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Article

Evaluation of oral supplementation with a casein hydrolysate-based formula to favor the clearance of HR-HPV infections and their derived lesions

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Abstract: Cervical cancer screening systems aim to detect established HPV infections early. However, if there are no high-grade lesions, the intervention choice is basically limited to observational follow-up with recommendations on life habits like diet, to favor infection control. Therefore, it is important to establish specific feeding guidelines that provide clear evidence about the benefit they may bring against HPV infections. The present study evaluates the benefits of nutritional supplementation with a casein hydrolysate-based formula in patients with HR-HPV infection, compared with a non-supplemented control group. A total of 118 patients completed 6 months of follow-up. Significant differences between supplemented and control groups were observed for total or partial HR-HPV clearance at 6 months (74.6% vs 35.6%). Supplemented patients also suffered a lower occurrence of new intracervical lesions (0% vs 28.6%), a significantly greater resolution (67.4% vs 41.9%) and less progression of pre-existing lesions (4.7% vs 9.7%) at 6 months. An increase in the effectors of cellular immunity that could be responsible for their effect was also observed in supplemented patients. We conclude that nutritional supplementation with this casein hydrolysate-based formula could improve the outcomes of observational management of HPV infection.

Keywords: HPV; papilloma; LSIL; HSIL; HPV clearance; immunomodulation; NK cells; casein hydrolysate; Ditriamino®; HuPaVir®

1. Introduction

The Human Papillomavirus (HPV) are double-stranded DNA viruses characterized by not having a lipid envelope. More than 100 different HPV types have been identified to date. They can be divided into cutaneous or mucosal; depending on the tissues they usually infect [1]. In parallel, HPVs can be classified as low risk (LR-HPV) or high-risk viruses (HR-HPV), depending on the risk of developing cancer by their infection persistence [2]. In this sense, fifteen HPV types are considered high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82) while 3 are classified as probable high-risk types (26, 53, and 66) [3].

HPV infection is caused by direct contact with the skin or mucous membranes of an infected individual, who may or may not have visible lesions. In the case of genital infection, vaginal or anal intercourse represents the main transmission way [4]. HPV is very common, and it is estimated that in the United States, approximately 80% of women will have acquired an infection by the age of 50 [5].

Most HPV infections do not cause symptoms or disease and are cleared between 12-24 months after infection. The small proportion of these infections that persist result in pre-cancerous lesions that can progress to cancer [6]. HPV infection is associated with virtually 100% of cases of cervical cancer and with a high rate of cases of anogenital and oropharyngeal cancer [7].

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According to the World Health Organization, the approach to cervical cancer prevention consists of a primary prevention through HPV vaccination to avoid HPV infection, and secondary prevention through screening programs, to achieve early detection of HPV infection [8]. Screening programs differ by country, but are mainly based on the determination of the presence of the virus by viral DNA detection tests and the determination of intraepithelial lesions by cytology (Pap test). The positive HPV DNA test implies the presence of the virus in the sample, while the positive cytology implies an alteration or injury in the tissue [9].

The morphology of squamous intraepithelial lesions caused by HPV in the lower anogenital tract is identical in all locations and in both sexes [10]. The Lower Anogenital Squamous Terminology (LAST) classifies the histological intraepithelial squamous lesions (SIL) associated with HPV in two grades, low-grade lesions (LSIL) and high-grade lesions (HSIL) [11]. The term LSIL also includes cervical intraepithelial neoplasia of grade 1 (CIN1) of the Richart classification [12], adopted by the OMS in 2004.

LSIL / CIN1 lesions are the histological manifestation of a self-limited infection by HPV which most times resolute spontaneously [10]. The strict follow-up of patients with LSIL lesions minimizes the risk of developing cervical cancer, since it allows to observe if the lesions become resolved or, on the contrary, to detect early if they progress to HSIL. The lesions of CIN2 and CIN3 are included within the term HSIL [13]. The lesions HSIL / CIN2 can still return to L-SIL or progress to neoplasia. In contrast, HSIL / CIN3 lesions are considered to be true intraepithelial neoplasms with a high potential for progression. They constitute the necessary precursor lesion of cervical cancer and should be treated by destructive or excisional methods [8] [p. 154-160].

An atypical squamous cell of undetermined significance (ASCUS) is another cytological alteration. ASCUS cytology may be caused by an HPV infection or by other causes, so when detected, it is recommended to perform the HPV-DNA test. Usually the presence of ASCUS is related to SIL lesions, mainly LSIL although HSIL cannot be ruled out [14].

The immune system is the natural defense mechanism that prevents the persistence and the progression of infections caused by HPV, among other pathogens. Previous studies report that the presence of oncogenic HPV is not enough for malignant progression and that additional steps are needed for the promotion of tumors [13].

The adequate nutritional status of patients with HPV infections is essential for the optimal functioning of the immune system. For this reason, within the strategies of observational treatment of patients with HPV infections, it is recommended to maintain an adequate diet, to stop smoking and to practice regular exercise. In some cases, supplementation of relevant macro and micronutrients may help boost the immune system and accelerate HPV clearance and its symptoms elimination.

The main objective of this study is to evaluate the benefits of the supplementation with a specific casein hydrolysate-based formula to favor the clearance of HR-HPV infections and their derived lesions. The specific casein hydrolysate is a mixture of dipeptides and tripeptides that are source of fast systemic absorption amino acids and bioactive peptides. This formula is combined with vitamins (Vitamin A, B3 and B9) and minerals (zinc) whose dietary deficiencies have been related to a greater persistence of HPV infections and progression of the derived lesions [15-20].

2. Materials and Methods

This observational, prospective, multicenter and controlled study have been carried out in the gynecology service of three different hospitals throughout Spain. The product under study is a nutritional supplement marketed under the name of HuPaVir® which contains 4.5g of patented casein hydrolyzate (Ditriamino®), 120µg (15% RDI) vitamin A, 30µg (15% RDI) vitamin B9 (folic acid), 2.4mg (15% RDI) vitamin B3 (niacin) and 1.5mg (15% RDI) zinc for each dosis of 6g (NTD Labs, Terrassa, Spain).

A total of 118 patients have completed the study. All patients have followed the recommendations included in the guideline for cervical cancer prevention of the Spanish Association of Cervical Pathology and Colposcopy (AEPPC or *Asociación Española de Patología Cervical y*

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Colposcopía) [10] without any modification of the usual clinical practice. All subjects gave their informed consent for inclusion, before they voluntarily participated in the study, in accordance with the Declaration of Helsinki. This observational study meets all legal requirements stipulated in the country where it was carried out, Spain.

Inclusion criteria: Patients with positive DNA test for at least one HR-HPV (HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82) with normal, ASCUS or LSIL cytology. Women from 20 to 65 years old.

Exclusion criteria: Patients that did not present positive test for at least one HR-HPV.

Patients with casein hydrolysate-based formula supplementation included in this study could not use jointly other topical or ingested alternative therapies aimed at fighting HPV infection that are not included in the AEPCC clinical guide.

The diagnostic procedure was performed by liquid cytology and DNA extraction for identification of viral DNA from part of the L1 region of HPV by multiplex PCR.

Patients were divided into four groups as detailed in **Table 1** depending on the cytology result and whether or not they received supplementation with casein hydrolysate-based formula.

Table 1. Study groups characterization.

Group name	Group characterization and guidelines	Patients (n)	Average age
1- Casein formula HR-HPV (+) / Cytology (-)	Positive patients for the HR-HPV DNA test but with normal cytology. Oral supplementation with casein hydrolysate-based formula 1 dose / day + observation for 6 months.	30	38.5
2- Control HR-HPV (+) / Cytology (-)	Positive patients for the HR-HPV DNA test but with normal cytology. Observation for 6 months.	14	35.4
3- Casein formula HR-HPV (+) / Cytology (+) (ASCUS/LSIL)	Positive patients for the HR-HPV DNA test but with altered cytology (ASCUS/LSIL). Oral supplementation with casein hydrolysate-based formula 1 dose / day + observation for 6 months.	43	37.5
4- Control HR-HPV (+) / Cytology (+) (ASCUS/LSIL)	Positive patients for the HR-HPV DNA test but with altered cytology (ASCUS/LSIL). Observation for 6 months	31	33.9

All patients included in the study were followed up after initial visit, attending medical visits at times 0 and 6 months in both of which they underwent cervical cytology and DNA test for HR-HPV.

Statistical analysis was performed using Prism GraphPad. In case of differences between supplemented and control groups, the Chi-square test was applied with a two-sided analysis and a confidence interval of 95%. In the case of immunological parameters, t-test was applied with a two-sided analysis and a confidence interval of 95%.

Patients with casein hydrolysate-based formula supplementation received the recommendation of taking the product separated from meals. For patients in casein hydrolysate-based formula groups who underwent blood tests, coinciding with visits from month 0 or 6, the determination of different immune parameters was requested. These immune parameters include levels of NK cells; TCD4+, TCD8+ and total lymphocytes; cortisol; IGF1; and IGM. A survey was conducted and voluntarily answered in patients taking casein hydrolysate-based formula to investigate tolerance to the product and other improvements in general conditions.

The main objective of this study is to evaluate the clearance degree of HR-HPV infections and their derived lesions in patients with or without nutritional supplementation with casein hydrolysate-based formula. The secondary objective is to evaluate the effect of the nutritional supplementation in the systemic immune system. Other parameters of evaluation are tolerability of the supplementation treatment and other improvements in the patient's general conditions.

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HR-HPV clearance is defined as a negative test for the individual HR-HPV type following a positive test for that type [21]. We will refer as "Total HR-HPV clearance" for a negative test for all HR-HPV types detected at baseline and "Partial HR-HPV clearance" for a negative test of at least one of the HR-HPV detected at baseline. "Total or partial HR-HPV clearance" represent a negative test for at least one or all HR-HPV types detected at baseline.

3. Results

A total of 118 patients have been included in this study. These patients were divided into 4 groups depending on whether their cytology at the beginning of the study was normal or had ASCUS / LSIL lesions, and whether they received supplementation with casein hydrolysate-based formula or not (**Table 1**). In all, 73 patients were supplemented with casein hydrolysate-based formula (Group 1, n=30, mean age 38.5 years. Group 3, n=43, mean age 37.5 years) and 45 underwent control observation without supplementation (Group 2, n=14, mean age 35.4. Group 4, n=31, mean age 33.9 years). Average age of all patients was 36.5 years old.

All of the 118 patients were positive for at least one type of HR-HPV at the beginning of the study. 46.7% of the cases (55/118) presented infection by more than one type of HR-HPV simultaneously at the beginning of the study. In the case of patients included in groups 1 and 3 (casein formula) or 2 and 4 (control), simultaneous infection by more than one type of HR-HPV at the beginning of the study was presented by 50.7% (37/73) and 40% (18/45) of the cases, respectively.

3.1. HR-HPV clearance

In this study we evaluated both total and total or partial clearance of any HR-HPV at 6 months of follow-up (**figure 1**).

The results of the DNA test of 6 patients indicated the presence of one or more HR-HPV but did not specify the types, so these patients could not be included for the analysis of partial HR-HPV clearance. For the rest, total or partial HR-HPV clearance at 6 months of follow-up was observed in 84.6% of cases (22/26) in group 1 vs 35.7% (5/14) in control group 2, and in 68.3% of cases (28/41) in group 3 vs 35.5% (11/31) in control group 4. Differences between treatment and control groups (1 vs. 3, 2 vs. 4 or 1+3 vs. 2+4) were statistically significant in both cases ($p < 0.05$ and $p < 0.1$ respectively). If we take into account the total number of patients supplemented with casein hydrolysate-based formula (groups 1 and 3) compared to the control groups (2 and 4), 74.6% (50/67) vs 35.6% (16/45) of total or partial HR-HPV clearance was observed respectively, with a significant difference observed between groups ($p < 0.01$) (**figure 1a**).

With respect to total HR-HPV clearance, complete clearance of all HR-HPV types at 6 months of follow-up was observed in 66.7% (20/30) for group 1 vs. 35.7% (5/14) for control group 2, and 39.6% (17/43) for group 3 vs. 22.6% (7/31) for group 4. If we take into account the total number of patients supplemented with casein hydrolysate-based formula (groups 1 and 3) compared to the control groups (2 and 4), 50.7% (37/73) vs 26.7% (12/45) of total HR-HPV clearance was observed respectively (**figure 1b**). In this case, differences between supplementation and control groups were not statistically significant.

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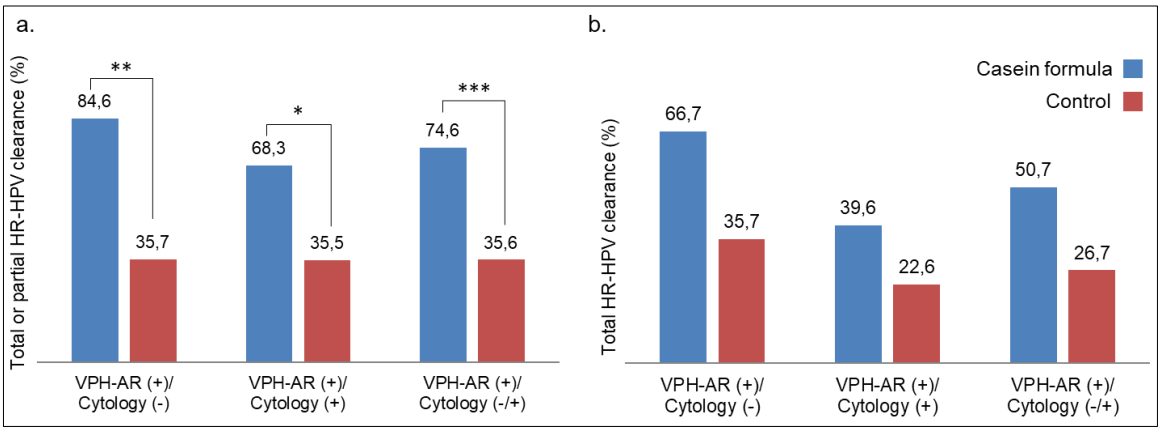

Figure 1. HR-HPV clearance rates at 6 months of follow-up. (**a**) Total or partial HR-HPV clearance; (**b**) Total HR-HPV clearance. The bars represent the clearance rate (%) of each group. From left to right, each bar corresponds to: Group 1; group 2; group 3; group 4; groups 1 and 3; groups 2 and 4. HR-HPV (+)/Cytology (-) represents patients that had positive DNA test for HR-HPV and normal cytology at the beginning of the study (groups 1 and 2). HR-HPV (+)/Cytology (+) represents patients that had positive DNA test for HR-HPV and altered cytology (ASCUS/LSIL) at the beginning of the study (groups 3 and 4). HR-HPV (+)/Cytology (-/+) represents patients that had positive DNA test for HR-HPV and normal, ASCUS or LSIL cytology at the beginning of the study (groups 1 and 3 (left) and 2 and 4 (right)).* $p < 0.1$ ** $p < 0.05$; *** $p < 0.01$.

3.2. Intracervical lesions evolution

In this study, the appearance of lesions was evaluated after 6 months of follow-up in patients who presented normal cytology at the beginning of the study. On the other hand, patients who had ASCUS / LSIL lesions at month 0 were evaluated after 6 months in order to observe if lesions persisted, progressed or, at best, remitted (**figure 2**).

From HR-HPV positive and lesion-free patients at the start of the study who received supplementation with casein hydrolysate-based formula (group 1), 100% (30/30) of them remained with normal cytology results after 6 months of follow-up. However, in the control group (group 2) we observed the appearance of new lesions in 28.6% (4/14) of the patients at 6 months. These newly appeared lesions were with cytological result of both ASCUS / LSIL and even HSIL lesions in equal parts (14.3% of the total cases for each lesion grade) (**figure 2a**).

Regarding the patients who presented cytological results of ASCUS / LSIL at the beginning of the study, we observed how 67.4% (29/43) of the patients supplemented with casein hydrolysate-based formula® (group 3) showed normal cytology after 6 months of follow-up, while in the control group (group 4) the cytological normalization occurred only in 41.9% of cases (13/31). On the other hand, 27.9% (12/43) of the supplemented patients (group 3) versus 48.4% (15/31) of the control patients (group 4) remained without cytological changes during the 6-month follow-up. Regarding the progression of the lesions, 4.7% (2/43) of the patients supplemented with casein hydrolysate-based formula (group 3) versus 9.7% (3/31) of the control patients (group 4) resulted with HSIL cytology after 6 months follow up (**figure 2b**).

Statistical analysis was performed taking into account the total number of patients with positive cytology at the beginning of the treatment and the remaining number of patients with positive cytology after 6 months of supplementation or observation, considering positive cytology both ASCUS/LSIL and HSIL. Statistical significance ($p < 0.1$) was found when comparing groups 3 and 4 (positive cytology at month 0, supplemented and control respectively). These results also show a tendency to a lower appearance of new lesions or progression of those existing in patients supplemented with the casein formula, although these results were not statistically significant.

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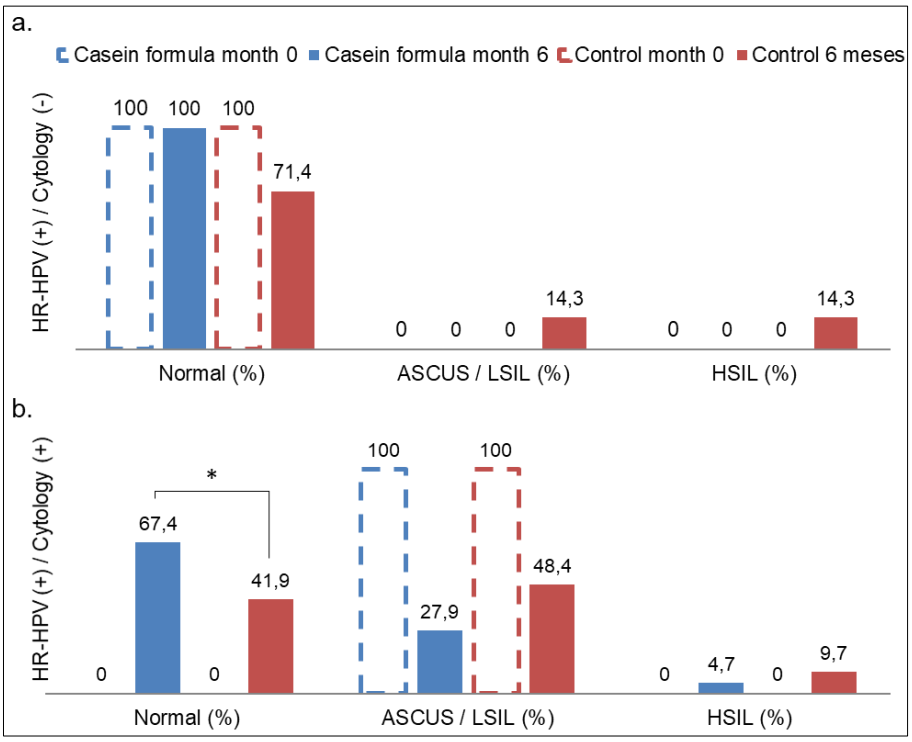

Figure 2. Intracervical lesions evolution at 6 months of follow-up. (**a**) Appearance of new lesions in patients HR-HPV (+) / cytology (-) (groups 1 and 2); (**b**) Evolution of pre-existing lesions in patients HR-HPV (+) / cytology (+) (groups 3 and 4). The bars represent the percentage (%) of patients with each grade of lesion (normal, ASCUS/LSIL and HSIL). Blue colored bars represent the patients after 6 months of casein hydrolysate-based formula supplementation. Red colored bars represent the patients without supplementation after 6 months of follow-up. Empty bars represent the patients at the beginning of the study. $p < 0.1$.

3.3. Effect of the nutritional supplementation in the systemic immune system

To evaluate the effect of the nutritional supplementation in the systemic immune system, we analyzed the blood tests available for patients supplemented with casein hydrolysate-based formula. We had a total of 12 analytics that coincided with the start of the study and another 10 analytics that coincided with the end of it. The immune parameters mean levels at months 0 and 6 and the increase during that period is represented in the **Table 2** for NK cells; TCD4+ and TCD8+ lymphocytes; total lymphocytes count; cortisol; IGF1; IgM and IgG. Differences between month 0 and month 6 were found to be non-significant in all cases.

Table 2. Blood immune parameters increase after 6 month supplementation.

Parameter	Month 0	Month 6	Increase (%)
NK cells (%)	9.1	10.5	+15.7
TCD4+ lymphocytes (%)	47.2	55.6	+17.6
TCD8+ lymphocytes (%)	26.4	31.1	+17.6
Total lymphocytes (cells/µL)	2308	2497	+8.2
Cortisol (µg/dL)	14.9	18.8	+26.20
IGF1 (ng/dL)	149.2	165.0	+10.6
IgM (mg/dL)	136.8	148.9	+8.8
IgG (mg/dL)	1149.3	980.9	-14.7

3.4. Tolerability and other effects in the patient general condition

A survey was conducted and voluntarily answered in patients with casein hydrolysate-based formula supplementation to investigate the tolerance to the product and other effects in the general

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condition. A total of 20 patients answered if they had noticed any adverse effects during the 6 months of supplementation. 95% (19/20) answered that they did not observe any adverse effect, while 5% (1/20) indicated having noticed a sensation of abdominal swelling but that it was not an impediment to continue with the supplementation.

18 patients answered the question of whether they had observed any other improvement on their general condition. 50% (9/18) answered that they observed other improvements as lower incidence of colds in 22.2% of the cases (4/18), greater vitality in 22.2% (4/18) or less recurrences of cold sores in 11.1% (2/18).

4. Discussion

At present no medication is indicated to treat HPV infections when they do not cause advanced-stage pre-cancerous lesions. The only therapeutic option in infected patients is observation until spontaneous remission or progression to pre-cancerous lesions (the "wait and see" approach). If the infection progresses and cervical lesions evolve to grade CIN2 or CIN3, excisional or destructive treatments are performed that require invasive surgery [10].

It has been known for a long time that a proteins or amino acids deficiency in diet alters immunological function and increases susceptibility to infectious diseases [25]. The findings of recent studies indicate an important role for amino acids in immune responses when regulating different processes. On the one hand, it has been shown that amino acids are essential for activating T lymphocytes, B lymphocytes, Natural Killer cells (NKs) and macrophages. On the other hand, they regulate the cellular redox state and the gene expression and proliferation of the lymphocytes. In addition, they are necessary to produce antibodies, cytokines and other cytotoxic substances [26].

This casein hydrolysate provides the 18 essential amino acids from diet. In particular, peptides from casein have been identified to possess an immunomodulatory action. Furthermore, multifunctional peptides encrypted within their amino acid sequence are activated after a specific hydrolysis [27, 28]. In addition to the importance of macronutrients in the immune state, the adequate supply of micronutrients such as minerals and vitamins is also essential. Notably, the contribution of micronutrients such as vitamin A, folates and zinc has been directly associated to the immune response to HPV infections [15-17, 29, 30].

Vitamin A and folates have been related to a protective effect against the appearance of cervical neoplasia due to the persistence of HPV [15]. Deficiencies of carotenoids such as vitamin A are clearly associated with the onset of cervical cancer and its precursor lesions, and folate deficiencies are related to the occurrence of pre-cancerous lesions of the cervix [17]. In a study conducted on 1,248 men with HPV infection, it was observed that patients who consumed more retinol, vitamin A and folates had a lower persistence of HPV infections [16]. Folates could play a role in regulating the integration and stability of the viral genome, thanks to its involvement in DNA synthesis, repair and methylation [15, 29]. On the other hand, both folate and vitamin A can inhibit cell proliferation, preventing DNA damage, and enhance immunological functions [15, 29, 30].

Zinc is an essential mineral for the proper functioning of the immune system. Zinc ions are involved in the regulation of the intracellular signaling pathways of the cells of the innate and adaptive immune system. In addition, it has an anti-inflammatory and antioxidant function [31]. Regarding its importance in HPV management, it has been observed that zinc deficiency in patients with warts is associated with greater persistence, progression and recurrence of these [19]. Different clinical studies have shown efficacy using both oral and topical zinc in the treatment of warts [18, 20].

In this study, we observe that patients supplemented with casein hydrolysate-based formula show higher rates of HR-HPV clearance, regardless of having cervical lesions or not. Taking all patients together, a significant difference is observed between the rates of total or partial HR-HPV clearance at 6 months in the supplemented patients versus the control patients (74.6% vs. 35.6% respectively).

In contrast, previous studies have reported that only a 29% of HR-HPVs are able to spontaneously clear in 6 months and a 41% after 18 months [32]. The results obtained in the control group are similar to those observed in the general population, while patients supplemented with the

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casein hydrolysate-based formula show virus clearance rates of almost double for the different groups.

It has been described that patients with cervical HPV present simultaneous infection by more than one type of HPV in more than 30% of cases [33-35]. For this reason, total HR-HPV clearance is of greater clinical importance, meaning that a patient negativizes the test for all HR-HPV types detected at baseline. Regarding this clinically ideal situation, we also observe a clearance of almost double between supplemented and control groups for total HR-HPV clearance (50.7% vs 26.7% respectively, $p = 0.19$), although the difference was not statistically significant. We speculate that a greater number of patients and/or a longer term follow-up could confirm the tendency and result in significant differences. This observation arises the interest of extending the follow-up period of the patients included in this study.

Regarding the intracervical lesions associated with HR-HPV, in this study we observed how supplementation with a casein-hydrolysate formula prevents the appearance of new lesions of both low and high grade, since no new lesions were observed in group 1 and in contrast, new lesions were detected in 28.6% of patients in the control group. Moreover, in cases of baseline ASCUS / LSIL , it was observed that supplemented patients suffered a significantly greater remission of the lesions than control patients (67.4% vs. 41.9% respectively, $p < 0.1$) and a lower progression of the lesions towards HSIL (4.7% vs. 9.7% respectively).

The immune effect of oral supplementation with a casein hydrolysate-based formula could be the responsible for the results observed in HR-HPV clearance and intracervical lesions remission rates, as well as for the other improvements in the general condition observed by the patients. In this regard, the increase in cellular immune effectors as NK cells and CD4+ and CD8+ lymphocytes is to be highlighted. Unlike the humoral immune response against HPV that prevents infection by the virus, the responsible for the clearance of HPV infections is the cell-mediated immune response [36, 37]. In this sense, T-cell homing and T-cell infiltration at the site of infection is related with the immune control and clearance of HPV infections [38]. However, there are times when the immune system is not able to control the progression of HPV infections or is unable to prevent recurrences in patients who have already been treated. Importantly, NK deficiency has been related to an increased susceptibility to HPV infections and to a loss of control of them, as well as to a greater appearance of cervical cancer [39-42]. Considering this, it is logical to think that helping the systemic cell-mediated immune system to fight HPV should improve the prognosis of infections by this virus.

The main objective of the observational treatment of patients with HPV infection is that the patients' own immune system controls the lesions, preventing their progression and favoring their remission. It should be noted that in other observational studies conducted in a general HR-HPV+ population without any kind of intervention, L-SIL lesions persisted after 2 years in as much as 40% of the cases [43]. In contrast, the results observed in this study are much better even after only 6 months with casein hydrolysate-based formula supplementation.

Importantly, the persistence of HR-HPV is associated with higher risk of the lesions progression to precancerous lesions and cervix cancer [44]. Therefore, being able to reduce the persistence of HR-HPV or their derived lesions with a food supplementation may help reduce the risk of cervical cancer in patients infected with HR-HPV, especially when there is no other management alternative available but to wait and see.

It is interesting to note that approximately half of the patients with low-grade lesions at the beginning of the study who achieved resolution at 6 months were able to clear any of the HR-HPV present at the beginning of the study (67.4% of lesion remission in contrast to 39.6% of total HR-HPV clearance in patients taking casein hydrolysate-based formula; or the respective 41.9% and 22.6% in control patients). This difference may be due to the fact that the resolution of the lesions depends mainly on the response of the patient to the infection, while the detection of the viral DNA depends both on the persistence of the infection and on the persistence of the exposure to the virus. In that sense, the control of sexual partners to prevent continued exposure to the virus may be very helpful. This highlights the need to evaluate the benefit of nutritional supplementation of both patients and their sexual partners, in addition to supplementing only patients. Another study where sexual partners receive nutritional supplementation will be necessary to evaluate this hypothesis.

5. Conclusions

The results of this study confirm that supplementation with a casein hydrolysate-based formula represents a well-tolerated and easily administered oral support that could help the own immune system of the patient fight against HPV infection, accelerating the clearance of the virus, favoring the remission of lesions derived from HPV infection and preventing their progression.

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Conflicts of Interest: C.P., A.D. and A.L. declare no conflict of interest. J.F. declares to be full-time employee of NTD Labs during the development of the present study as scientific director. J.F. has participated in the development of the study, but not in the recruitment of patients, or the follow-up of the same or data collection.

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