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Risk of connective-tissue disease in men with testicular or penile prostheses: a preliminary study

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Abstract **Aim:** To help clarifying the possibility of connective-tissue diseases in men with penile or testicular prostheses. **Methods:** Eight patients underwent inflatable penile prostheses and 15, testicular prostheses consented to the study. Their medical records were reviewed and a follow-up interview and physical and serological examinations were performed. **Results:** In patients with penile prostheses, there was no abnormal antinuclear antibody (ANA) or IgM elevation. The serum levels of the rheumatoid factor (RF), C4, IgA and IgG were abnormal in one patient, and the levels of erythrocyte sedimentation rate (ESR) and C3, abnormal in two. Four had elevated IgE. In patients with testicular prostheses, there was no abnormal RF, ANA or IgM. The serum levels of ESR and IgA were abnormal in two, and three had abnormal C4, ten abnormal C3, and eleven decreased IgG. All had increased IgE. Men with penile prostheses had higher serum levels of IgG and IgM than those with testicular prostheses (P=0.001, P=0.016, respectively). The rates of abnormal values of IgE and IgG were higher in men with testicular prostheses than in men with penile prostheses (P=0.008, P=0.009, respectively). Physical examination was normal in all patients and nobody had documented symptoms pertinent to connective-tissue diseases. **Conclusion:** Our findings suggest that the risk of connective-tissue diseases is not higher in patients wearing prostheses as the ANA is negative and there is no apparent manifestation suggestive of connective-tissue diseases. *(Asian J Androl 2002 Mar; 4: 67-72)*

1 Introduction

Disorders closely resembling autoimmune diseases have been reported in patients injected or implanted with various substances. In 1982, Van Nunen et al. [1] first indicated an association between breast implants and connective-tissue diseases. Women receiving breast implants have been shown to expose to many health risks, unknown to them at the time of surgery. Affected patients may have a variety of autoimmune diseases, including Sjogren's syndrome, progressive systemic scleroderma, rheumatoid arthritis, systemic lupus erythematosus and mixed connective tissue disorders. These patients typically experience certain combination of fatigue, myalgia, joint pain, sicca syndrome, synovitis, rash, alopecia, muscular weakness or lymphadenopathy, and autoantibody formation [2]. Recognition of health hazards has prompted the Food and Drug Administration to restrict the implantation of these devices before comprehensive safety studies have been undertaken.

While the exact mechanism is yet to be determined,

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silicone gel filled prostheses may have the potential to induce immune reactivity. In 1991, Barrett et al. [3] demonstrated silicone shedding from the genitourinary prostheses although no correlation was noted with connective-tissue diseases. To date, much attention has been given to the silicone gel filled breast implants but little is known regarding the penile and testicular prostheses. For this reason, we evaluated the possibility of the occurrence of connective-tissue diseases in men with penile or testicular prostheses clinically and immunologically.

2 Subjects and methods

2.1 Patients

Medical records of the patients underwent implantation of inflatable penile prostheses or silicone gel filled testicular prostheses from 1995 to 1999 were reviewed for information concerning preexisting medical conditions, age at implantation, reason for implant insertion and perioperative complications. Attempts were made by telephone to obtain current follow-up interview, physical examination and baseline serological examination. Telephone contacts were successful in 8 patients underwent inflatable penile prostheses (penile prosthesis group) and 15, silicone gel filled testicular prostheses (testicular prosthesis group). The study was approved by the Human Subjects Review Board of the Administration. Informed consent was obtained for the procedure and the study from all subjects.

2.2 Serological tests

Serological tests to identify human adjuvant disease were performed according to Henderson et al. [4] and Sergott et al. [5]. These tests included erythrocyte sedimentation rate (ESR, normal range: 0-9 mm/h), complement 3 (C3, normal range: 45-105 mg/dL), complement 4 (C4, normal range: 10-40 mg/dL) and quantitative serum immunoglobulin (Ig) levels including IgA (normal range: 0.9-3.8 g/L), IgE (normal range: 0-100 IU/mL), IgG (normal range: 7.5-17 g/L) and IgM (normal range: 0.6-2.95 g/L), antinuclear antibody titer (ANA, normally negative) and rheumatoid factor (RF, normally negative). During the follow-up interview, questions about the symptoms or signs of connective tissue diseases were asked to obtain the diagnostic details based on the classification criteria of the American College of Rheumatology for rheumatoid arthritis [6], systemic lupus erythematosus [7], and systemic sclerosis [8], and on Alarcon-Segovia and Cardiel's criteria for mixed connective-tissue disease [9], Bohan and Peter's criteria for inflammatory myositis [10] and Fox et al.'s criteria for Sjogren's syndrome [11].

2.3 Data processing

Data are presented as the median (25th-75th percentile) for the variables. Mann-Whitney *U*-test and Fisher's exact test were used to compare continuous and nominal variables between two groups, respectively. A 5% level of significance was used for statistical testing and all statistical tests were two-sided. Statistical analyses were performed using a commercially available analysis program.

3 Results

3.1 Personal data

The patients of the penile prosthesis group underwent implantation due to erectile dysfunction caused by spinal fracture, Peyronie's disease, or diabetes mellitus. Testicular implantation had been performed due to monoorchism secondary to cryptorchidism, testicular injury, torsion of spermatic cord or unknown etiology. The median age of surgery in penile and testicular prosthesis groups was 38 (range 26 to 84) and 23 (range 17 to 52) years, respectively. The median time since implantation in penile prosthesis group was 37 (range 2 to 86) months and that in testicular prosthesis group was 9 (range 1 to 69) months. One patient in the testicular prosthesis group experienced scrotal hematoma.

3.2 Serological tests

The results of serological tests in the 2 groups are shown in Table 1. In the penile prosthesis group, 2 patients (25.0%) had no abnormal item, 3 (37.5%) had a single abnormal item, 2 (25.0%) had 2 abnormal items and 1 (12.5%) had 4 abnormal items. Tabulating by serological results, 2 patients (25.0%) had elevated ESR, 1 (12.5%) abnormal RF, 2 (25.0%) abnormal C3 (decreased and increased in one each) and 1 (12.5%) increased C4. One patient (12.5%) had decreased IgA, 4 (50.0%) elevated IgE and 1 (12.5%) decreased IgG. Nobody had abnormal ANA or IgM.

In the testicular prosthesis group, all patients had more than one abnormality. One patient (6.7%) had only a single abnormal item, 3 (20.0%) had 2, 8 (53.3%) had 3, and 3 (20.0%) had 4. Tabulating by serological results, 2 patients (13.3%) had elevated ESR, 10 (66.7%) had abnormal C3 (decreased in 7 and increased in 3) and 3 (20.0%) had abnormal C4 (decreased in 2 and increased in 1). Two patients (13.3%) had decreased IgA and 11 (73.3%) had decreased IgG. All patients had increased IgE. Nobody had abnormal RF, ANA, or IgM.

Comparing the 2 groups, the serum IgG level was higher in the penile prosthesis group than in the testicular prosthesis group (median 11.8 versus 6.5 g/L, $P<0.01$);

Table 1. Serological results of penile and testicular prosthesis groups.

Group	ESR (mm/h)	RF	ANA	C3 (mg/dL)	C4 (mg/dL)	IgA (g/L)	IgE (IU/mL)	IgG (g/L)	IgM (g/L)
Penile prosthesis	1	Negative	Negative	84.2	41.2*	2.5	10.6	10.7	2.0
	5	Negative	Negative	42.0*	20.7	3.0	949.6*	13.5	1.5
	10*	Negative*	Negative	81.0	29.0	0.2*	145.5*	6.9*	0.8
	14*	Negative	Negative	64.1	35.1	2.6	227.3 *	12.9	1.6
	2	Negative	Negative	58.7	35.0	3.3	50.9	10.1	1.4
	3	Negative	Negative	120.1*	26.4	2.9	12.0	13.1	2.0
	2	Negative	Negative	99.0	34.2	1.8	120.1	14.0	1.6
	5	Negative	Negative	84.7	22.9	1.1	13.2	9.2	1.3
Testicular prosthesis	3	Negative	Negative	45.2	10.1	2.2	131.1*	6.5*	1.0
	2	Negative	Negative	21.0*	10.0	0.8*	187.0*	6.5*	0.8
	2	Negative	Negative	45.1	4.3*	2.2	120.5*	6.2*	0.8
	2	Negative	Negative	19.9*	22.0	2.3	118.3*	6.5*	1.4
	2	Negative	Negative	20.2*	22.5	2.2	120.0*	6.5*	0.8
	3	Negative	Negative	24.5*	10.1	2.3	150.3*	6.5*	0.8
	2	Negative	Negative	22.3*	10.2	0.8*	120.1*	6.2*	1.4
	2	Negative	Negative	45.0	5.0*	1.0	130.3*	6.2*	1.0
	2	Negative	Negative	23.0*	10.0	0.9	113.2*	6.5*	1.0
	17	Negative	Negative	74.0	28.4	1.0	313.7*	1.3*	2.3
	22	Negative	Negative	114.1*	18.8	1.5	482.0*	6.6*	0.7
	3	Negative	Negative	105.3*	43.2*	3.3	193.4*	15.5	1.3
	7	Negative	Negative	149.5*	26.9	2.8	211.4*	10.9	0.8
	5	Negative	Negative	80.0	28.0	2.0	1000.0*	15.5	1.7
	3	Negative	Negative	25.0*	18.2	1.4	549.2*	8.5	0.8

ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; ANA: antinuclear antibody; C: complement; Ig: immunoglobulin.
*Abnormal value

the same was true in case of the IgM level (median 1.6 versus 1.0 g/L, $P< 0.05$). No significant differences were found in other items (Table 2). The rates of abnormal values of IgE and IgG were higher in the testicular prosthesis group than in the penile prosthesis group (50.0 versus 100.0%, 12.5 versus 73.3%, respectively, both $P<0.01$). There were no statistical differences between the two groups in other tests (Figure 1). Physical examination was normal in all the patients and nobody had any symptom pertinent to connective-tissue diseases.

4 Discussion

Human adjuvant disease is an immunologically mediated disorder manifested by arthritis, arthralgias, skin lesions, malaise, pyrexia and weight loss, but not diagnostic of a connective-tissue disease. Surgical implantation of silicone breast prostheses has been conducted and considered safe for over 30 years. However, some plant recipients complain of a group of symptoms similar to those observed in connective-tissue disorders.

Table 2. Comparison of serological results between penile and testicular prosthesis groups.

Tests	Median (25th-75th percentile)		*P*-value*
	Penile prosthesis	Testicular prosthesis	
ESR (mm/h)	4.0 (2.0-8.8)	3.0 (2.0-5.0)	>0.05
C3 (mg/dL)	82.6 (60.1-95.4)	45.0 (22.3-80.0)	<0.05
C4 (mg/dL)	31.6 (23.8-35.1)	18.2 (10.0-26.9)	<0.05
IgA (g/L)	2.5 (1.3-3.0)	2.0 (1.0-2.3)	>0.05
IgE (IU/mL)	85.5 (12.3-206.9)	150.3 (120.2-313.7)	<0.01
IgG (g/L)	11.8 (9.4-13.4)	6.5 (6.2-8.5)	<0.01
IgM (g/L)	1.6 (1.3-1.9)	1.0 (0.8-1.4)	>0.05

*Mann-Whitney U-test

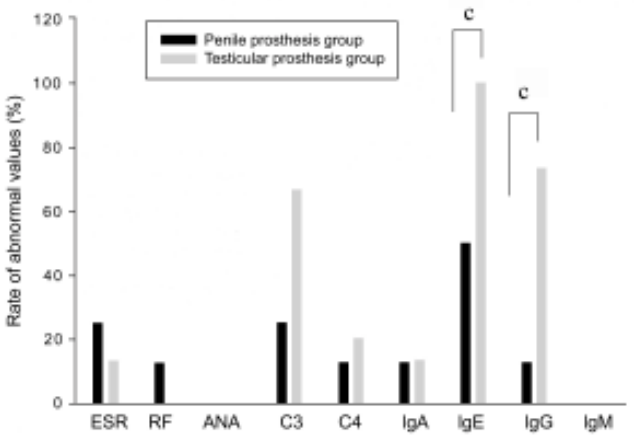

Figure 1. Rate of abnormal serological values between penile and testicular prosthesis groups. $^{c}P<0.01$.

The human body's initial response to the silicone material is the adsorption of various plasma proteins, including clotting and complement proteins and the conformational integrity of this adsorbed macromolecular layer affects much of the subsequent biological reaction [12]. Abbondanzo et al.[13] evaluated the immunophenotypic characteristics of silicone gel-filled breast and testicular implant capsules. They demonstrate that silicone implants induce chronic inflammatory responses in many adjacent capsules, which consist of anamnestically responding T cells, reactive B-lymphocytes and macrophages. Many complex substances sharing siloxane structure develop T cell memory. This memory links the immunohistopathology and autoimmune attributes of silicosis and the lesions of silicosis are typical of those for persistent antigens and delayed cell mediated hypersensitivity [14].

Investigations into the effects of prior silicone exposure on subsequent capsule formation around silicone implants assumed particular relevance because the inert nature of silicone had been in question with regard to its effects on the immune system, specifically whether or not it might act as a hapten or antigen. Klykken and White [15] suggested that in the absence of premixing the antigen with the silicone material, there did not appear to be any silicone induced adjuvant response. Moreover, Brantley et al. [16] noted that even prior exposure to silicone did not alter the capsule histology, thickness, or pressure in an animal model. However, Smith et al. [17] suggested that a cellular or a humoral-mediated immunologic response to silicone carpal prostheses could be detected in animals previously sensitized to silicone.

The controversy concerning the use of silicone prosthetics as breast implants also affected genitourinary prostheses. Barrett et al. [3] demonstrated that genitourinary prostheses including penile devices and artificial urinary sphincters sheded silicone particle that can be found in the fibrous capsule and draining lymph nodes. However, Pidutti and Morales [18] noted that a specific pattern of diseases did not emerge in men harboring a scrotal silicone gel implant for a mean period of over five years. Henderson et al.[4] removed the testicular prosthesis in one patient due to signs and symptoms suggestive of human adjuvant disease but they did not find evidence of silicosis in adjacent tissues.

In our study, physical examination was normal in all patients and nobody had any symptom pertinent to connective-tissue diseases. In other words, no one was confirmed as having definite connective-tissue diseases. However, in regard to the serologic tests, only 25% of the penile prosthesis group had no abnormalities and every one of the testicular prosthesis group had more than one abnormality, although no one had an abnormal ANA. ANA is associated with the development of autoimmune complications in women with silicone breast implants [19]. Scleroderma is the connective-tissue disease most strongly suspected to be associated with prior exposure to silicone [20,21] and ANA is demonstrated in the sera of 96% patients with progressive systemic sclerosis [22]. Claman and Robertson [23] suggested that women with breast implants could be at a risk for the development of ANA, although there was no correlation between ANA positivity and the type of implant, indication for implantation, time since first implantation, total number of implants, and implant leak or rupture.

The construction of testicular prostheses is similar to that of breast implants but the local implant environments are different. The scrotum offers a position with low tension, less vascularity and a low temperature; these factors may contribute to the lack of demonstrated leakage of silicone gel or shedding

of the silicone envelope [4]. Our findings support the concept that there is no conclusive evidence that silicone gel implants are related to the development of connective-tissue diseases. It is also possible that the results of serological tests may precede the development of autoimmune symptoms, because there is often a latent period with diseases related to silica.

In our patients, 50.0% of the penile prostheses and all of the testicular prostheses group had elevated IgE. Mancino et al. [24] demonstrated that silica, a degradation product of silicone, induced elevated IgE levels in animal models. However, it is difficult to conclude that there is a direct association between IgE and penile or testicular prostheses; a more common etiology of this finding is atopic allergy [4]. In contrary to earlier observations, the penile prosthesis group had higher serum levels of IgG and IgM than the testicular prosthesis group. Naim et al. [25,26] demonstrated that only silicone gel is a very potent humoral adjuvant capable of inducing the production of autoantibodies in rats, whereas silicone fluid, which has a much lower molecular weight, and the solid silicone elastomer sheeting possess minimal adjuvant properties.

To date, there seems to be no conclusive evidence associating connective disorders or autoimmunity with silicone implants. The literature fails to support an correlation between silicone gel implants and systemic diseases. Although silicone gel breast implants may rupture and cause local symptoms, they have not been demonstrated to be a systemic health hazard for patients who have undergone augmentation mammoplasty or postmastectomy reconstruction [27]. Comprehensive epidemiologic studies have concluded that there is no connection between breast implants and known connective-tissue diseases. However, silicone gel-filled prostheses may have the potential to induce immune reactivity. Thus, long-term follow-up and awareness of the importance of continuous care are needed.

In summary, our findings suggest, but cannot establish, that the risk of connective-tissue diseases in patients with silicone gel-filled prostheses is not higher, although men with prostheses may develop atypical immunologic reactions. However, our study was limited by substantial methodological flaws, including uncontrolled, retrospective, no population-based design, vary small samples as well as a relatively short duration of follow-up. Therefore, our results cannot be considered definitive proof of the absence of an association between penile or testicular prostheses and connective-tissue diseases. Extensive epidemiologic studies pertinent to this topic should be conducted before any statements about the safety of implants can be made.

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