Effect of the treatment with β-glucan in women with cervical cytologic report of atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesions (L-SIL)

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***Aim*. The aim of this study was to evaluate the effect of β-glucan in women with ASCUS or L-SIL, as detected by cervical cytologic screening.**

***Methods*. A total of 356 women with ASCUS or L-SIL were enrolled and divided into two groups: 1) 176 patients, treated with topical β-glucan; and 2) 180 patients who were only followed-up. The treatment consisted of two cycles of topical β-glucan applied once a day for 20 consecutive days and treatment separated by ten days. The effect of β-glucan was evaluated comparing Pap cytology results and colposcopic findings between treated patients and controls after 6 and 12 months of follow-up.**

***Results*. After 6 months from enrollment, 63.1% (111/176) of patients treated with β-glucan had a negative Pap smear *versus* 45% (81/180) of controls (P<0.001), and 43.4% (36/83) of treated patients *versus* 18.2% (14/77) of controls experienced the disappearance of colposcopic lesions (P=0.001). At the end of the 12-month follow up, 83.5% (147/176) of treated patients *versus* 60% (108/180) of controls had a negative Pap smear (P<0.001), and 55.4% (46/83) of treated patients *versus* 24.7% (19/77) of controls experienced the disappearance of colposcopic lesions (P<0.001). No side effects were observed in treated patients.**

***Conclusion*. β-glucan increases the spontaneous regression rate of low-grade cytologic abnormalities as well as cervical findings.**

KEY WORDS: Glucans – Colposcopy – Cervix uteri.

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It has been estimated that approximately 75% of sexually active women will contract a Human Papilloma Virus (HPV) infection in the course of their lives.[1, 2] Most of these infected women are able to clear the virus within several months, although a few of them develop a persistent infection. Cells persistently infected with HPV present precancerous changes, leading to the development of cancer years after infection.[1, 3-6] The persistence of HPV infection is associated with cigarette smoking, long-term oral contraceptive use (five or more years), high parity (five or more full-term pregnancies), coinfection with human immunodeficiency virus (HIV), immunosuppression, coinfection with Herpes Simplex Virus type-2 or *Chlamydia trachomatis*, diets poor in fruits and vegetables and low levels of vitamins.[1, 2, 7-11] The persistence of the viral infection is strictly associated with the risk of developing cervical cancer, as 95-99% of cases of cervical cancer are attributed to HPV infection. Therefore, cervical cancer has been recognized by World Health Organization as the first cancer that is wholly due to a viral infection.[2, 7, 12]

The management of low grade cervi-

cal abnormalities found on a Pap smear consists of two different possibilities. The first is to treat the lesion, after biopsy, by means of excisional or ablative procedures, and the second is to wait for the spontaneous regression of the abnormalities while the patient is followed-up with Pap smears and colposcopy that are performed every 6 months for up to 2 years after the diagnosis.[2] In consideration of the high probability of the spontaneous regression of cervical lesions induced by HPV, the tendency to select conservative treatment appears to be justified.[2] As β-glucan is effective in the treatment of the recurrent vulvar candidiasis and vulvar lesions caused by HPV infection and induces the reparative process of the epidermis, it should also be an effective and safe method to support the simple "wait and see" approach in women with HPV-related, low-grade cervical lesions.[2, 13] β-glucan is a polysaccharides found inside the cellular wall of numerous bacteria and fungi and an immune response modifier; thus, we decided to evaluate the effect of β-glucan on the treatment of women with a cytological diagnosis of ASCUS or L-SIL and cervical lesions induced by HPV.[2, 13, 14]

Materials and methods

Study population

From January 2010 to September 2012, a total of 400 women were enrolled into the study after receiving abnormal cervical cancer screening results and being referred to the Ambulatory of Colposcopy, Lasersurgery and Cervico-Vaginal Pathology of the Department of Obstetrics and Gynecology of Policlinico Umberto I of Rome. Inclusion cytologic criteria were HPV-positive, atypical squamous cells of undetermined significance (ASCUS) and low grade squamous intraepithelial lesions (L-SIL). Exclusion criteria were previous treatment for cervical disease (including loop electrosurgical excision procedure (LEEP), cold-knife conization, cryotherapy, LASER therapy or hysterectomy), prior chemotherapy or radiation treatment for cervical neoplasia, HIV infection, immunocompromised status, immunosuppressive therapy, pregnancy, squamocolumnar junction partially visible or not visible, abnormal colposcopic findings that were grade 2 or were suspicious for invasion at colposcopic examination and inability to provide informed consent. Women with H-SIL at Pap results and abnormal colposcopic findings that were grade 2 (major) or were suspicions for invasion at colposcopic examination were excluded for the assessment of the biopsy procedures and standard treatments.

The enrolled population was randomized using Stat Trek's Random Number Generator; 44 patients (24 assigned to the intervention group and 20 to the control group) were excluded from the study because of noncompliance or intercurrent illness, resulting in a final study population of 356 women (176 treated with β-glucan and 180 belonging to the control group); their ages ranged from 16 to 75 years, with a mean age of 32.7 years. Written informed consent was obtained from all participating subjects. The study was conducted in accordance with good clinical practice guidelines and the principles outlined in the Declaration of Helsinki.

Among patients with ASCUS, 76 had a negative colposcopy (normal colposcopic findings), and 43 had a positive colposcopy (abnormal colposcopic findings Grade 1). Among patients with L-SIL, 120 had a negative colposcopy, and 117 had a positive colposcopy.

Thus, women belonging to the treated group and to the control group were divided into 4 subgroups: 1) patients with a cytologic report of ASCUS and positive colposcopy; 2) patients with a cytologic report of L-SIL and positive colposcopy; 3) patients with a cytologic report of ASCUS and negative colposcopy; 4) patients with a cytologic report of L-SIL and negative colposcopy.

β-glucan gel spray (Colpofix®, Progine Farmaceutici, Campi Bisenzio, Florence, Italy) was applied once a day for 20 consecutive days followed by a 10 day-long pause; the pause was followed by a further 20

consecutive days of therapy with β-glucan. In women that menstruated regularly, the 10-day pause coincided with menstruation. The active ingredient was carboxymethylβ-glucan, and the medium contained micronized silver and polycarbophil. The dose of the medication administered daily was 5 sprays (2 mL), and β-glucan was applied vaginally by the means of a proper distributor that could be used once. The distributor indicated that β-glucan could be uniformly applied on the vaginal mucosa without any residue and without side effects, such as itching or burning.

Statistical analysis

The effect of topical β-glucan was evaluated by means of colposcopy and Pap smear, which were performed 6 and 12 months after enrollment. Pap smears were interpreted in local laboratories according to the 2001 Bethesda system for cytologic diagnoses. Colposcopy was performed according to 2002 and 2011 Colposcopic Terminology of the International Federation of Cervical Pathology and Colposcopy.

Data from the study were tabulated, and the χ^2 test has been used to assess the statistical significance of any difference in the regression of cervical lesions induced by HPV between women treated with β-glucan and those who were only followed-up. P-value <0.05 was considered significant. Statistical calculations were performed using SPSS Statistical Software (IBM, Armonk, NY, USA).

Results

The number of patients treated with β-glucan was 176; their ages ranged from 16 to 75 years, with a mean age of 33.3 years.

Among the 176 women who were treated with β-glucan: 59 patients had L-SIL on cytology report and negative colposcopy; 58 patients had L-SIL on cytology report and positive colposcopy; 34 patients had ASCUS on cytology report and negative colposcopy; 25 patients had ASCUS on cytology report and positive colposcopy.

All of the 176 patients started the treatment with β-glucan in accordance with the proposed therapeutic plan. None of patients interrupted their treatment or reported side effects.

A total of 180 patients belonged to the control group, their age ranged from 18 to 70 years, with a mean age of 32.2 years.

Among the 180 patients of the control group: 61 patients had L-SIL on cytology report and negative colposcopy; 59 patients had L-SIL on cytology report and positive colposcopy; 42 patients had ASCUS on cytology report and negative colposcopy; 18 patients had ASCUS on cytology report and positive colposcopy (Table I).

At the sixth month of follow-up, the Pap cytology results were as follows (among patients who were treated with topical β-glucan):

— thirty-three patients out of 58 (56.9%) with L-SIL and a positive colposcopy experienced the disappearance of cytologic abnormalities, as shown by a negative Pap smear (26/59 patients in the control group, 44.1%; P=0.23, not statistically significant);

— sixteen patients out of 25 (64%) with ASCUS and a positive colposcopy experienced the disappearance of cytologic abnormalities, as shown by a negative Pap smear (6/18 patients in the control group, 33.3%; P=0.09, not statistically significant);

— overall, 49 patients out of 83 (59.0%)

TABLE I.—*Number of patients treated with* β*-glucan and number of patients assigned to the control group.*

		Pap smear					
		L-SIL			ASCUS		
		Total	Treated with β-glucan	Control group	Total	Treated with β-glucan	Control group
Colposcopy	Negative	120	59	61	76	34	42
	Positive	117	58	59	43	25	18

with a positive colposcopy and cervical cytologic abnormalities had a negative Pap smear 6 months after the start of β-glucan topical treatment (32/77 patients in the control group, 41.6%; P=0.04, statistically significant);

— thirty-eight patients out of 59 (64.4%) with L-SIL and a negative colposcopy experienced the disappearance of cytologic abnormalities, as shown by the last negative Pap smear (28/61 patients in the control group, equivalent to 45.9%; P=0.06, not statistically significant);

— twenty-four patients out of 34 (70.6%) with ASCUS and a negative colposcopy experienced the disappearance of cytologic abnormalities, as shown by the last negative Pap smear (21/42 patients in the control group, 50.0%; P=0.11, not statistically significant);

— overall, 62 patients out of 93 (66.7%) with cervical cytologic abnormalities and a negative colposcopy had a negative Pap smear 6 months after their enrollment into the study and the start of topical therapy (49/103 patients in the control group, 47.6%; P=0.01, statistically significant).

— overall, 111 patients out of 176 (63.1%) were enrolled with cervical cytologic abnormalities, ASCUS or L-SIL and had a negative cytologic exam 6 months after starting the treatment (81/180 patients in the control group, 45%; P<0.001, statistically significant) (Table II).

— At the end of the follow up, 12 months after enrollment, the Pap cytology results were as follows (among the patients treated with topical β-glucan):

— forty-five patients out of 58 (77.6%) with L-SIL and a positive colposcopy experienced the disappearance of lesions, as shown by a negative Pap smear (34/59 patients in the control group, 57.6%; P=0.03, statistically significant);

— twenty-one patients out of 25 (84%) with ASCUS and a positive colposcopy experienced the disappearance of cytologic abnormalities, as shown by a negative Pap smear (9/18 patients in the control group, 50.0%; P=0.04, statistically significant);

— overall, 66 patients out of 83 (79.5%) with cytologic abnormalities and a positive colposcopy experienced the disappearance of lesions, as shown by the last Pap smear (43/77 patients in the control group, 55.8%; P=0.002, statistically significant);

— fifty-one patients out of 59 (86.4%) with L-SIL and a negative colposcopy experienced the disappearance of cytologic abnormalities, as shown by their last negative Pap smear (38/61 patients in the control group, 62.3%; P=0.005, statistically significant);

— thirty patients out of 34 (88.2%) with ASCUS and a negative colposcopy experienced the disappearance of cytologic abnormalities, as shown by their last negative Pap smear (27/42 patients in the control group, 64.3%; P=0.03, statistically significant);

— overall, 81 patients out of 93 (87.1%) with cytologic abnormalities and a negative

TABLE II.—*Number and percentage of patients having negative Pap smears at the sixth month of follow-up.*

	Patients treated with β-glucan		Control group		P value
	Number of patients	%	Number of patients	%	
L-SIL + positive colposcopy	33/58	56.9	26/59	44.1	0.23
ASCUS + positive colposcopy	16/25	64.0	6/18	33.3	0.09
Positive colposcopy (total)	49/83	59.0	32/77	41.6	0.04
L-SIL + negative colposcopy	38/59	64.4	28/61	45.9	0.06
ASCUS + negative colposcopy	24/34	70.6	21/42	50.0	0.11
Negative colposcopy (total)	62/93	66.7	49/103	47.6	0.01
L-SIL (total)	71/117	60.7	54/120	45.0	0.02
ASCUS (total)	40/59	67.8	27/60	45.0	0.02
TOTAL	111/176	63.1	81/180	45.0	<0.001

colposcopy had a negative Pap smear at the twelfth month of follow up (65/103 patients in the control group, 63.1%; P<0.001, statistically significant);

— mainly, 147 patients out of 176 (83.5%) with cervical cytologic abnormalities at recruitment had a negative Pap smear at the twelfth month of follow up (108/180 patients in the control group, 60.0%; P<0.001, statistically significant) (Table III).

With regard to the colposcopic examination, among patients treated with topical β-glucan, at the sixth month of follow-up, the results were as follows:

— twenty-three patients out of 58 (39.7%) with L-SIL and a positive colposcopy at enrollment experienced the disappearance of lesions at the second colposcopic examination (11/59 patients in the control group, 18.6%; P=0.02, statistically significant);

— thirteen patients out of 25 (52%) with ASCUS and a positive colposcopy experienced the disappearance of lesions at the second colposcopic examination (3/18 patients in the control group, 16.7%; P=0.04, statistically significant);

— overall, 36 patients out of 83 (43.4%), with cervical cytologic abnormalities and a positive colposcopy at recruitment experienced the disappearance of lesions at the second colposcopic examination (14/77 patients in the control group, 18.2%; P=0.001, statistically significant) (Table IV).

At the twelfth month of follow-up, among patients treated with topical β-glucan, the colposcopic findings were as follows:

— thirty-one patients out of 58 (53.4%) with L-SIL and a positive colposcopy experienced the disappearance of lesions at the last colposcopic examination (15/59 patients in the control group, 25.4%; P=0.004, statistically significant);

— fifteen patients out of 25 (60%) with ASCUS and a positive colposcopy experienced the disappearance of lesions at the last colposcopic examination (4/18 patients in the control group, 22.2%; P=0.03, statistically significant);

— overall, 46 patients out of 83 (55.4%) with cervical cytologic abnormalities of low grade and a positive colposcopy at recruitment experienced the disappearance of lesions at the third and last colposcopic examination (19/77 patients in the control

TABLE III.—*Number and percentage of patients having negative Pap smears at the twelfth month of follow-up.*

	Patients treated with β-glucan		Control group		P-value
	Number of patients	%	Number of patients	%	
L-SIL + positive colposcopy	45/58	77.6	34/59	57.6	0.03
ASCUS + positive colposcopy	21/25	84.0	9/18	50.0	0.04
Positive colposcopy (total)	66/83	79.5	43/77	55.8	0.002
L-SIL + negative colposcopy	51/59	86.4	38/61	62.3	0.005
ASCUS + negative colposcopy	30/34	88.2	27/42	64.3	0.03
Negative colposcopy (total)	81/93	87.1	65/103	63.1	<0.001
L-SIL (total)	96/117	82.1	72/120	60.0	<0.001
ASCUS (total)	51/59	86.4	36/60	60.0	0.002
TOTAL	147/176	83.5	108/180	60.0	<0.001

TABLE IV.—*Number and percentage of patients with positive colposcopic examinations at enrollment with negative colposcopy at the sixth month of follow-up.*

		Negative colposcopy at the sixth month of follow-up				P value
		Treated patients		Control group		
		Number of patients	%	Number of patients	%	
Positive colposcopy at enrollment	L-SIL	23/58	39.7	11/59	18.6	0.02
	ASCUS	13/25	52.0	3/18	16.7	0.04
	TOTAL	36/83	43.4	14/77	18.2	0.001

TABLE V.—*Number and percentage of patients with positive colposcopic examination at enrollment with negative colposcopy at the twelfth month of follow-up.*

		Negative colposcopy at the twelfth month of follow-up				P value
		Treated patients		Control group		
		Number of patients	%	Number of patients	%	
Positive colposcopy at enrollment	L-SIL	31/58	53.4	15/59	25.4	0.004
	ASCUS	15/25	60.0	4/18	22.2	0.03
	TOTAL	46/83	55.4	19/77	24.7	<0.001

group, equivalent to 24.7%; P<0.001, statistically significant) (Table V).

At the end of the follow-up, no correlation between the age and effectiveness of treatment with topical β-glucan was observed, and neither systemic nor local side effects were reported.

Discussion

According to our study, topical β-glucan is effective in inducing the regression of low grade cervical cytologic abnormalities detected by Pap smear (ASCUS, L-SIL). The difference in the regression of cervical cytologic abnormalities between the two groups of women (patients treated with β-glucan and patients belonging to the control group) was statistically significant, both at the end of the sixth month of follow-up and at the end of the 12-month follow-up. At the twelfth month of follow-up, topical β-glucan stimulated the regression of cervical cytologic abnormalities in 79.5% of women with a positive colposcopy (55.8% in women belonging to the control group) and in 87.1% of the patients with a negative colposcopy (63.1% in women belonging to the control group). Thus, β-glucan improved the spontaneous regression rate of HPV-related low grade cervical cytologic abnormalities of 23.7-24% at 12 months.

Similarly, topical β-glucan is effective in provoking the disappearance of low grade colposcopic lesions. The difference between the two groups of women (patients treated and patients belonging to the control group) was clinically and statistically significant, both at 6 and 12 months after the start of treatment. In fact, topical β-glucan induces the disappearance of cervical lesions in 55.4% of women within 12 months (24.7% in patients belonging to the control group) and improves the spontaneous regression rate of low grade colposcopic lesions of 30.7% at 12 months.

The effectiveness of β-glucan was independent from the age of patients. No side effects have been described.

Our study confirms data from another clinical trial with topical β-glucan treatment, in which, among women with negative colposcopy, a regression rate for cytologic abnormalities of 100% was found in treated patients with ASCUS. In treated patients with L-SIL, regression rates for cytologic abnormalities of 70% after 6 months and of 85% after 12 months were found. According to the same study, among treated patients with positive colposcopies, the probability of regression of low grade cytologic abnormalities is 60% at six months and 80% at twelve months.[2]

According to our study, β-glucan is an effective and safe immune response modifier that is able to induce the disappearance of cervical HPV-related lesions and to stimulate reparative processes.

β-glucan, once administered, is recognized as a "non-self" antigen and is bound by Dectin-1, Toll-Like Receptors (TLRs), complement Receptor 3 (CR3) and lactosylceramide receptor. This process provokes the release of proinflammatory cytokines and the activation and proliferation of macrophages, neutrophils, dendritic cells, lymphocytes and natural killer cells. β-glucan also induces T-cells to become T-reg cells,

which likely alters the types and concentrations of cytokines to enact a protective effect against Human Papillomavirus infection, toxins and harmful substances.[2, 13, 15, 16]

Still, the specific molecular mechanisms and immunomodulatory functions of β-glucan remain unclear. For example, the way in which β-glucan polarizes the subset of T cells is unclear. Further studies are required to improve our knowledge about β-glucan to optimize its rational application.

Conclusions

Based on the promising results of our study, even if 5-17% of the patients with ASCUS and 15-30% of the women with L-SIL found on Pap smear are at risk of having a histological diagnosis of CIN-2/CIN 3 after biopsy, the management of these patients may give priority to treatment with topical β-glucan in addition to a close follow-up, involving the period of colposcopic examinations and Pap smears at least every six months during the first two years after the cytologic diagnosis and the start of treatment. This recommendation contrasts with more standard procedures, such as biopsy and excision or ablation. Treatment and follow up with topical β-glucan are justified if we consider that the cost of excisional procedures is much higher than that of treatment with β-glucan. At the very least, treatment with topical β-glucan in women with cytologic results of ASCUS or L-SIL is a promising and low-cost alternative to standard management, lacking both the risk of overtreatment of standard management techniques and the risk of failing to recognize and treat high grade lesions of the simple "wait and see" approach.

Riassunto

Effetto del trattamento con β-glucano in donne con ASCUS o L-SIL

Obiettivo. Lo scopo di questo studio è valutare l'effetto del β-glucano in donne con Pap-test deponente per ASCUS o L-SIL.

Metodi. Un totale di 356 donne con ASCUS o L-SIL sono state reclutate e divise in due gruppi: 1) 176 pazienti trattate con β-glucano e 2) 180 pazienti sottoposte a follow-up. Il trattamento consisteva in due cicli di β-glucano applicato localmente una volta al giorno per 20 giorni consecutivi; i due cicli di trattamento erano separati da una pausa di 10 giorni. L'effetto del β-glucano è stato valutato confrontando il risultato del Pap-test e della colposcopia tra le pazienti trattate e le pazienti appartenenti al gruppo di controllo dopo 6 e 12 mesi di follow-up.

Risultati. Dopo 6 mesi dal reclutamento, il 63,1% (111/176) delle pazienti trattate avevano un Pap-test negativo contro il 45% (81/180) delle pazienti del gruppo di controllo (P<0.001) e il 43.4% (36/83) delle pazienti trattate contro il 18,2% (14/77) delle pazienti del gruppo di controllo manifestarono la scomparsa delle lesioni diagnosticate mediante colposcopia (P=0,001). Al termine dei 12 mesi di follow-up, l'83,5% (147/176) delle pazienti trattate contro il 60% (108/180) delle pazienti del gruppo di controllo avevano un Pap-test negativo (P<0,001) e il 55,4% (46/83) delle pazienti trattate contro il 24,7% (19/77) delle pazienti del gruppo di controllo avevano una colposcopia negativa (P<0,001). Non furono osservati effetti collaterali nelle pazienti trattate.

Conclusioni. Il β-glucano aumenta il tasso di regressione spontanea delle anomalie citologiche di basso grado e delle lesioni cervicali colposcopicamente visibili.

PAROLE CHIAVE: Glucano - Colposcopia - Cervice uterina.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Received on January 9, 2014.
Accepted for publication on January 15, 2014.
Epub ahead of print on February 5, 2015.