Original Article

Capsule formation around breast implants

R. Bayston[*]

School of Medicine, University of Nottingham

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A B S T R A C T

All implants are rapidly coated by the host with glycoproteins forming a thin capsule, and this is a normal response. Where an inflammatory stimulus such as infection is present, the capsule can thicken and become microvascularised and sometimes calcified. This inflammatory stimulus can take the form of leachable chemicals from the implant, or bacteria live or dead. The presence of live bacteria can lead to biofilm development, which is part of the chronic infective, inflammatory process. *Staphylococcus epidermidis* and *Cutibacterium acnes* have been implicated in chronic infection around breast implants, and some animal models suggest their involvement in capsule contracture. Molecular methods have revealed an array of microorganisms from samples of removed capsular material, though they are extremely sensitive to contamination. The relevance of the results to capsular contracture remains poorly understood.

Bacteria of low virulence are shown associated with capsular contracture and calcification, and measures beyond those conventionally applied need to be investigated to limit perioperative contamination.

* Corresponding author: Professor Roger Bayston, School of Medicine, C Floor West Block Queen's Medical Centre, Nottingham, NG7 2UH. Tel 07739490789.
E-mail address: roger.bayston@nottingham.ac.uk

Introduction

All implants of every material are coated with glycoproteins and other materials derived from plasma and extracellular matrix immediately after implantation into host tissue.[1] This is a normal response which in itself does not involve an inflammatory reaction to the biomaterial; however, it can act to reduce this. However, fibroblasts and macrophages then begin to accumulate and collagen is deposited forming a thin fibrous capsule around the material. In the presence of biocompatible (i.e. non-irritant) materials, foreign body reaction usually has no adverse consequences. In some cases, the process develops to involve inflammation and the capsule can thicken. Here a three-layered structure has been described[2,3] with acellular as well as microvascularised regions, and in some cases, calcification develops near to the implant surface. This calcification consists of crystals of hydroxyapatite (calcium phosphate).[4] These authors found no silicone in the capsule material using electron probe microanalysis and infrared spectroscopy. However, studies show that the silicone shell of the implant might undergo microdegradation by lipids or by hydrolytic components of macrophages and neutrophils that lyse at the silicone surface. This could trigger the release of small silicone particles which, in turn, could exacerbate the inflammatory process. Refractile silicone fragments were found inside macrophages from implant capsules by Prantl et al.[3] These do not appear to be the result of the leak of the gel as this has been shown to give rise to siliconoma.[5] Other studies have documented experimental evidence of low molecular weight silicone "bleeding" from the shell, possibly a source of silicone "droplets" in macrophages.[6] Medical grade silicone contains small amounts of uncrosslinked low molecular weight and extractable siloxanes, which might contribute to the chronic inflammatory environment.

The degree of inflammation and the presence of silicone in the capsule have shown a correlation,[7] though whether this is the initial cause of the inflammation or the result of cellular inflammatory reaction from another cause is unknown. Contractile myofibroblasts have been identified in the capsules around the implants and these might be the possible cause of capsule contracture[8]. Fibroblasts have been shown to be the progenitors of osteoblasts,[9] and this could account for their calcification. In all these situations, a chronic inflammatory process appears to be at work.

A few studies have suggested that subclinical bacterial infection might be the initiator of the chronic inflammatory process.[3,10]

Possible role of bacteria in capsule formation

Frank acute infection around breast implants is uncommon. It can appear long after implantation, and the source of the infecting organisms might be contiguous from the nipple ducts, which are known to bear bacteria,[11] or from hematogenous seeding from a distant site.[12] Though contamination can cause acute infection during surgery, no association has yet been established between positive perioperative cultures and subsequent capsular contraction.

All implantable devices of all materials have a risk of bacterial infection. The rationale for this and the significantly higher risk than in surgery without implants is explained by an early series of experiments, that were performed by Elek and Conen[13]. The effect of including biomaterial in human challenge experiments with *Staphylococcus aureus* was to demonstrate that the number of bacteria needed to cause infection was reduced by approximately 10,000-fold by the presence of this biomaterial. This can be explained as once bacteria make contact with the biomaterial, they rapidly undergo a metabolic change that makes them much less susceptible to antibiotics and phagocytosis.[14] Thereafter, the development of a biofilm occurs.

The biofilm mode is thought to be the normal form of microbial existence, and planktonic populations are either transient or occur only in artificial conditions such as laboratory cultures. Biofilms are accumulations of microorganisms, usually single species in surgical infections, that are adherent to a surface and to each other, which surround themselves with a matrix consisting of glycosaminoglycans, proteins, and bacterial extracellular DNA. Microorganisms in a biofilm undergo down-regulation of most of the genes associated with planktonic growth and adopt a dormant existence because levels of nutrients such as carbon, phosphorus and iron, and oxygen are low in the biofilm, leading to a crisis in the generation and transport of energy (via ATP) in the bacterial cell.[15] Syntheses not required

in biofilm modes, such as most cell wall manufacture, proteins such as haemolysins and toxins, and enzymes involved in DNA turnover are significantly reduced, and genes governing the production of the biofilm matrix are upregulated. As the downregulated syntheses are the targets for common antibiotics, the failure of systemic antibiotic therapy can occur for most biofilm infections. Biofilm infections tend to be chronic, especially if they involve "low-virulence" bacteria such as coagulase-negative staphylococci (CoNS) or *Cutibacterium (Propionibacterium) acnes*. Though biofilm bacteria do not produce toxins, the breakdown product of their cell wall material, peptidoglycan, is pro-inflammatory[16,17] and leads to sterile abscess formation around some biomaterials but not others.[18] The dormant cells also possess the ability to survive and multiply inside phagocytes after ingestion,[19] further enhancing chronicity.

Bacteria growing as biofilms on implants are difficult to detect and unexpectedly negative cultures are common. Sonication techniques have been employed to dislodge and disperse the biofilm on removed implants, and this has resulted in the detection of bacteria in breast implants removed because of capsular contracture.[20] The implants were subjected to sonication; the sonicate was then centrifuged 100-fold to concentrate the implants, and cultured aerobically and anaerobically for up to 14 days. The number of colonies was then determined. These technical details are important as the concentration step increases the sensitivity, and the prolonged anaerobic culture ensures that *C acnes* are not missed. The quantitative culture allows few colonies that might represent contaminants to be distinguished from those where significant counts are found. The authors found nine significant positive cultures from 27 cases of capsular contracture and only one in the remaining 18 cases with no history of contracture. The predominant isolate was *C acnes* (seven implants) with CoNS in four implants. Tissue samples processed in the same way gave fewer positives. Histology of the capsule material showed evidence of calcification in 29% of those with contracture, and none in those without. Material consistent with silicone was found in a similar proportion (∼30%) of each group, though it remains unclear whether this was particulate or was in the form of intracellular droplets. Other studies have isolated bacteria from either capsular tissue or removed implants but the technical methods are variable and often do not meet the standards of Pozo's study.[20] Nevertheless, the most common isolates are CoNS, and in many cases *C acnes*. There seems to be a strong association between the presence of either CoNS or *C acnes* or both and chronic inflammation, thicker capsule formation, and calcification with contracture, though the relationship between this association and cause remains unknown.

Studies with Animal Models

Though several animal models have been investigated, the study by Tamboto et al[21] represents a systematic approach with up-to-date techniques. Fifty-one miniature breast implants were implanted into seven pigs, with full surgical asepsis and antisepsis. Of these, 36 were inoculated with up to 1×10^6 colony-forming units of *S. epidermidis* after implanting but before closure, the remaining 15 implants were uninoculated. After 13 weeks, no pig showed signs of overt sepsis. The implants were assessed for capsular contracture by palpation, and the pigs were humanely killed and the implants removed with strict aseptic precautions. Capsular material was removed, macerated, and sonicated, and then quantitative aerobic and anaerobic cultures were set up. Samples were also fixed and examined by scanning electron microscopy (SEM). Of the 36 inoculated implants, 72% showed biofilm formation and 78% showed capsular contraction, Baker III or IV. Of the 15 uninoculated implants, 27% showed biofilm formation and 47% showed capsular contraction. However, the uninoculated implants showing biofilm had inadvertently been contaminated during implantation by a porcine strain of *S. epidermidis*. Overall, of the 31 biofilm-positive implants, 25 (81%) showed significant capsular contracture. Hence, biofilm formation showed a strong association with capsular contracture (p=0.0213).

The number of bacteria recovered from the inoculated implants and those contaminated during surgery were very low after 13 weeks. Almost 30% of the first, intentionally inoculated group were culture-negative even when bacterial biofilm was identified on SEM. A similar result was found by Kossovsky et al[22] whose inoculated implants were all culture-negative after 40 days of implantation. Though this might be due to the recognized difficulties in culturing bacteria from biofilms, Tamboto et al[21] used accepted techniques for this, and their findings support the possibility that that non-

viable bacteria or their breakdown products might provide the cellular stimulus for capsular thickening and calcification leading to contracture.

Molecular methods

Perhaps because of the low culture-positive rates, several authors have employed molecular methods, particularly sequencing. In one study, DNA that was identified from 42% of tissue samples taken perioperatively, revealed 120 "unique" bacterial species and six "unique" fungi.[23] Some of these species, such as *S epidermidis* and *C acnes*, have been identified by conventional culture but many other species are rarely reported in medical microbiology practice. Similar results have been reported by other researchers.[24] A question arises as to the clinical relevance of these results to infection, and particularly to capsular contracture. Importantly, the results represent the presence of bacterial DNA, not necessarily viable or even intact bacteria. Environmental contamination by very small amounts of bacterial DNA during manufacture or implantation or explantation, cannot be ruled out. Dissemination of bacterial DNA from colonized sites in the healthy body, such as skin or gut, is possible. Furthermore, DNA from environmental bacteria may accumulate in the tissues with no clinical consequence. Until more evidence is known about the results of molecular studies, their contribution is difficult to evaluate their importance for understanding the aetiology of capsular contracture.

Conclusions and recommendations

There is mounting evidence that the presence of bacteria of low virulence, particularly *S epidermidis* /CoNS and *C acnes*, is associated with thickening of the naturally occurring capsule, and its subsequent calcification and contracture, and the cellular biology of the process needs further elucidation. It is important to note that bacteria do not need to be viable or at least culturable in order to cause a pathological response.[25]

There is a possibility that the bacteria reach the implant at some time after implantation from haematological transfer. However, if the bacteria access the implant during implantation, as happens with many other implants, an opportunity can arise to apply preventive measures at this time. Contiguous contamination from the ducts is also possible, which is known to harbour *S epidermidis* and *C acnes*, in the immediate post-operative period, and the protective activity of any measure would need to persist until the tissue around the implant had healed and the normal capsule had formed. Beyond conventional perioperative antibiotic prophylaxis, the application of high- concentration local antisepsis, either by application of antibiotics in the form of irrigation or powder is possible, as is now commonly used in spine surgery,[26] or some form of antimicrobial impregnation of the shell of the implant. The latter strategy has been discussed by Lam et al.[27] Some of the coatings suggested for other implants might not be readily accepted in this situation. Coating with polyethylene glycol or metallic nanoparticles such a silver could be viewed as an unacceptable cytological risk because of the current lack of understanding of the cell biology of capsular contracture, and perhaps particularly Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL). However, a doxycycline-coated silicone breast implant has shown promise compared to a standard antibiotic wash.[28] Some antimicrobial impregnation processes have already been used and have been shown to be safe for implantation into the central nervous system[29,30]. Moreover, an animal implant study of breast implants[31] showed that impregnation of the silicone shell with a combination of rifampicin and minocycline protected against *S aureus* infection for at least 4 weeks. However, these authors could not comment on capsule formation or contracture. A version of these approaches might be considered in the future.

Conflict of interests

Funding

Ethical Approval

Not applicable

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