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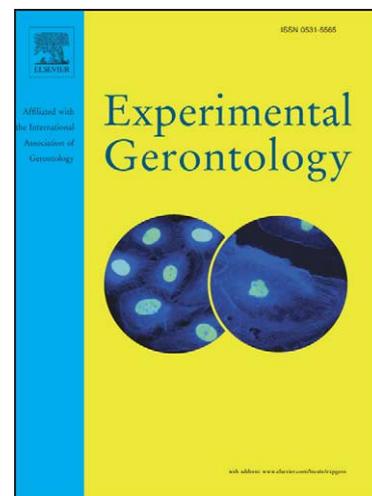
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Mini Review

Silicone mammary implants – can we turn back the time?Aleksandar Backovic¹ and Dolores Wolfram²

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Abstract

Mankind remains infatuated with finding the "fountain of youth", and plastic surgery has become a very important component in the search for eternal youth. Invasive procedures such as face-lifts, body contouring, and implantation of silicone mammary implants (SMI) as well as less invasive procedures such as wrinkle decreasing protocols using filler substances or botulinum toxin, effectively reshape and rejuvenate the aging face or body. However, despite the improved cosmetic appearance of the individual, these treatments disrupt normal aging processes on cellular and molecular level. For example, silicone degradation products promote protein denaturation and activate cells of both the innate and adaptive immune systems, thus perpetuating chronic proinflammatory response of the local tissue. In this review, we concentrate on SMI and summarize the current clinical approaches, and the immunological and biochemical effects of those interventions.

Introduction

The desirability of youth and beauty have been a constant in the continually evolving history of mankind (Pitanguy ,2000; Zimble ,2004). Current fashion trends and beauty stereotypes are promulgated via print and electronic medias and highlight the importance of fitness, youthfulness and beauty in our lives. Plastic surgery, unsurprisingly, has increased in popularity as a way to look younger despite chronological age (Rohrich ,2000). Medical advances in this century have enabled safe and efficient surgical corrections of contour deformities resulting from the aging process, and the use of less invasive "anti-aging" procedures, such as dermal filler substances or botulinum toxin is a rapidly growing sub-field in plastic surgery (Coleman and Carruthers ,2006; Wise and Greco ,2006; Wolfram et al. 2006).

Defining aging as an illness makes the benefits of surgical interventions self-evident. If volume loss of the aging face or body is considered a pathological rather than a physiological process, dissatisfaction with appearance is inevitable and youth-promoting procedures are indispensable for a personal perception of good health. The phrases like „treatment of the aging face” are often used in literature in the same ways as treatment of cancer or hypertension. By using the aging face or body as an object of treatment, aging is falsely defined as a disease, and this concept of aging is reinforced by stereotypes of beauty in contemporary consumerist societies. However, there is a theoretical problem with defining aging as illness, because it would implicitly define life as an illness as well (Ringel ,1998), since it is a process with the inevitable result being death.

From a surgical point of view, aging is a complex process involving two important factors: volume loss, and repetitive muscle contractions causing wrinkles and folds (Glashofer and Lawrence ,2006; Zimbler et al. 2001). The aging process thus leads to alterations of facial or general body contours that, in a youth-oriented culture, usually result in a decline in body image that provokes a strong psychological motivation for surgical correction (de Maio ,2004). According to the American Association of Plastic Surgeons, more than 128,000 face lifts were performed in 2003, representing an increase of 9% over the year before, and Botulinum toxin injections increased by more than 150% during the same period (Christie ,2004). In France, breast implant sales rose by 383% (61 800 implants) from 1995 to 2004(Petit ,2005).

Although the mentioned surgical interventions enhance the appearance of the individual, they often have deleterious effects on the molecular and cellular levels and can actually enhance the normal aging processes, for example by disrupting normal inflammatory processes (Bailey et al. 2005; Kossovsky and Stassi ,1994; Wolf et al. 1993), causing posttranslational modifications or protein denaturation (Hamilton ,2003; Somasundaram et al. 2000; Sun et al. 1997), and development of extensive local fibrotic reactions (Hu et al. 2001; Shanklin and Smalley ,1999; Wong ,1996).

This review concentrates on the use of silicone mammary implants (SMI) for body contour improvement in cosmetic surgery as an increasingly utilized intervention in the aging population, and discusses their adverse effects from medical, immunological and biochemical viewpoints in the context of normal aging processes.

2. Silicone mammary implants

2.1. Indications for silicone breast implants

Breast augmentation with mammary implants continues to be one of the most commonly performed procedures in plastic surgery. Despite the controversy about the safety and efficacy of silicone gel implants (Bar-Meir et al. 2003; Janowsky et al. 2000; Teuber et al. 1999), the desire for enhanced self-image and perfectly-formed breasts has led to a boom in cosmetic breast augmentation. The medical indication for breast augmentation is glandular hypoplasia, which may be developmental or involutional (“age-related”). Patients undergoing breast augmentation range from stable, well-adapted, and socially outgoing persons to depressed women with low self-confidence and self-esteem (Birtchnell et al. 1990; Meyer and Ringberg ,1987).

2.2 Implant types, operation techniques and complications of SMI

Currently, the two implant types in widespread use are silicone gel-filled or saline-filled implants, both of which have a highly polymerized silicone shell. Both implant types may be smooth or microtextured, spherical or anatomic. Both types of implants can be placed in a subglandular or submuscular location using three common incisions well-described in literature, namely the transaxillary, periareolar and inframammary, depending on surgeon’s preference (Mofid et al. 2006; Tebbetts ,2006). Although serious complications are rare after cosmetic breast augmentation, two categories of complications, early and late, can occur. Early complications are considered to be those arising from the operative procedure (e.g. hematoma, seroma, infection, asymmetry), while later complications are those based on the body’s response to the implant (e.g. capsular contracture, deflation or rupture, systemic complications) (Henriksen et al. 2003; Henriksen et al. 2005). Whether silicone breast

implant exposure results in systemic manifestations (e.g. connective tissue diseases, fibromyalgia-like syndrome) in some recipients remains controversial in the literature (Gabriel et al. 1994; Tugwell et al. 2001; Vasey et al. 2003). Large epidemiologic studies and meta-analyses have been performed by the FDA and other institutions to determine whether there was a relationship between breast implants and connective tissue diseases, (Janowsky et al. 2000) and a clear-cut causal connection between SMI and the appearance of systemic side effects could not be verified. However, these studies have been challenged and contradict single case reports describing autoimmune phenomena in women with breast implants(Asherson et al. 2004; Gurvits ,2006; Varga et al. 1989; Williams et al. 1977).

3. The stability of silicone polymer in vivo

Medical grade silicone (polydimethylsiloxane) is used both as the gel filling of a silicone breast implant and in construction of the outer shell. Although the chemical structure of silicones suggests great stability, they nevertheless undergo degradation with aging, and although the role of their breakdown derivatives in the tissue around the implants is unclear, immunogenic properties have been shown for at least some low molecular weight silicone compounds (Hamilton, 2003; Naim et al. 1997). In the connective, fat and muscle tissue around the SMIs, siloxane levels in the range of 1-1400 ng/g, and silicone from 9-85 µg/g were found. The same study found that siloxane concentrations in the fatty tissue were strongly associated with “gel bleeding” of an individual SMIs (Flassbeck et al. 2003). In addition to inducing protein denaturation (Sun et al. 1997), these silicone degradation products constitute a protracted stimulus to cells such as macrophages (Rhie et al. 1998; Tavazzani et al. 2005) that increase their cytotoxic properties, but the exact nature of such signals remains to be elucidated.

The interaction of silicone and its degradation products with various cell types has been described in several studies reporting various outcomes (Ciapetti et al. 1995; Ojo-Amaize et al. 1994; Tavazzani et al. 2005; Zhang et al. 1998). They agree that the cell response to silicone resembles a silent perpetuated foreign body reaction, but the exact mechanism of cell activation remains unclear. Elevated secretion of TNF- α has been found in fibroblasts and macrophages after silicone uptake, as well as the recruitment of T-cells to the surrounding tissue (Smalley et al. 1996; Wick et al. 1987). We have also noticed large silicone particles in fibroblasts and macrophages isolated directly from the fibrotic capsule surrounding the SMIs, as shown in Figure 1.

Platinum complexes are used in the production of SMIs as catalysts for cross-linking of the silicone chains. In addition to being a potent allergen itself, depending on the amount of ionized Pt that is liberated from the SMIs by the degradation process, proteins interacting with those ions may become vulnerable to denaturation (Brook, 2006). Denaturation most likely occurs through binding of ionized Pt by the sulfhydryl bridges that control the folding of the proteins (Lykissa and Maharaj, 2006). Furthermore, significantly elevated Pt concentrations have been found in blood (470-688pmol/L), urine (0.4-2.95µg/L) and local binding tissue (0.003-0.272µg/g) as well as in hair, nails, sweat and breast milk (Flassbeck et al. 2003; Lykissa and Maharaj, 2006).

Although they are highly irritant, hydrophobically modified amorphous silicates are used to reinforce the shell of SMIs, improving strength and tear resistance (Brook, 2006; Leyva et al. 2000; Shen and Ojo-Amaize, 1996). Silicates have been detected in the fibrotic capsule surrounding the SMIs (Jensen et al. 2003; Shen et al. 1996), and we have found silicate crystals in the liquid inside the autoinflated SMIs. Interestingly, several groups have reported the presence of silicate antibodies in carriers of SMIs (Brandon et al. 2002; Brody, 1997; Marotta et al. 2002; Vermeulen and Scholte, 2003), indicating their active biological role in those individuals.

Data from our and other groups (Backovic et al. 2007; Jansson and Tengvall, 2001; Wettero et al. 2002; Yoshida et al. 1994; Zhang et al. 1998) yielded a noteworthy amount of evidence that silicone does not stay intact *in vivo*, as was suggested according to the chemical properties of silicone polymer. Although silicone itself has

low immunogenic properties, its degradation products induce a strong host response, and can be associated with numerous side effects.

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4. Protein – silicone interaction

4.1. Protein affinity for silicone

A thin proteinaceous film forms on the surface of silicone almost instantaneously after the implantation (Tang and Eaton ,1993). Laterally Resolved Ellipsometry and Fourier Transform Infrared Attenuated Total Internal Reflection are methods routinely used to study conformational changes of proteins on such surfaces as implanted devices and materials (Ortega-Vinuesa et al. 1998), but numerous other proteomic strategies can be employed as well (Dierick et al. 2002; Westergren-Thorsson et al. 2001; Zerkowski et al. 2004). Proteins on the surface of SMIs play a decisive role in the subsequent reaction of local tissue, since a decrease in protein adsorption leads to a concomitant decrease in cellular attachment. Moreover, upon binding to hydrophobic surfaces, many proteins tend to unfold, and in a short period undergo surface denaturation. Early interactions between silicone implants and inflammatory cells are thus mediated by a layer of host proteins on the material surface (Chittur ,1998; Ortega-Vinuesa et al. 1998).

In an equilibrium state spontaneous protein adsorption is mainly controlled by the adsorption probability or sticking coefficient of each of the proteins. Sticking coefficients of proteins are generally found to be in the range 10^{-5} - 10^{-8} (Tang and Eaton ,1999), and they are depending on the protein structure, temperature, adhering surface, and the ionic strength of the surrounding milieu (Weaver and Pitt ,1992). Although albumin, fibronectin and IgG predominate on many types of biomaterials (Elwing ,1998), the adsorption of proteins is a very dynamic process. To understand these dynamics, flow parameters, conformational changes, displacement effects, early events in blood clotting and complement activation all must be considered in addition

to sticking coefficient. Although the adhesion of each protein from serum is somewhat related to its concentration in the surrounding liquid, over a time frame of ~100 min, proteins present in higher amounts in solution (e.g. blood) are replaced by those present in much smaller concentrations, but with higher surface affinities (Ortega-Vinuesa et al. 1998). This phenomenon is known as the “Vroman effect”, which is defined as the time- and concentration-dependant exchange of adsorbed fibrinogen with kininogen when blood plasma is incubated with silicone surfaces. After the state of equilibrium has been reached, around 4-16 mg of protein adhere to cm^2 of silicone surface (Zhang et al. 1998).

In this sense, it is important to determine the degree to which the hydrophobic silicone surface promotes exposure of cryptic antigens and/or “altered self”, and how these events correspond to the local inflammatory and fibrotic processes, and perhaps also systemic immune effects. These findings will provide the knowledge needed to modify silicone to avoid immune reactions and fibrosis are minimize the risks for implant patients.

4.2. Aged proteins and silicone

Accumulation of altered proteins and their modification with age have been recently widely discussed in this journal (Hipkiss ,2006; Schoneich ,2006), thus we focused solely on the effects of aged proteins in the reaction to silicone. Protein aging is usually defined as a progressive, age-dependent, covalent and nonenzymatic modification of a protein backbone and/or side group/s. This aging process is important in the context of reactions with silicone because the post-translational modifications that proteins undergo in the circulation and *in situ* may lead to the loss

of immune tolerance (Berlett and Stadtman ,1997; Dierick et al. 2002; Glomb and Monnier ,1995; Grune et al. 2005; Hudson et al. 2005; Newkirk et al. 2003).

Conversely, posttranslational modifications of proteins can alter their biological activity and function.

Although aged proteins are detected and removed via several mechanisms, some aged proteins consistently escape this process. They are usually seen as foreign by the immune system, but because they share structural motives of native proteins, tolerance is often broken and autoimmune reactions towards their native conformations subsequently also occur. Furthermore, accumulation of aged proteins occurs in numerous diseases such as atherosclerosis, synovitis, cataract, rheumatoid arthritis and diabetes. Silicone surfaces promote deposition and formation of non-enzymatically-modified proteins, comprising a plausible link with autoimmune-like syndromes that occur in some SMI patients. Modified proteins on the surface of silicone can trigger an immune response, and are responsible for at least part of adverse reaction development.

5. Conclusion

Youth has been the foundation of human concepts of beauty and well-being from the dawn of civilization, and the technological advances of the last decades have only reinforced this ideal. The natural processes of senescence are scientifically understood as a disease, and both cosmetic surgeons and the pharmaceutical industry continually develop elaborate armamentarium to fight the new “War on Aging”. Conversely, once the initial excitement over new surgical procedures and presumably biocompatible materials such as silicone in tissue remodelling has faded, inevitably the scientific

community is inundated with case reports of various adverse effects these techniques and materials may cause. Herein, we have focused on the side effects of cosmetic procedures that influence known mechanisms of aging on molecular and cellular levels. Although such procedures indeed yield the promised outcome of a more youthful appearance, they also interfere with the normal physiological processes of tissue remodelling. Silicone degradation products activate chronic pro-inflammatory responses in the surrounding tissues, and the surface of the silicone implant itself presents numerous modified autologous proteins to the host defence system. Therefore, we believe the public should be constantly reminded that the promises of “anti-aging” treatments are often only skin-deep, and that the attendant risk of detrimental side effects are clearly presented to anyone seeking cosmetic interventions. It is likely that the future will see improvement in both the results and diminished risk of cosmetic procedures thanks to findings from diverse scientific and clinical areas.

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Table 1
Silicone degradation products *in vivo*. In comparison to normal population, carriers of SMIs have elevated levels of silicone degradation products in various tissues.

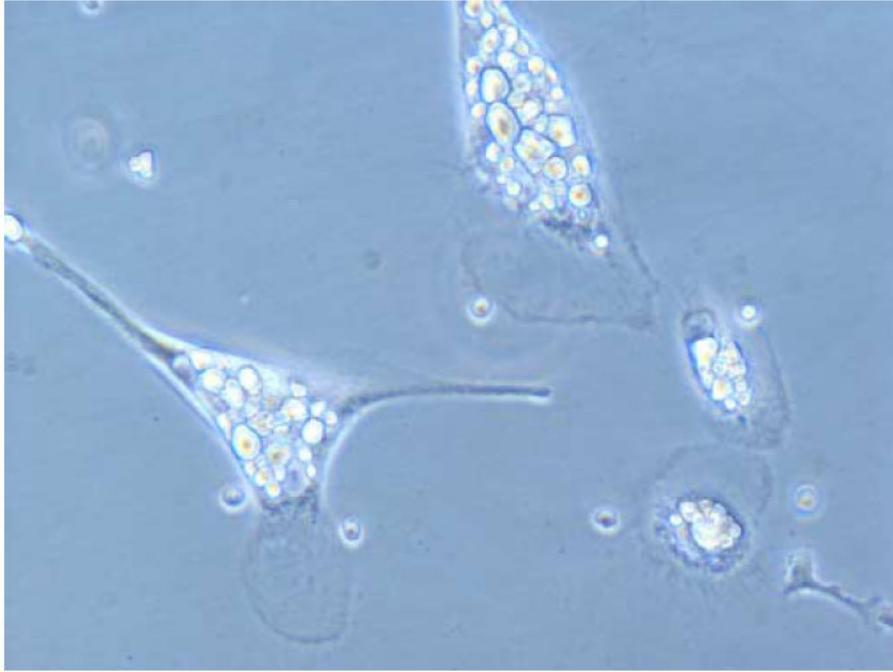
Tissue	Silicone component	Concentration	Reference
Local binding tissue	siloxane	1-1400 ng/g	Flassbeck et al. 2003
Local binding tissue	Low molecular weight silicone	9-85 μ g/g	Flassbeck et al. 2003
Blood	Platinum	470-688pmol/L	Lykissa and Maharaj, 2006
Urine	Platinum	0.4-2.95 μ g/L	Lykissa and Maharaj, 2006
Local binding tissue	Platinum	0.003-0.272 μ g/g	Lykissa and Maharaj, 2006
Local binding tissue	Silicates	Concentration not determined*	Jensen et al. 2003
Blood	Silicates	Concentration not determined*	Shen et al. 1996

*These studies compared relative silicate levels in SMI carriers.

Figure 1. Caption**Cells isolated from the fibrotic capsule formed around the silicone mammary implant (SMI)**

Fibrotic capsule forms around the SMIs in a period from several months to several years. It is usually causing pain and discomfort, and impairing implant's aesthetic function. We have obtained such a capsule from a patient undergoing SMI reimplantation after diagnosed "gel-bleeding" from a damaged implant. The fibrotic capsule was digested with collagenase type IV (Sigma, Vienna, Austria) and we attained a single cell suspension that was cultivated in plastic 6-well plates. In most of the cells accumulations of silicone particles were noticed, as depicted here.

Fig.1



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