants while others say the connection lacks evidence. The argument remains impugned, but scientists are eager to conduct studies on this topic to find answers.

A study conducted in 2018 by Watad et al. is for the argument that the connection exists and is relevant. The study found that there is an increased odd ratio between autoimmune disorders and silicone breast implants. Autoantibodies were found in patients with silicone breast implants. The autoantibodies are thought to emerge due to circulating silicone particles that elicit immune responses. They can also produce antibodies against collagen, which could lead to arthritis-like condition (Khachigian 2006). Moreover, patients with silicone breast implants have an increased risk of developing connective tissue disease, the study found. They also reviewed other studies, which found that 30-50 % of symptomatic patients had Raynaud’s disease. Furthermore, patients were often linked to sarcoidosis, which could be supported by the natural formation of granulation tissue after an injury occurs. Some women in the study were relieved from the symptoms

after explantation but those who evolved autoimmune conditions were symptomatic even after the removal of the implants. All in all, inconsistencies due to difficult clinical evaluations were acknowledged. (Watad et al. 2018) These findings are still significant despite having limitations due to the complexity of the study, but the topic should nevertheless be studied further to prove whether the argument stands.

US FDA Large Postapproval Studied states that silicone breast implants are indeed associated with greater than double the general population to autoimmune diseases like Sjögren's syndrome, scleroderma, rheumatoid arthritis, stillbirth and melanoma. However, it is noted that the association is highly dependent on the fact, whether patients actually tell the truth and if clinicians are able to diagnose the symptoms accurately. Nonetheless, scientists are comfortable with the results of connection between arthritis-like symptoms and breast implantation. Furthermore, only 10 % of rheumatoid-like symptomatic patients had saline implants, which raises questions again of the safety of silicone implants. The connection between connective tissue disease and breast implants is dependent on patient stories too and remains relevant because connective tissue disease is known to cause stillbirths. (Coroneos et al. 2019) (Balk et al. 2016)

One of the strongest opposing arguments to the connection of autoimmune diseases and silicone breast implants is age. Susceptibility to autoimmune diseases is said to increase along aging whether a person has gone through augmentation mammoplasty or not. (Doloff et al. 2021) Still, the findings of the US FDA Breast Implant Postapproval Studies were consistent even after age-adjusted analysis. The common symptoms of the conditions are for example, fatigue, exhaustion, joint swelling and pain, numbness and frequent muscle cramps. The increase of these symptoms has not been caused solely because of aging in patients with silicone breast implants. Statistics made from the data gathered by the study shows that one-in-nine patients undergo reoperation and of those patients one-in-four undergo reconstructive surgery. One-in-three of first-time augmentation patients, and half of reoperation patients will face complications due to augmentation mammoplasty. (Coroneos et al. 2019) Even so, capsular contracture remains the leading complication of patients with one-in-four occurrence (Peters et al. 2012, chapter 6)

4. REGULATION

Regulation regarding the safety of silicone breast implants vary between the United States and the European Union. In 1980's the safety of silicone in breast implants was questioned, which resulted in pulling off silicone gel filled breast implants from the US market in 1992. Silicone breast implants were moved to Class III, higher-risk products needing premarket approval. FDA thought that companies had not met the safety standard of silicone breast implants and required research of the safety of their products from them. Saline filled implants remained on the market. A committee conducted a large study called the Safety of Silicone Breast Implants (Bondurant et al. 2000), which researched widely the safety of silicone gel. The study then showed that silicone gel was not evidently connected to autoimmune diseases and cancer. Later in 2006, two companies—Allergan® and Mentor®—were able to provide FDA sufficient proof of the safety of their products and thus, silicone gel filled implants returned to the market. (FDA 2011)

So, the breast implants are strictly regulated in the US. To be able to get breast implants to the market, one must provide six post-approval studies for the FDA. This is believed to increase the quality of the silicone breast implants and give enough information for patients to make informed decisions. Information of the studies can be released during the process of conducting them, as FDA believes this gives valuable information for clinicians and patients. The six post-approval studies are as follows: Core Post-Approval Studies (Core Studies), Large Post-Approval Studies (Large Studies), Device Failure Studies (Failure Studies), Focus Group Studies, Annual Physician Informed Decision Survey (Informed Decision Study) and Adjunct Studies. (FDA 2011) The data from these studies is easily accessible through the FDA website, which increases the feeling of safety and definitely is in good taste for open research.

On the contrary to the restrictions FDA has set, the EU is more approving of such medical devices like silicone breast implants. Clinical trials are not required for medical device approval in the EU, and there are merely directives of what materials are suitable for such devices. The European Commission followed FDA in the beginning of 1993 with restricting the market of silicone gel filled implants and soon after the breast implants were thought to be non-active medical devices and regulatory requirements were put in place. Following FDA almost 10 years later, the EU described silicone breast implants as high-risk medical devices in 2003. Yet, clinical trials are still not required, and safety

can be proven with as small sample size as 100 patients. These inadequacies are believed to be the reason why a company called Poly Implant Prothèse (PIP) was able to sell harmful breast implants to patients. (Zuckerman et al. 2012)

PIP manufactured implants called PIP implants, which caused a transatlantic breast implant scandal. The company used industrial grade silicone in the breast implants, which were prone to silicone gel bleeding and ruptures with rupture rate of 12.2 % of cases. (Thomson et al. 2018) The scandal caused world-wide fear among patients with breast implants and raised health concerns as well as safety concerns. The implants were made of low-molecular weight silicone gel, which allowed the gel to bleed into tissues in a case of a rupture. Studies have shown that the longer PIP implants were implanted, the risk of rupture grew higher. The particles bleeding from the implant are known to cause inflammatory responses, which explains various symptoms experienced by PIP implant patients. The defective implants also require reconstructive surgery more often than other clinically proven safe implants like those of Allergan's® or Mentor's®. (De Lorenzi et al. 2015)

The EU has since stricten regulations of medical devices. Medical device products must meet the General Safety and Performance Requirements (GSPR) to achieve CE mark on the products. The marking provides valuable information to consumers, assuring the safety of the product. The EU has also lengthened the acceptance process, as there are more clinical evaluations needed than before. In addition, manufacture processes and manufacturers have been obliged to notify any changes of products and manufacturing even if their products have been assessed and accepted before. All violations to the new directives are liable by national laws. (Regulation (Eu) 2017/745 of the European Parliament and of the Council) Last year in 2021, FDA also strengthened its regulation of breast implants. The regulation mainly concerns patient communications with sufficient safety warnings and a checklist to go through with patients before breast augmentation as FDA has noted concerns of BIA-ALCL. The materials used in breast implants were also updated, labeling of the products were stricten and screening recommendations for capsular contractures (for silicone gel filled implants) were made. (FDA 2021)

All in all, the US is still stricter with regulations regarding the safety of silicone breast implants than the EU. They have implemented restrictions to the breast implant market the earliest, done thorough research on safety concerns and have been more active in controlling the breast implant market. However, FDA sometimes lacks implementing of their own restrictions, which undermines their trustworthiness. Nonetheless, it is safe to

say the EU has improvable regulations of medical devices, and fortunately some re-evaluations of directives have already been put in action. (Zuckerman et al. 2012)

5. CONCLUSIONS

Augmentation mammoplasty is a multistage procedure, where many aspects must be considered. This thesis brought together the immune reactions caused by silicone implants along with a background on the surgery process and regulation of implants. It was noted that there is little evidence of PDMS itself having a significant effect on FBR compared to the shape and shell type of a silicone implant. The most important attributes of a silicone implant to the FBR seemed to be the size, shape and topography of the implant. In addition, the filling of the implant —silicone gel or saline —had a slight effect on the immune responses. It was stated that silicone gel has more adjuvant activity compared to saline, and that silicone implants are 100 times more likely to cause rheumatoid symptoms. Yet, there was little to no studies found of proper mechanisms behind saline's effects, but it was generally thought out to be biocompatible as well.

The complications of augmentation mammoplasty should be studied more. Some studies showed connections between biofilm formation and BIA-ALCL. Same studies found that the genesis of a biofilm could be controlled with the topography of an implant. Other topography studies backed this statement adding that the topography also has an effect on adaptive immunity, which plays a role in the genesis of cancers and autoimmune diseases. However, there were controversial studies contradicting these statements, but they could be victims of bias or product of their time. In addition, vast clinical studies of the connection between autoimmune diseases and silicone breast implants have been conducted. They stated that evidence of autoimmune diseases caused by silicone implants is not clear and susceptible to diagnostic errors. Nonetheless, scientist generally agree that the small indications of autoimmune diseases is enough evidence to require more thorough studies on the topic.

Breast implantation is a procedure, of which purpose is to make permanent change to the appearance of the breasts. The silicone implants that are implanted in the operation are thus, required to endure immune responses and varying chemical conditions for a long period of time. This elicits an advanced FBR, where chronic inflammation might not subside. The chronic inflammation the leads to fibrous capsulation and one out of four cases capsular contracture. It is noted that knowledge on how to control the FBR is essential for better recovery after augmentation mammoplasty.

Because of all the possible complications and safety questions still unanswered, silicone breast implants are quite restricted in the US. In 1990's silicone gel implants were pulled

off the market, and only those implants came back, of which companies provided sufficient proof of their safety. Breast implants in the EU are regulated quite differently. There are merely directives of how class III medical devices like breast implants can be brought to the market but the regulation regarding materials is unclear. There are also no evident restrictions of specific implant types. This may be behind the reason why toxic industrial silicone (PIP) implants were able to come available for surgeons in 2000's.

However, the scandal caused by these implants lead to new surge of safety studies on breast implants like the one conducted in the US, which had almost 100 000 evaluated cases. Till this day, studies are being conducted as scientists have learned more about the effects of topography and silicone to BIA-ALCL and autoimmune diseases respectively, which proves there is a lot of unknown factors contributing to the complex symptoms present after augmentation mammoplasty. And in the end, the further research goes on the safety of silicone implants, the more assured patients can be whether they have made the right choices regarding the procedure. The ultimate goal is to decrease the complications and suffering of patients, as well as improve the methodology of augmentation mammoplasty.

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