

SILICONE, MAMMAL GLAND AND AUTOIMMUNITY: A YEAR FOLLOW-UP IN MAMMOPLASTY RECIPIENTS

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Disclosure:

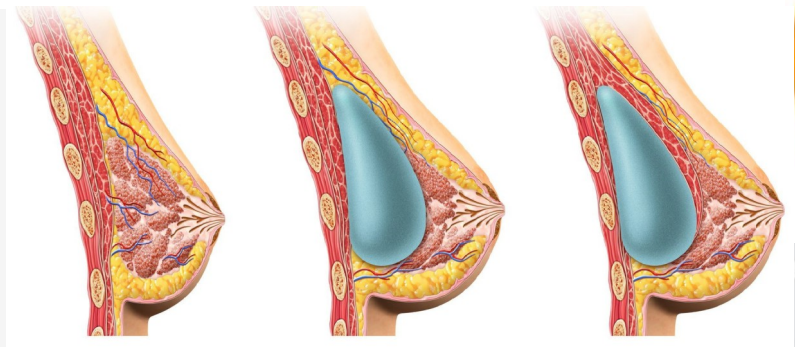
I have nothing to disclose, just say thanks to organizers and mention funding:

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Silicone mammoplasty is one of the most frequent interventions in plastic surgery. According to International Society of Aesthetic and Plastic Surgery (ISAPS), in average 1.8 mln of such surgical interventions are performed in the world annually. In terms of popularity, this operation confidently holds the first position among all aesthetic surgical interventions



The number of aesthetic surgeries of breast exceeds that of curative replacements. There is no common opinion as regards to safety of silicone, the position of controlling bodies (like US FDA and other national units) fluctuated from initial idea of complete inertness of this material to precautions as regards to risk of autoimmune disorders, Kikuchi disease and even anaplastic large cell lymphomas...

BREAST IMPLANT RISKS

- Lowered self esteem
- Suicidal thoughts
- ALCL, a type of cancer
- Autoimmune symptoms
- Fatigue
- Trouble concentrating
- Memory loss
- Back and shoulder pain
- Breast pain, rupture, hardness, sensitivity
- Joint pain

If you are experiencing any of these symptoms or are looking for more information, visit BREASTIMPLANTINFO.ORG

NC HR NATIONAL CENTER FOR HEALTH RESEARCH
The Voice For Prevention, Treatment And Policy

Quotations from the leaflets of SBI producers: a lot of discrepancies



The variety of opinions leads to questions. Questions lead to truth.

~ Thomas Jefferson

AZ QUOTES



Producer	Counterindications:	Use with caution:	Implant influence on development of autoimmune and connective tissue diseases
Allergan©	No	Autoimmune diseases	No causal relation
Mentor©	Lupus and systemic sclerosis	no	No causal relation
Sebbin©	Diagnosed or suspected autoimmunopathies	no	No causal relation , but implantation is not recommended in case of familiar predisposition
Motiva©	No	Autoimmune and connective tissue diseases	No causal relation
Polytech©	The section absent	Systemic diseases, unusual immune reaction after implanting, systemic pathology of connective tissue	No causal relation
Silimed©	No	Autoimmune diseases	Not recognized so far

Prospective follow-up study of immunoendocrine changes after SBI in comparison with breast surgeries without silicone:

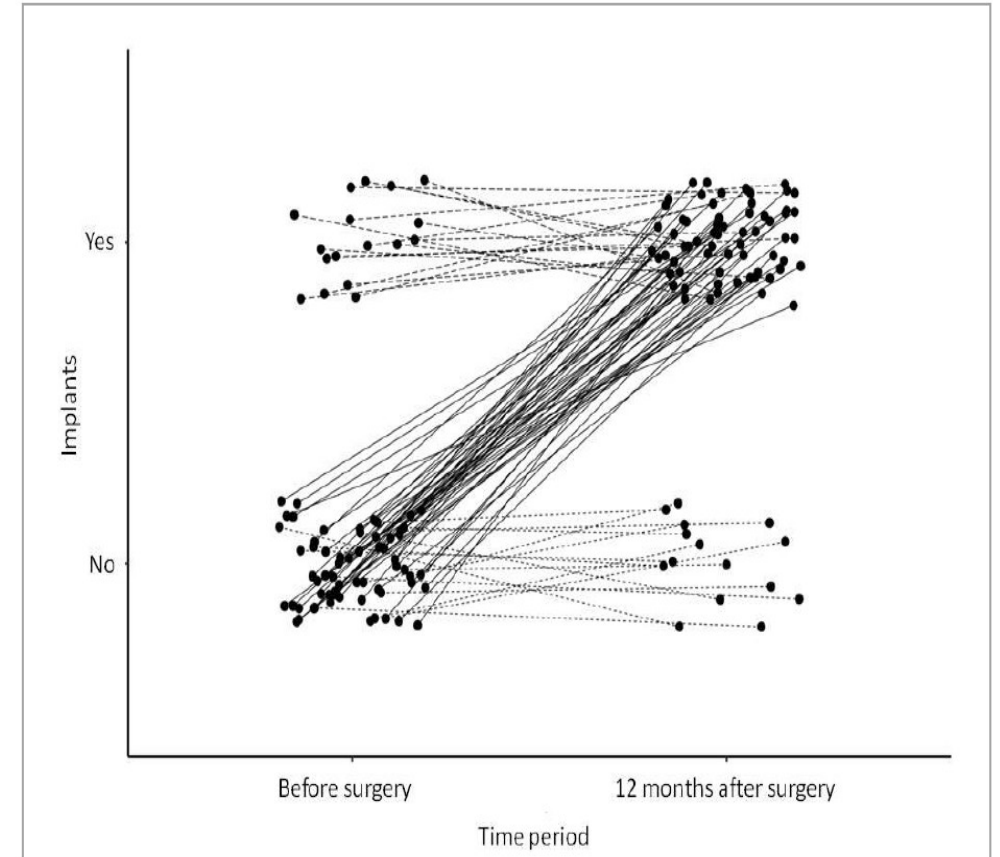
119 clinically healthy female patients were investigated before and in different terms after silicone mammoplasty;

- I group, n=90, – with breast silicone implants;
- II group, n=29 – no silicone implants, other surgeries upon breast;

Checkpoints for every case were: 0 (before surgery), 3, 6 and 12 months after surgery;

By immunoenzyme method 8 different autoantibodies were checked (against: MCV, CL (both IgG & IgM), β 2GP, TG, TSH-R, annexin V (both IgG & M) plus immunofluorescent HEp-2 test);

- Serum levels of: prolactin, testosterone, estradiol, calcitriol, TSH & thyroid hormones were checked
- In 12 cases pathohistological and immunocytochemical studies of tissue biotates were performed



Long dash-dotted line – patients who had BSI in both points.

Solid line – patients who hadn't had BSI in the initial study point, but received them during study.

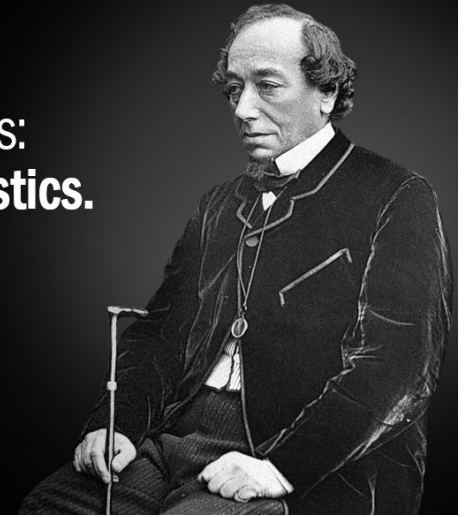
Short dash-dotted line – control patients who had no SBI in any point.

Methods/Statistics:

There are three kinds of lies:
lies, damned lies, and statistics.

– Benjamin Disraeli

AZ QUOTES



- All calculations were performed in the programming language Rv3. 6. 1 (R Core Team, <https://www.R-project.org/>).
- Descriptive parameters: n (%), mean and standard deviation (M (σ)), median, 1-3 quartiles (Md[q1;q3]), min. and max. values (min-max).
- The correlation analysis - Spearman's correlation coefficient (r-statistics)
- W-statistics - Mann-Whitney criterion, the exact Fischer criterion.
- Beta-regression with mixed effects (GLMMadaptive library).
- The Benjamini-Hochberg correction used to correct p-values.
- The results were considered statistically significant at $p < 0.05$

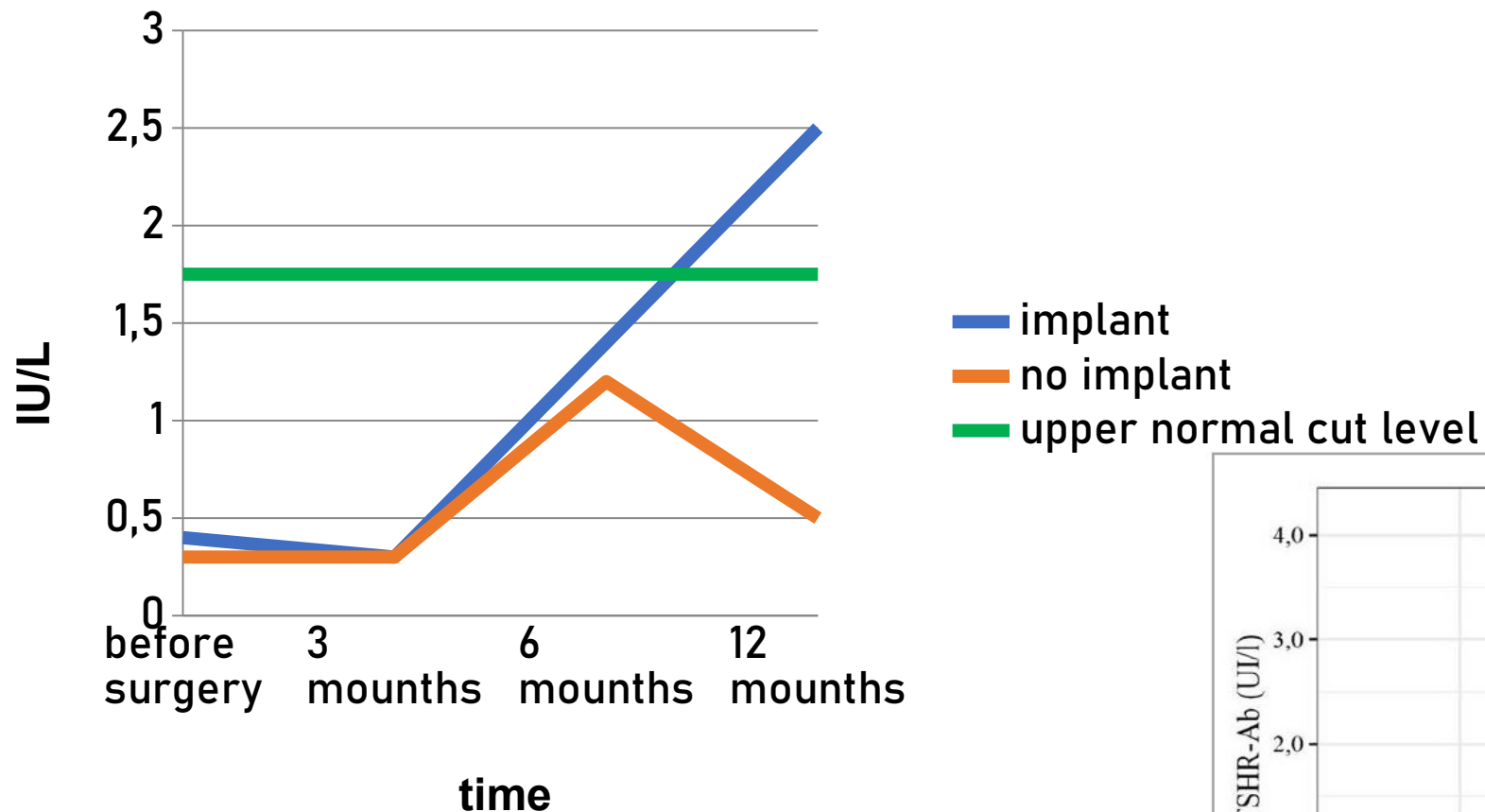
RESULTS:

Dynamics of the TSHR-autoantibodies (IU/L), Statistically reliable increase is matched with RED and circled

time	name	group	mean	med	range	p.value
Before surg.	anti-TSH-R	No implant	0,3 (0,1)	0,3 [0,2;0,4]	0,2;0,6	p=0,247
		implant	0,4 (0,1)	0,4 [0,3;0,4]	0,1;0,7	p=0,247
3 mo	anti-TSH-R	No implant	0,3 (0,1)	0,3 [0,2;0,4]	0,2;0,5	p=0,524
	anti-TSH-R	implant	0,3 (0,1)	0,3 [0,2;0,3]	0,1;0,5	p=0,524
6mo	anti-TSH-R	No implant	1,0 (0,4)	1,2 [0,9;1,3]	0,3;1,6	p=0,042*
	anti-TSH-R	implant	3,4 (14,3)	1,4 [1,3;1,5]	0,3;98,1	p=0,042*
12 mo	anti-TSH-R	No implant	1,4 (1,7)	0,5 [0,5;2,1]	0,2;7,2	p=0,003**
	anti-TSH-R	implant	2,4 (1,3)	2,5 [2,0;3,0]	0,2;7,2	p=0,003**

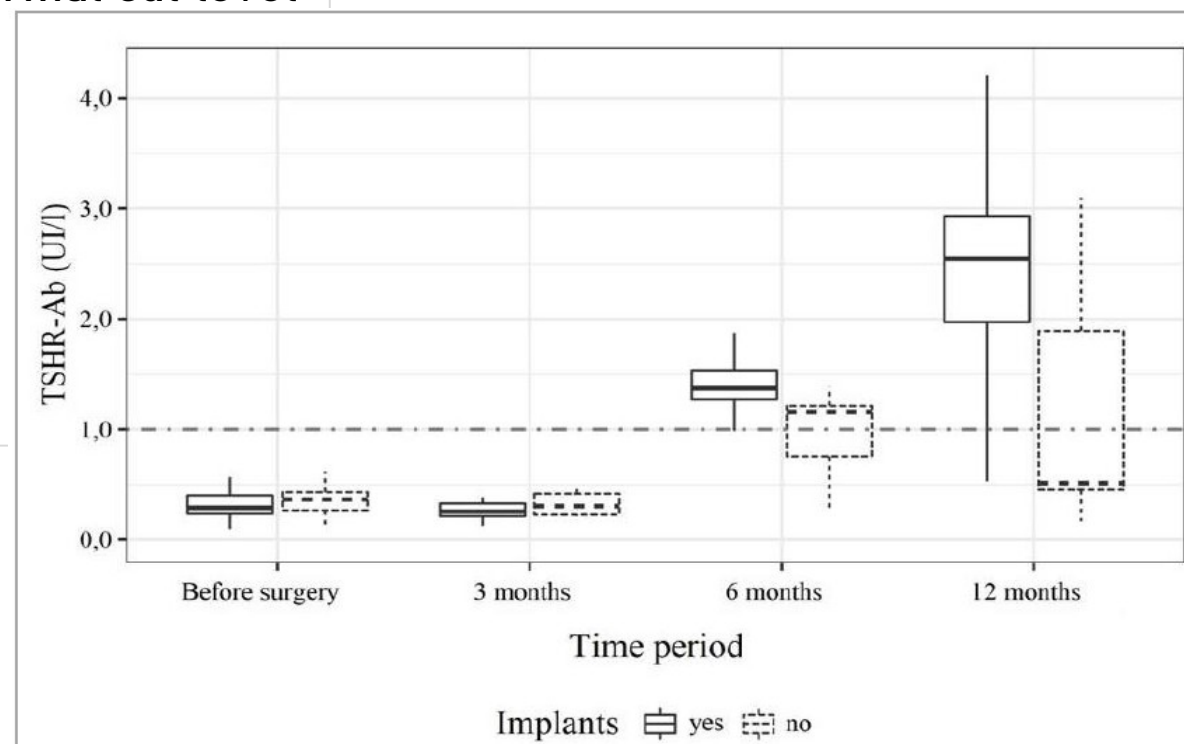
Upper normal cut level common for local population – 1.75 IU/L

Dynamics of the anti-TSHR-autoantibodies



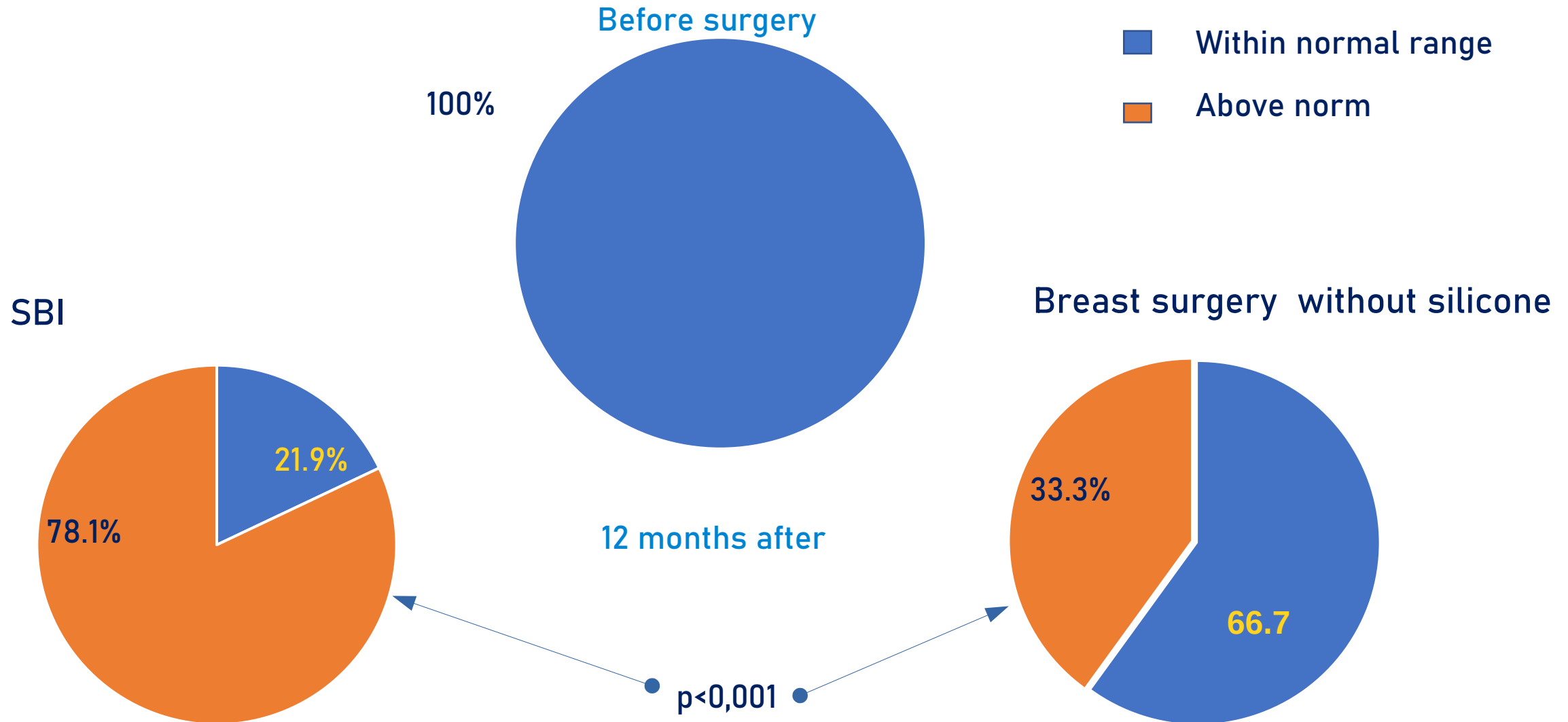
After SBI there was significant increase in concentration of anti-TSHR autoantibodies: Starting at 6 mo and progressing above the upper cut level of pathology to 12 mo. [P<0.003 with non-silicone breast surgeries]

After non-silicone breast surgeries there was some increase in concentration of anti-TSHR autoantibodies to 6 mo, but later it get down to normal range, almost to initial level.



Dash-dotted horizontal line borders the upper normal level.

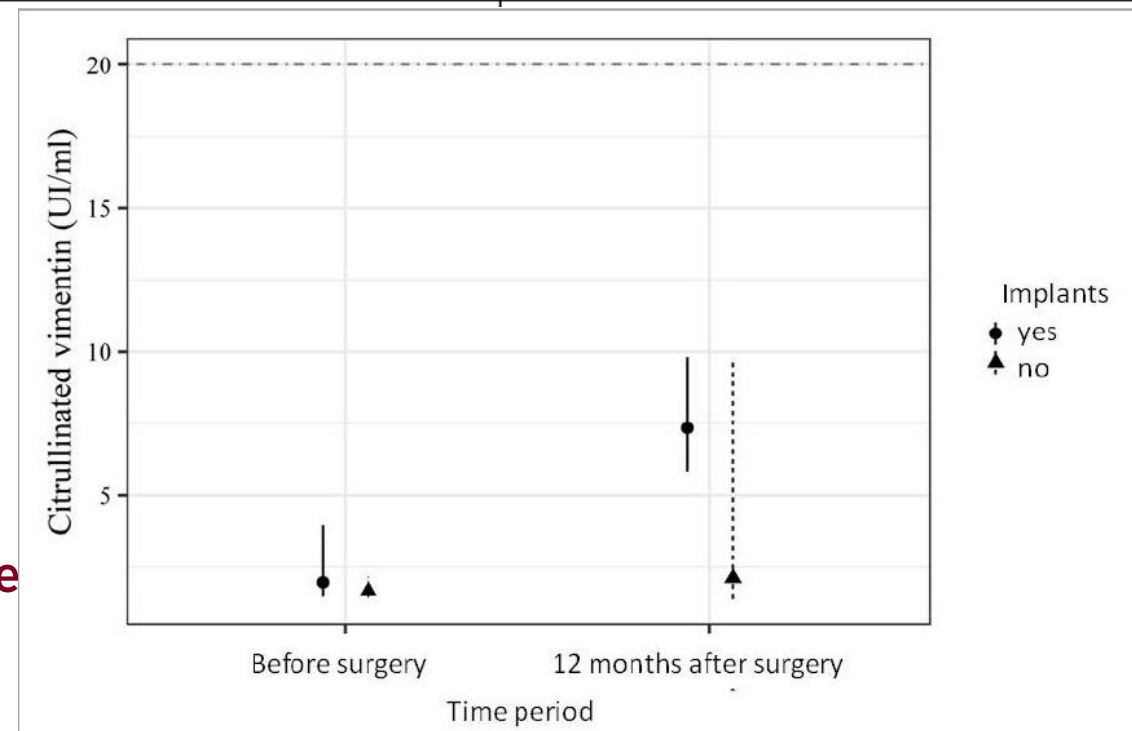
Not only average concentration of anti-TSHR, but also % of cases with anti-TSHR level exceeding normal range was greater 12 months after surgery in SBI recipients compared to non-silicone surgery:



AT	Control point	With implants, Md [Q1; Q3]	Without implants, Md [Q1; Q3]	p for comparison between groups
		p for intra-group dynamics		
MCV-Ab, U/ml, N<20	pre-op.	2.0 [1.5; 3.9]	1.7 [1.2; 2.8]	0.11 (0.28), p=0.680
	12 mths	7.3 [3.6; 11.7]	3.3 [1.3; 7.7]	0.63 (0.28), p=0.050
		-0.80 (0.27), p=0.013	-0.28 (0.28), p=0.425	

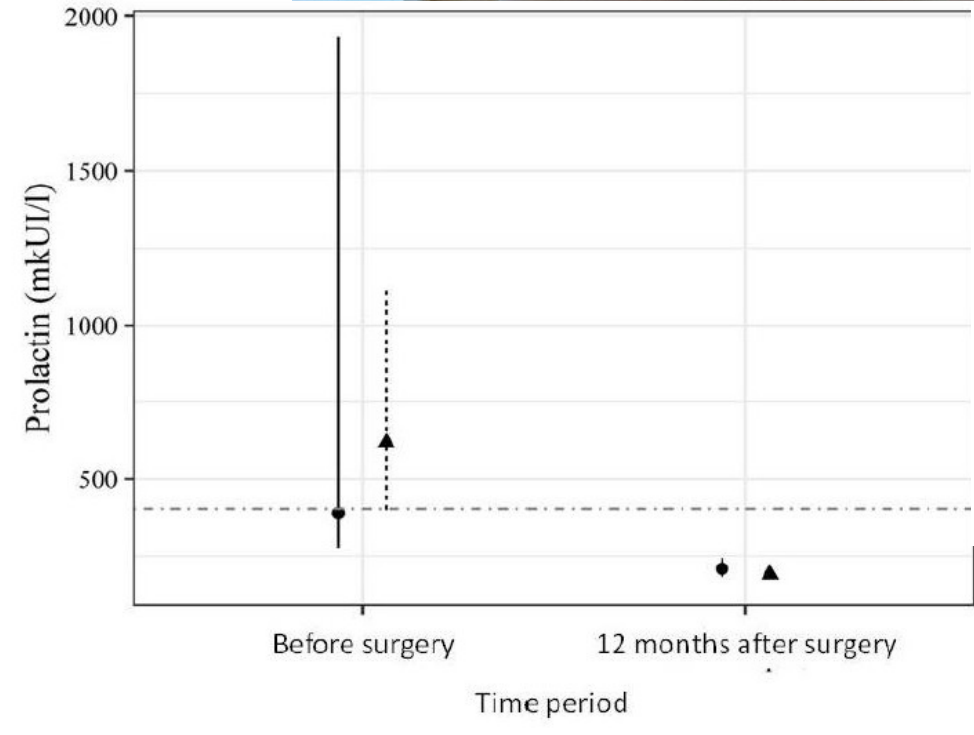
The level of autoantibodies to MCV tended to **increase** during a 12 months of follow-up in SBI group (p=0.013 compared to initial level and p=0.05 compared to non-silicone breast surgery), but **STILL WITHIN NORMAL RANGE**. The levels of all other 7 autoantibodies checked were very close in SBI and non-silicone breast surgery groups and remained below upper cut levels of healthy donors — in both groups and in all terms

. Autoantibodies which level increased **positively correlate** with each other and had **inverse correlation** – with testosterone. No correlation of any autoantibody with smoking anamnesis or surgical complications existed.



Dash-dotted horizontal line corresponds to the upper normal cut level.

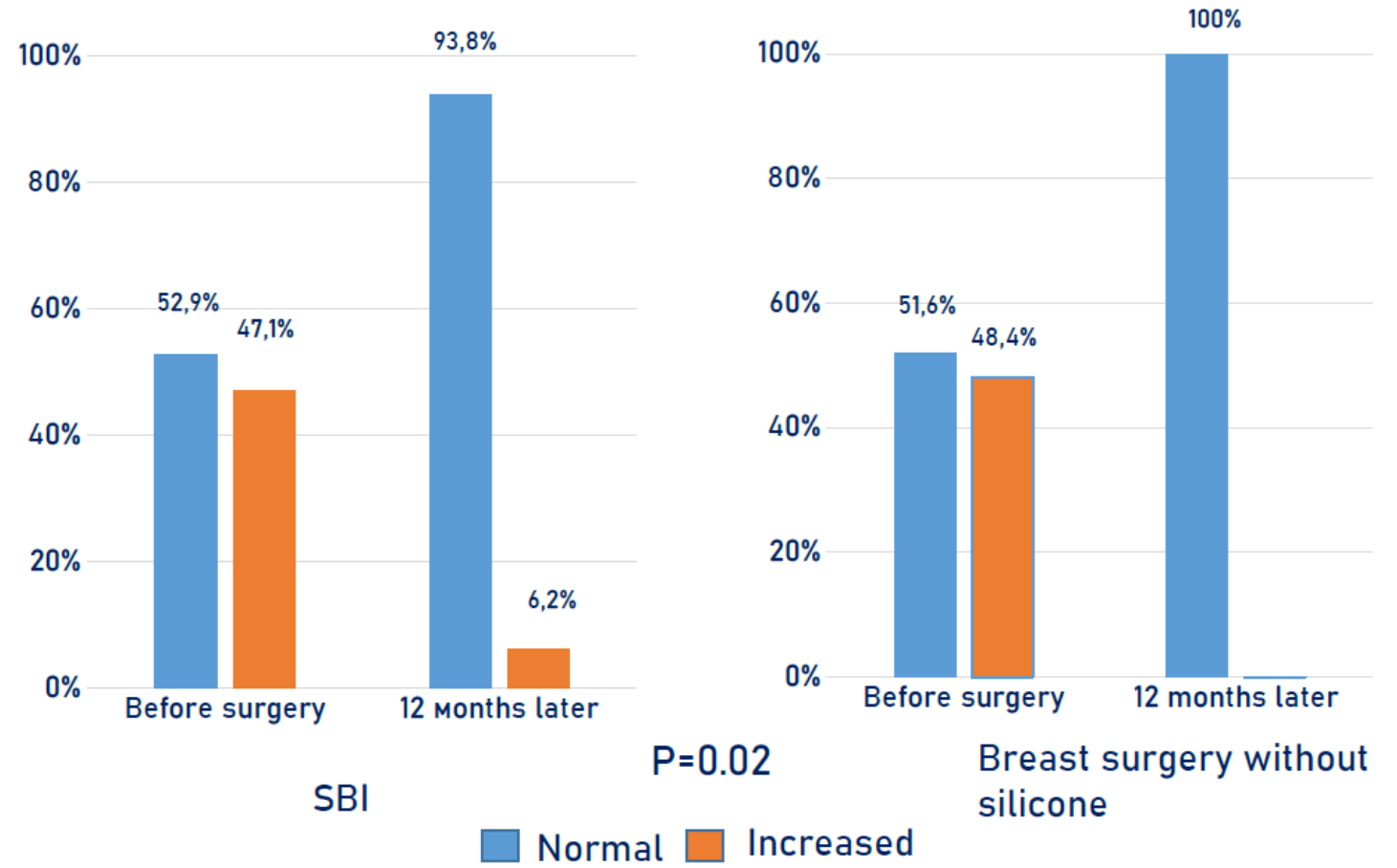
We encountered 2 cases of galactorrhea, both in SBI group, 14 & 17 days after implantation, both treated by prolactostatics



Dash-dotted line conforms to the upper normal level.

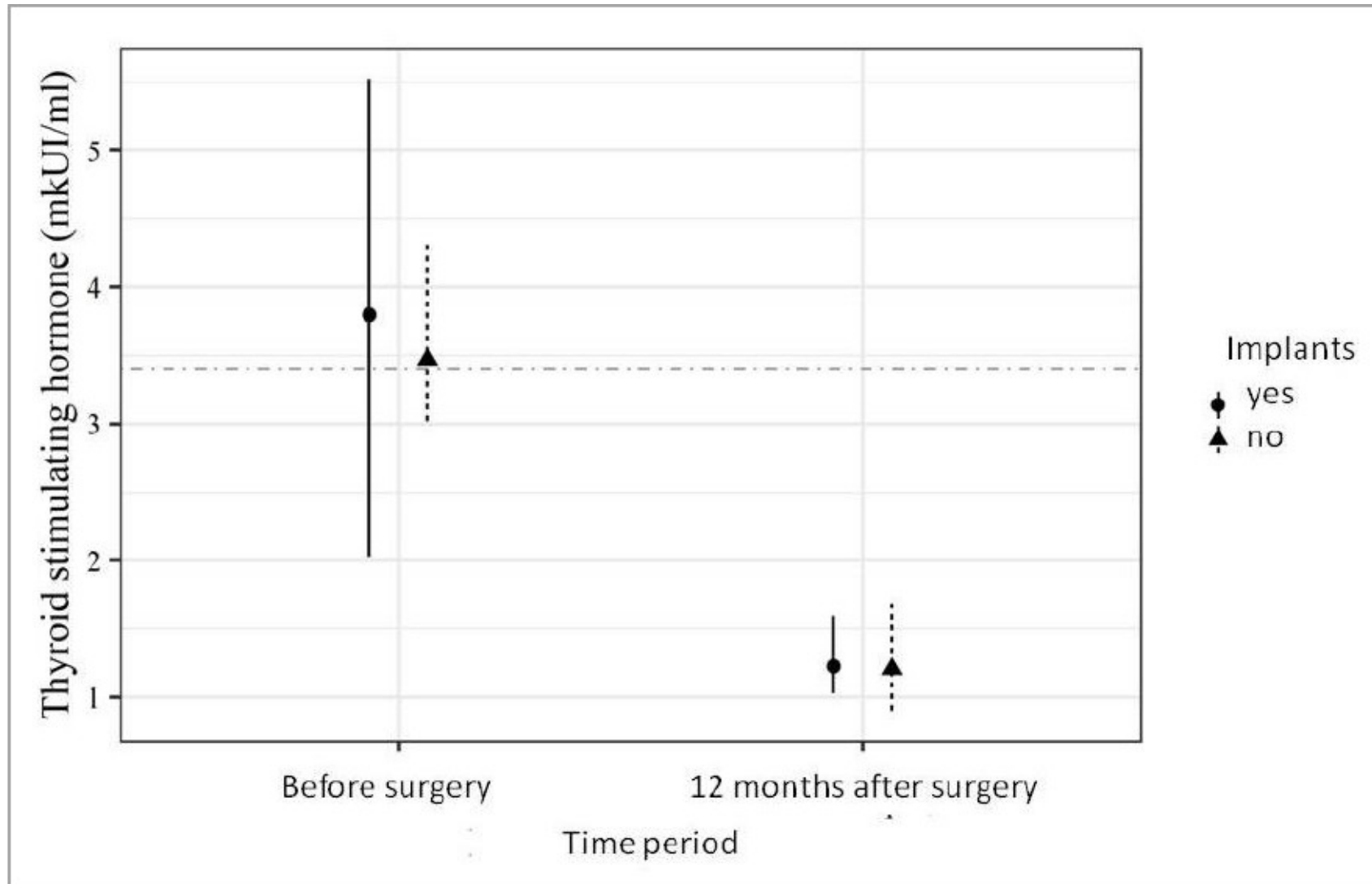
PROLACTIN

% of cases with normal (blue) either increased (orange) serum levels of prolactin [before surgery and 12 months after it] (n=79)



Over 50% of cases (both in SBI and non-silicone breast surgery groups) had hyperprolactinemia before operation, but as a rule it disappeared without medicines in 3 months. Presumably it derived from psychogenic effect/pre-surgical stressful manipulations. Prolactin level did not correlate with any of the autoantibodies.

CHANGES OF TSH LEVEL WERE SIMILAR TO THAT OF PROLACTIN

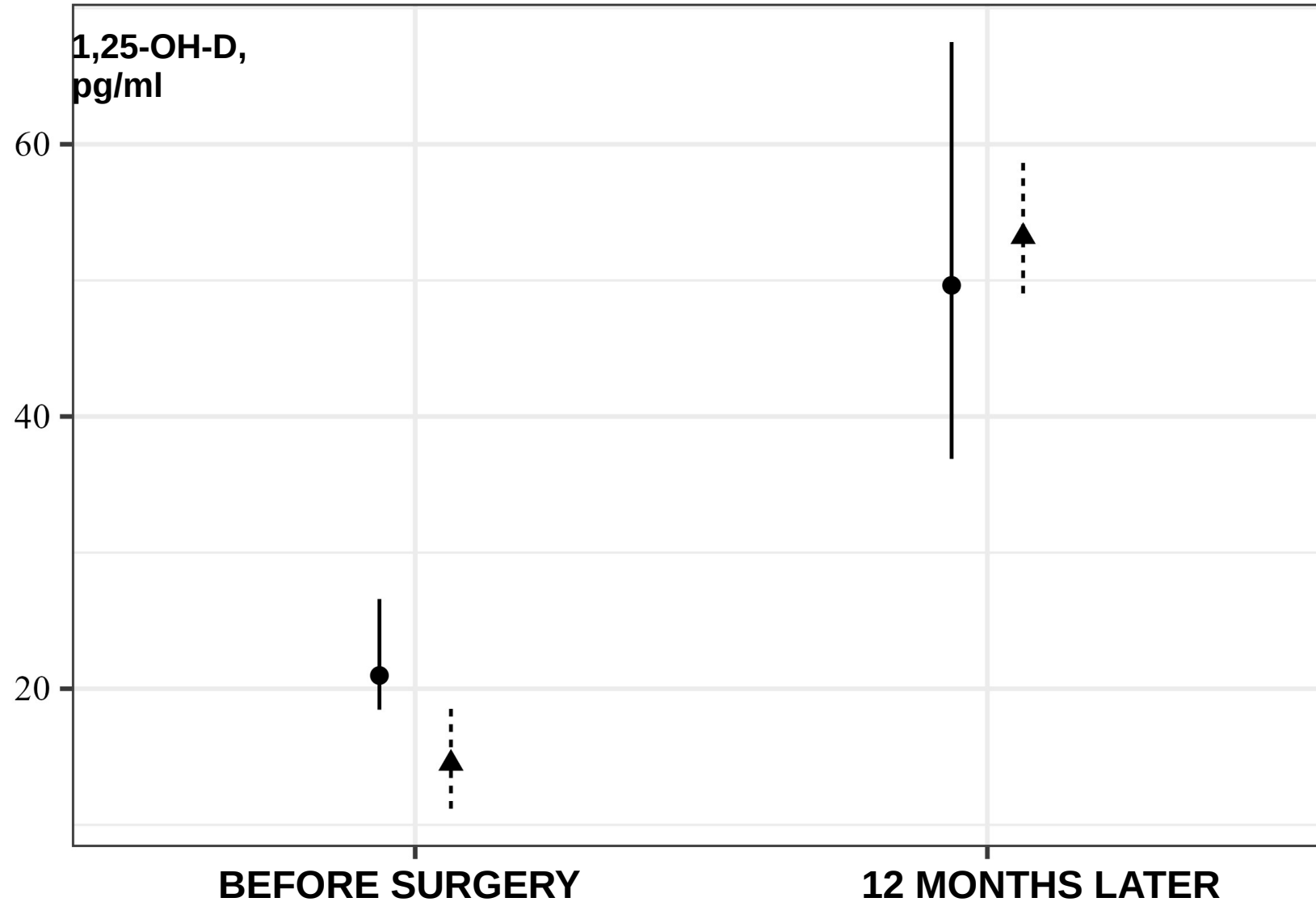


Dash-dotted line conforms to the upper normal level.

Supposingly, this concordance is explained by the fact that the same hypothalamic tripeptide possess with both thyroliberin and prolactoliberin activities [Sneider PJ, 1973].

Dynamics of sex hormones as well as thyroid hormones was during all follow-up within normal ranges in both groups.

CALCITRIOL (1,25-OH-D) LEVEL WAS BEFORE SURGERY LOW (AT THE BORDER OF DEFICIENCY) IN BOTH GROUPS, BUT 12 MONTHS LATER (IN THE SAME SEASON) IT INCREASED SIGNIFICANTLY, ESPECIALLY IN SBI



IMPLANTS
● NO
▲ YES

Supposingly, it grows up as a matter of compensatory response of the body on immune challenge related to surgery and in an attempt to quench down an autoimmunity/

But, who knows, perhaps with new breast the ladies just started to spend more time on the beach?

% OF WOMEN POSITIVE FOR ASIA CRITERIA INCREASED WITHIN 12 MONTHS OF FOLLOW-UP AFTER SURGERY (P<0,01)

Table 15 – Ratio of patients with ASIA syndrome with and without SBI before and in 1 year after the surgery

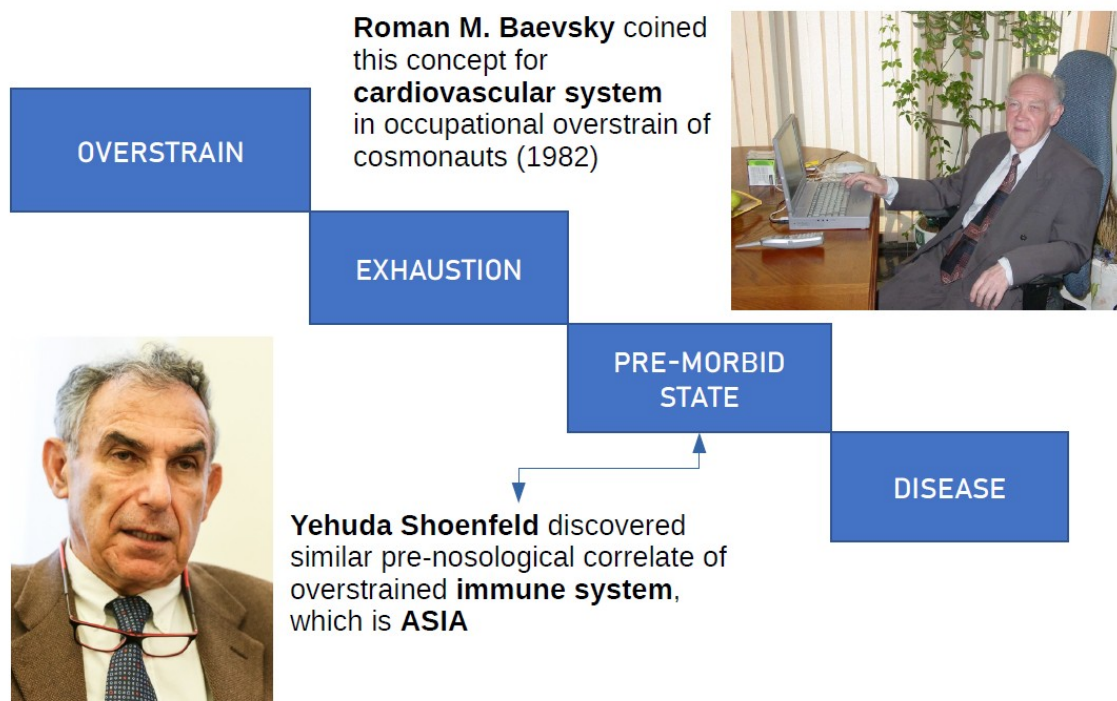
Control point	Implants	ASIA yes, n (%)	ASIA no, n (%)	Total n (%)	p
Pre-op.	yes	2 (2.5%)	15 (19%)	79 (100%)	0.609
	no	5 (6.3%)	57 (72.2%)		
12 mths	yes	16 (20.3%)	48 (60.7%)	79 (100%)	0.733
	no	3 (3.8%)	12 (15.2%)		

Note – Pre-op. – before surgeries, mths – months.

ASIA COMPLAINTS OCCURRED MORE OFTEN AFTER ANY KIND OF BREAST SURGERY EXPERIENCED, SBI OR NON-SILICONE ONES.

NONE OF WOMEN DEVELOP ANY CLINICALLY DIAGNOSED AUTOIMMUNOPATHY WITHIN 12 MONTHS.

ASIA: DISEASE OR PRE-NOSOLOGICAL ENTITY?



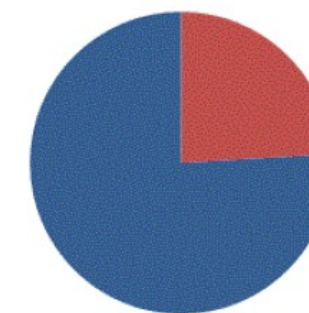
Before surgery



■ ASIA yes 7 (8,9%)

■ ASIA no 72 (91,1%)

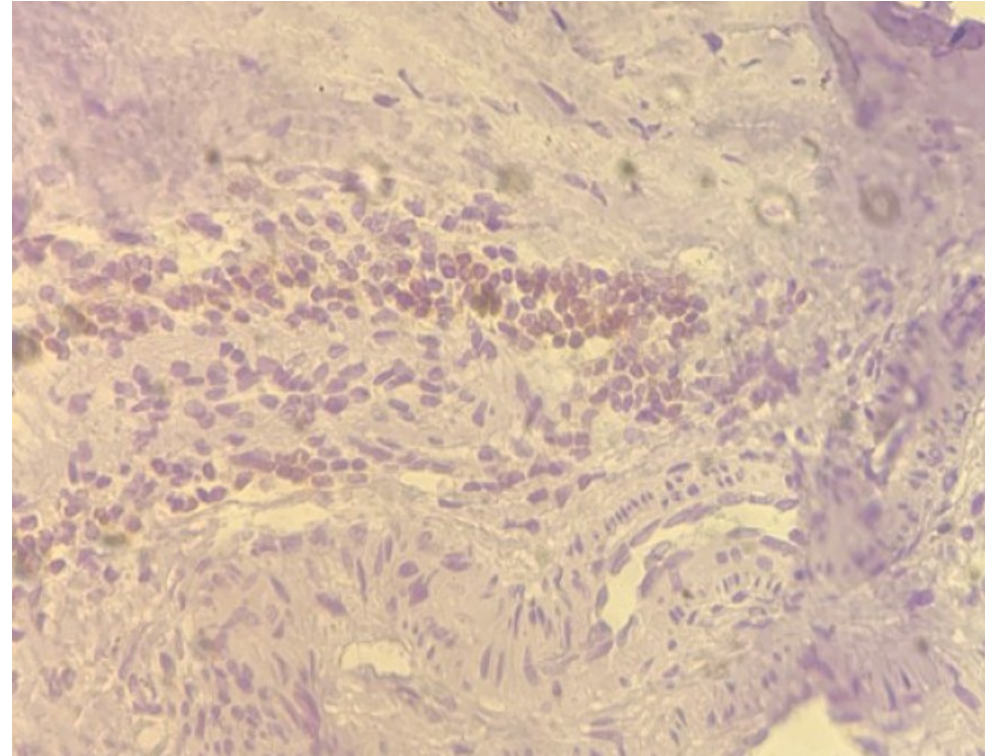
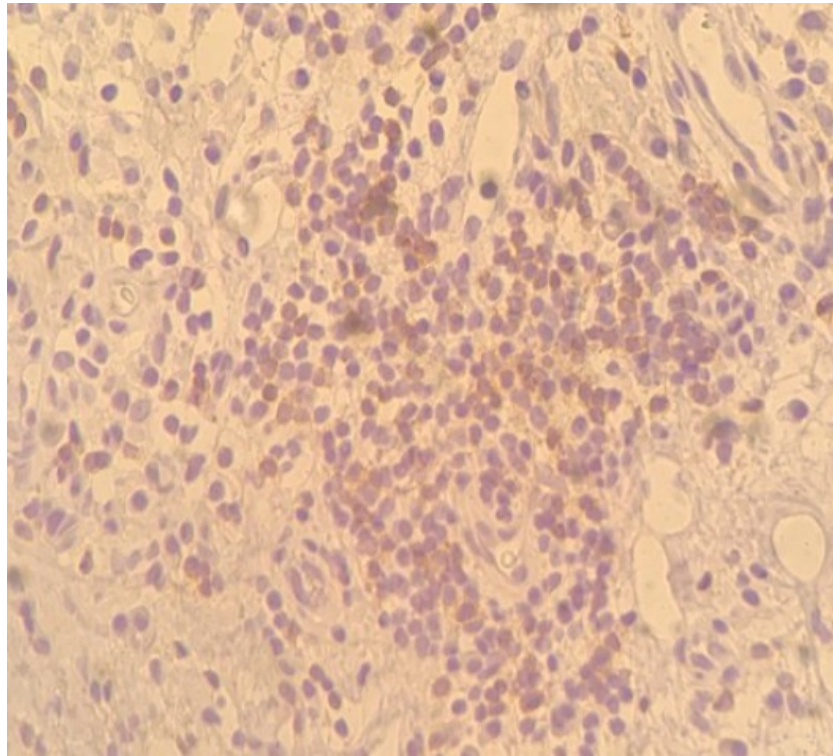
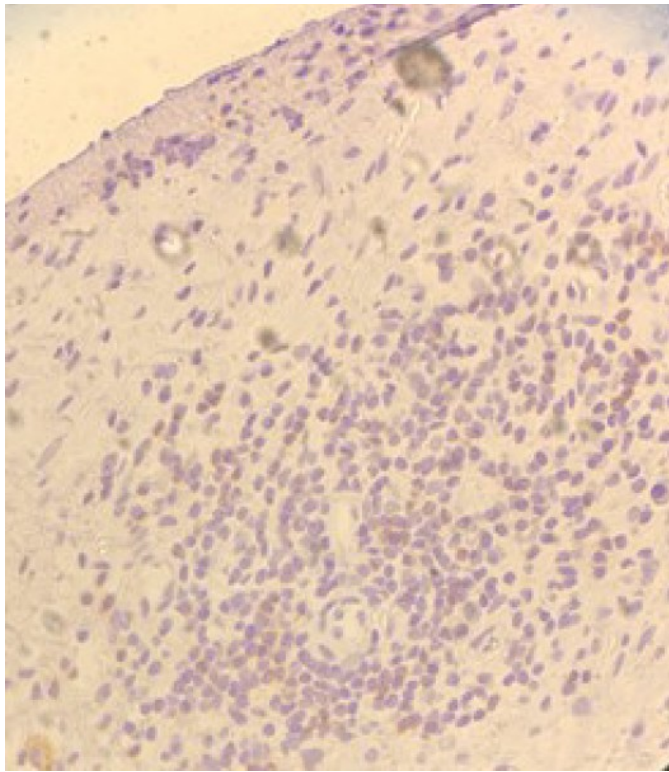
12 months



■ ASIA yes 19 (24,1%)

■ ASIA no 60 (75,9%)

Figure 6 – Share of patients, who has criteria of ASIA syndrome before and in 1 year after the operation, n=79 (100%), p=0.001



CD3+ T-lymphocytes (17-58 per mm²) in infiltrate of the external edge of capsule

Large lymphocytic infiltration with **CD4+** T-cells (13-59 per mm²), external edge of capsule

CD20+ B-cells (12-61 per mm²) in infiltrate

In all cases, the implant capsule was represented by outer dense fibrous connective tissue and inner looser fibrous tissue facing the silicone material. Dense layer was represented mainly by collagen fibers. In all cases, **hernial protrusions** of the connective tissue were observed; in some cases, these **protrusions contain small lymphocytic infiltrates**.

In the dense part of the capsule, small **fragments of the silicone** were determined as well as **foreign body granulomas** with giant multinucleated cells of foreign bodies and small infiltrates, consisting mainly of lymphoid cells.

In 7 out of 12 cases, **focal lymphoid infiltrate was detected**, located mainly **around small vessels** and the formation of **foreign body granulomas**.

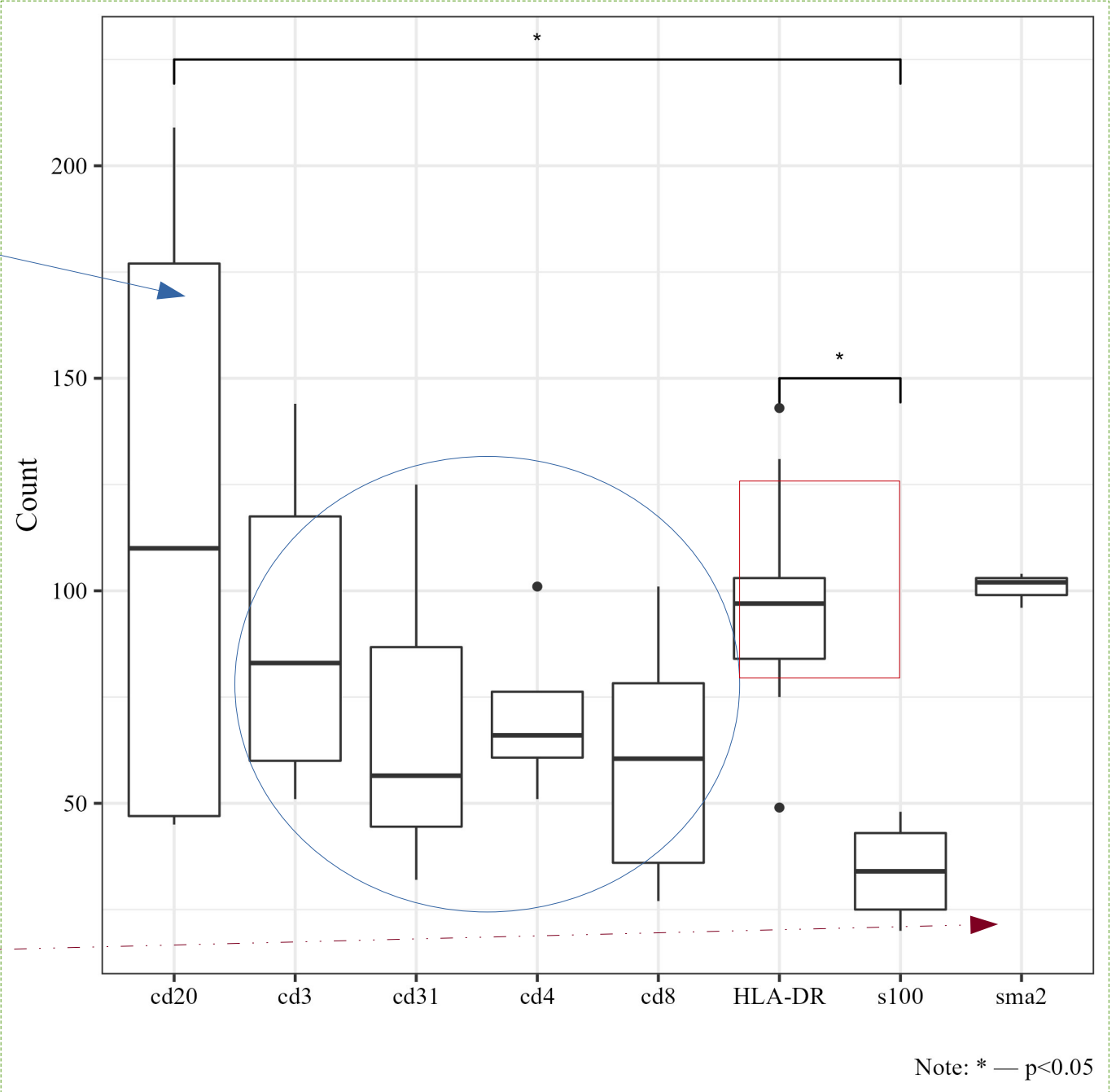
WHAT KIND OF CELLS THESE INFILTRATES AND GRANULOMAS AROUND UMPLANT CAPSULE CONSIST OF?

- prevailing are **B-lymphocytes (CD20+)**;

- **T-cells**, mostly helpers (**CD3+CD4+**) and those associated with microvasculature (**CD31+**) dominate over scarce T cytotoxic/suppressors (**CD8+**);

- **antigen-presenting cells** with Class II HLA proteins (**HLA-DR+**) are multiple;

- intensive generation of connective tissue matrix and microvasculature is accompanied by expression of **calcium-binding non-epithelial protein S100** and marker of myofibroblasts (**SMA2**);



DISCUSSION:

1/ TSH receptor is expressed in breast, hence adjuvant effect of silicone could increase its autopresentation:

Shi, X., Xue, L., Jin, X. et al. Different expression of sodium-iodide importer (NIS) between lactating breast and thyroid tissues may be due to structural difference of thyroid-stimulating hormone receptor (TSHR). *J Endocrinol Invest* 40, 41–48 (2017).
<https://doi.org/10.1007/s40618-016-0524-7>

2/ There was a case of Graves -von Basedow disease described which debuted and 2 cases of Hashimoto thyroiditis debuted after silicone mammoplasty [in all cases **several years** after SBI] :

Bernet VJ, Finger DR. Graves' disease following silicone breast implantation. *J Rheumatol.* 1994;21(11):2169.

Vayssairat M, Mimoun M, Houot B, Abuaf N, Rouquette AM, Chaouat M. Thyroïdite de hashimoto et prothèses mammaires en silicone: 2 observations. *J Mal Vasc.* 1997;22(3):198-199.

3/ A clever man warned about increase of anti-thyroid autoimmunity after silicone implants as long as 30 years ago, it was Prof. A. Vojdani:

Vojdani A, Campbell A, Brautbar N. Immune functional impairment in patients with clinical abnormalities and silicone breast implants. *Toxicol Ind Health.* 1992;8(6):415-429.

4/ Anti-TSH -R autoantibodies were associated with higher risk of breast cancer:

Szychta P, Szychta W, Gesing A, Lewiński A, Karbownik-Lewińska M. TSH receptor antibodies have predictive value for breast cancer - retrospective analysis. *Thyroid Res.* 2013;6(1):8. Published 2013 May 16. doi:10.1186/1756-6614-6-8

Conclusion

- SBI-related risk of autoimmune thyroid disease should be taken into account among **contraindications** for SBI and thyroid disease markers should be checked during **dispensary observation** of SBI recipients.



THANK YOU FOR ATTENTION!
Σας ευχαριστώ για την προσοχή σας!
СПАСИБО ЗА ВНИМАНИЕ!