Natural Remedies for *Herpes simplex*

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Abstract

***Herpes simplex* is a common viral infection of the skin or mucous membranes. The lesions caused by this infection are often painful, burning, or pruritic, and tend to recur in most patients. Short-term treatment with acyclovir can accelerate the healing of an acute outbreak, and continuous acyclovir therapy is often prescribed for people with frequent recurrences. While this drug can reduce the recurrence rate by 60-90 percent, it can also cause a wide array of side effects, including renal failure, hepatitis, and anaphylaxis. Safe and effective alternatives are therefore needed. There is evidence that certain dietary modifications and natural substances may be useful for treating active *Herpes simplex* lesions or preventing recurrences. Treatments discussed include lysine, vitamin C, zinc, vitamin E, adenosine monophosphate, and lemon balm (*Melissa officinalis*). (*Altern Med Rev* 2006;11(2):93-101)**

Introduction

Herpes simplex virus (HSV) infections of the skin are caused by one of two viruses (HSV-1 or HSV-2). Cutaneous *Herpes simplex* is characterized by painful, burning, or pruritic clusters of vesicles on the lips, oral mucous membranes, genital region, or other areas of the body. HSV infection of the eye results in keratoconjunctivitis, a serious condition that sometimes leads to corneal blindness. HSV may also cause encephalitis or other systemic infections, particularly in immunocompromised patients. This review will be limited to cutaneous *Herpes simplex* infections.

After a primary infection, the virus travels to a nerve cell ganglion where it persists in a dormant phase. Various factors such as sun exposure, chapping or abrasion of the skin, fever, stress, fatigue, or menstruation can reactivate the virus, resulting in a recurrence at the site of the original infection. Recurrences are common, particularly in the case of genital infections.

While *Herpes simplex* can occur in seemingly healthy people, patients with cancer, acquired immunodeficiency syndrome (AIDS), and other diseases associated with impaired immune function are especially prone to such infections. Immune system deficiencies that are more subtle, but not necessarily associated with a serious disease, might also increase the risk of experiencing *Herpes simplex* infections. For that reason, a comprehensive prevention-and-treatment plan should include measures designed to enhance immune function.

Dietary Factors

Ingestion of large amounts of refined carbohydrates impairs certain parameters of immune function. In rats, the addition of sucrose to the diet (10-20% of energy) caused a dose-dependent reduction in the capacity to produce antibodies.[1] In healthy humans, acute ingestion of 75 g of glucose significantly depressed cell-mediated immune function after 30 and 60 minutes.[2] Although the relationship between refined-carbohydrate intake and susceptibility to *Herpes simplex* has not been investigated, many patients have observed that herpetic lesions recur when they eat too many sweets. In some cases, ingestion of even small amounts of refined sugar appears to trigger an exacerbation. Restriction of refined-carbohydrate intake should, therefore, be considered on a case-by-case basis.

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Elimination of refined carbohydrates is also a key component of an "anti-candida" program. *Candida albicans* produces various immune-suppressing toxins,[3] and patients with "chronic candidiasis" as described by Truss[4] and others may have an impaired capacity to control opportunistic organisms such as HSV. This author has treated several patients whose *Herpes simplex* infections became much less frequent after treatment for candidiasis with antifungal medication.

Repeated ingestion of allergenic foods might strain the immune system, potentially reducing its capacity to keep HSV in its dormant state. Although the potential association between food allergy and recurrent *Herpes simplex* has not been studied, patients often report that outbreaks become less common after they identify and avoid allergenic foods.

Interventions aimed at increasing the lysine/arginine ratio in the diet might also be beneficial; these are described below.

Lysine/Arginine

The proteins synthesized by HSV contain more arginine and less lysine than proteins synthesized by host cells,[5] and arginine is required for HSV replication.[6] Lysine appears to antagonize arginine by several mechanisms: it functions as an antimetabolite of arginine; it competes with arginine for reabsorption at the renal tubule, thereby increasing arginine excretion; it competes with arginine for intestinal absorption; it induces the enzyme arginase, resulting in degradation of arginine; and it competes with arginine for transport into cells.[7] In tissue culture, lysine antagonized the growth-promoting action of arginine on HSV.[6] These observations raise the possibility that increasing either absolute lysine intake or the ratio of lysine-to-arginine intake would be of value for the prevention and treatment of *Herpes simplex* infections.

Forty-five patients with frequently recurring *Herpes simplex* infections received lysine (usually 312-1,200 mg per day) for periods of two months to three years. Foods high in arginine were restricted. Lysine treatment appeared to reduce the frequency of recurrences. When lysine was discontinued, lesions usually recurred within 1-4 weeks.[8]

Nine patients with recurrent *Herpes simplex* infections received 500 mg per day lysine hydrochloride and reduced their intake of high-arginine foods. In comparison with past experiences, recurrences were less frequent, less severe, and of shorter duration. Lesion formation was invariably associated with high arginine intake 12-36 hours previously.[7]

Forty-one patients with recurrent *Herpes simplex* infections were randomly assigned to receive, in double-blind fashion, lysine hydrochloride (624 or 1,248 mg per day) or placebo for 24 weeks, and then the alternate treatment for an additional 24 weeks. All patients were prescribed a diet high in lysine and low in arginine. In the high-dose group, there were significantly fewer recurrences during the lysine period than during the placebo period. The lower dose of lysine was ineffective.[9]

One hundred-fourteen patients with recurrent orofacial or genital herpes, or both, were randomly assigned to receive, in double-blind fashion, 1 g lysine hydrochloride three times daily or placebo for six months; 52 patients completed the trial. Among those who completed the trial, the proportion of patients who reported the treatment to be effective or very effective was 74 percent in the lysine group and 28 percent in the placebo group ($p<0.01$). Lysine was significantly more effective than placebo in terms of frequency and severity of lesions and healing time.[10]

Sixty-five patients with recurrent *Herpes simplex* infections received, in double-blind fashion, by alternating allocation (even/odd), lysine hydrochloride (500 mg twice daily) or placebo for 12 weeks and then the alternate treatment for an additional 12 weeks. Significantly more patients were recurrence-free during lysine treatment than during placebo treatment (27.7% versus 12.3%; $p<0.05$). The total number of recurrences was 12.5-percent lower in the lysine group than the placebo group, although this difference was not statistically significant.[11]

Twenty patients with frequently recurring oral or genital *Herpes simplex* lesions were randomly assigned to receive, in double-blind fashion, 400 mg lysine hydrochloride three times daily or placebo for 4-5 months. Lesions were present on 41 percent of the study days in the lysine group, compared with 46 percent of the study days in the placebo group (difference not statistically significant). The true difference may

have been greater than that reported, however, since three of the 10 patients in the placebo group had continuous lesions and dropped out of the study within four weeks.[12]

These studies suggest that lysine supplementation reduces the recurrence rate of *Herpes simplex* infections. The effectiveness of lysine may vary according to the dosage used, the lysine and arginine content of the diet, and the efficiency of lysine absorption, which appears to vary from person to person.[13]

The optimal lysine dose for *Herpes simplex* prophylaxis is not known, but a reasonable dosage range is 500-3,000 mg daily. It was not always clear in the cited studies whether the dosage being tested referred to lysine hydrochloride or pure lysine (lysine hydrochloride is 80% lysine). Doses up to 6 g per day are said to be safe,[14] but long-term toxicity studies have not been conducted in humans. By comparison, the estimated dietary lysine requirement for a 70-kg human is in the range of 800-3,000 mg per day.[15,16]

Table 1. Lysine and Arginine Content of Some Common Foods

Food	Amount	mg/lysine	mg/arginine	Ratio Arg to Lys
Tuna 3 oz	1/2 can	2400	1450	0.6
Turkey (baked light meat)	3 oz	2400	1770	0.74
Chicken (baked light meat)	3 oz	2232	1584	0.71
Halibut, baked	3 oz	2083	1357	0.65
Salmon	3 oz	2014	1311	0.65
Liver, beef	3 oz	1671	1363	0.82
Cheese	3 oz	1650	600	0.4
Cheese, ricotta	1/2 cup	1600	800	0.5
Pork	3 oz	1586	1470	0.83
Cheese, cheddar	3 oz	1497	729	0.49
Wild game	3 oz	1300	962	0.75
Cheese cottage	1/2 cup	1200	700	0.6
Sardines, canned in oil	3 med	814	531	0.65
Meat, luncheon	3 oz	740	592	0.8
Yogurt	1 cup	700	250	0.35
Milk, whole	1 cup	650	300	0.45
Beans, red canned	1/2 cup	630	510	0.8
Oatmeal flakes	1 cup	600	600	1.0
Granola	1 cup	500	900	1.85
Wheat germ, toasted	1/4 cup	500	675	1.3
Bacon	3 slices	500	525	0.9
Duck	3 oz	480	407	0.85
Sausage	3 oz	420	315	0.8
Egg	1 med	400	400	1.0
Peanuts	1/4 cup	363	1080	3.0
Avocado	1 med	200	100	0.5
Cashews	10 nuts	185	490	2.6
Almonds	18 nuts	145	683	4.7

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Lysine intake can be increased by increasing consumption of lysine-rich foods, such as legumes and animal proteins, and reducing intake of lysine-poor foods such as grains and refined sugars. Emphasizing foods that are not processed or cooked in ways that destroy lysine or render it non-bioavailable would also improve lysine nutritional status. Making these dietary changes might obviate the need for lysine supplementation in some cases. Food preparation methods that reduce the amount of bioavailable lysine include heating of protein-containing foods in the presence of a reducing sugar (e.g., fructose, glucose, or lactose), heating protein-containing foods in the presence of sucrose and yeast, or cooking at high temperatures or in the absence of moisture.[17,18] With respect to temperature and moisture, boiling or poaching a high-protein food would preserve lysine to a greater extent than would grilling, broiling, or frying.

According to anecdotal reports, lysine supplementation accelerates the healing of acute *Herpes simplex* outbreaks. Short-term administration of 1-3 g lysine daily has been found to reduce the duration of attacks, with higher doses being more effective than lower doses.[8,19] In a double-blind trial, however, administration of 1 g lysine at the first sign of infection, followed by 500 mg twice daily for a total treatment period of five days, had no significant effect on the healing rate.[20] Although anecdotal reports suggest higher doses of lysine might be effective during acute outbreaks, no controlled trials have confirmed this.

Some patients report that eating arginine-rich foods such as chocolate, nuts, and seeds causes them to experience herpes outbreaks, but the importance of dietary arginine as a causative factor has not been investigated scientifically. No harm would occur from encouraging *Herpes simplex* sufferers to avoid chocolate. However, because of the many health benefits of nuts and seeds, it would seem unwise to restrict those foods in the absence of clinical evidence that they cause adverse effects for a particular person. Table 1 illustrates dietary sources of lysine (mg/serving), arginine levels (mg/serving) of these same foods, as well as the arginine:lysine ratio.

Vitamin C

Ascorbic acid has been shown to inactivate a wide range of viruses *in vitro*,[21] including *Herpes simplex* virus,[22] and to enhance immune function. As early as 1936, vitamin C was reported to be of value in the treatment of *Herpes simplex*.[23] Klenner stated in 1949 that administering massive parenteral doses of vitamin C accelerated the healing of herpes lesions.[24] Cathcart later noted that herpes lesions in AIDS patients responded to a combination of oral and intravenous vitamin C and frequent topical application of vitamin C paste (ascorbic acid or sodium ascorbate mixed with water).[25]

In a small, double-blind trial, patients with *Herpes simplex* outbreaks received 200 mg ascorbic acid and 200 mg water-soluble flavonoids (apparently from citrus) three times daily for three days or a placebo. Randomization was not specified. The mean time until remission of symptoms was 57-percent shorter in the active-treatment group than in the placebo group (4.2 versus 9.7 days; $p<0.01$). Treatment was most effective when initiated during the prodromal stage.[26] The importance of flavonoids as a component of this treatment is uncertain, although several different flavonoids have demonstrated antiviral activity against HSV-1 *in vitro*.[27]

Thus, supplementation with vitamin C, with or without flavonoids, appears to be a worthwhile treatment for *Herpes simplex*. Although a relatively low dose of vitamin C was effective in the study described above, clinical observations suggest that the antiviral effect of vitamin C is more pronounced at higher doses. For treatment of an acute episode, up to 10,000 mg per day or more, according to bowel tolerance, for 5-10 days might be considered. For long-term prophylaxis, 500-3,000 mg vitamin C daily is reasonable for most patients, although there have been no studies evaluating the effect of vitamin C prophylaxis.

Zinc

Animal and In vitro Evidence

Zinc ions have been shown to inhibit the replication of HSV-1 and -2 *in vitro*.[28-31] At a concentration of 0.1 mM, the inhibition was almost complete and appeared to result from selective inhibition of the

viral DNA polymerase. In mice inoculated intravaginally with HSV-2, daily intravaginal application of a zinc sulfate solution (0.1 mM) decreased the severity of the infection.[32,33] Zinc applied in a collagen sponge tampon or in a douche was significantly more effective than zinc administered in a cream.

Topical Zinc Treatment

Topical application of various zinc preparations has been reported to be effective in the treatment of cutaneous *Herpes simplex* infections in humans.

Eighteen patients with recurrent *Herpes simplex* infections of the skin applied a topical solution of zinc sulfate (4%) in water four times daily for four days. The solution was administered as a wet dressing, and each application was left in place for at least one hour. Treatment was begun within 48 hours of symptom onset, after the vesicles had been lanced and unroofed with a needle. In all patients, pain, tingling, and burning stopped within the first 24 hours. Mean time to complete healing was 41-percent less with this treatment than with other therapies used to treat previous attacks (9.5 days versus 16 days).[34] No adverse effects were reported.

Twenty-five patients with *Herpes simplex* infections recurring every two weeks to two months were treated with a solution of 0.025- to 0.05-percent zinc sulfate. A gauze compress soaked in the lukewarm solution was placed on the skin for 10 minutes. Infections of the oral mucous membranes were treated with mouth rinses of a 0.01- to 0.025-percent solution for 1-3 minutes. The lower concentrations were used for acute infections and the higher concentrations were applied to normal skin at the site of a previous infection. During an acute episode, zinc was applied daily until the lesions disappeared. Maintenance treatment of healed lesions was continued once weekly for one month, then twice a month. During a follow-up period of 16-23 months, none of the patients experienced a recurrence of lesions. Preliminary results also showed that application of a 0.05-percent zinc sulfate solution, before and during sun exposure, to clinically normal skin at the site of previous *Herpes simplex* infections prevented or decreased relapses induced by sun exposure.[35]

Two hundred patients with acute *Herpes simplex* lesions applied 0.25-percent zinc sulfate in a saturated solution of camphor water. When the solution was applied 8-10 times per day, beginning within 24 hours of an outbreak, lesions usually disappeared within 3-6 days. With topical applications every 30-60 minutes, the itching, burning, stinging, and pain usually ceased within 2-3 hours; with continued application, crusts dried and sloughed off within 3-5 days. The earlier the treatment was begun, the shorter the duration of infection. Women with genital herpes had "excellent results" (details not provided) with a 0.25-percent zinc sulfate solution administered as a vaginal douche. The author of this report considered zinc sulfate to be "the most practical, most effective, and most economical treatment available" for *Herpes simplex* infections.[36]

One hundred fifty-eight patients with cold sores received zinc monoglycerolate (n=102) or zinc oxide (n=56) powder for transdermal application. The amount of each compound to be applied was not specified and it was not stated whether the powder was applied on the lesions or elsewhere on the skin. By day 13, 70 percent of the lesions in patients receiving zinc monoglycerolate had healed, compared with only nine percent of the lesions in patients receiving zinc oxide.[37] Zinc monoglycerolate has been shown by 65Zn tracer studies to enter the bloodstream if applied directly to the skin without the use of excipients.

Forty-six patients with facial or oral herpes infections of no more than 24 hours' duration were randomly assigned, in double-blind fashion, to apply a zinc oxide-glycine cream or placebo cream every two hours until the lesions had resolved or for 21 days, whichever was less. The mean duration of the infection was 23-percent lower in the active-treatment group than in the placebo group (5.0 versus 6.5 days; $p<0.02$). Adverse effects of topical zinc included mild-to-moderate burning, stinging, itching, or tingling, all of which resolved spontaneously.[38]

These studies indicate that topical zinc preparations can shorten the duration of *Herpes simplex* skin infections and possibly prevent recurrences (both spontaneous and sunlight-induced). While most studies used zinc sulfate, zinc monoglycerolate or zinc oxide-glycine may also be effective. Zinc oxide,

however, is not beneficial because it does not release sufficient numbers of zinc ions to exert an antiviral effect.[39]

Topically applied zinc solutions can cause pain, irritation, unpleasant dryness, or nausea and vomiting, unless used in very low concentrations. Although a four-percent zinc sulfate solution was well tolerated in one study, concentrations as low as 0.025- to 0.25-percent have been found to be effective, so these lower concentrations should be considered for clinical use.

Oral Zinc Treatment

Ten patients with recurrent genital herpes outbreaks at least once a month for three months received a daily supplement containing 50 mg zinc (sulfate) and 5 mg each magnesium, thiamine, and riboflavin. The total number of days for all patients on which herpes lesions were present fell by 57 percent. Two patients reported that they could prevent an attack by temporarily doubling the dosage when premonitory signs (paresthesias or thigh pains) occurred. The reduction in attack frequency became more pronounced with each successive month of treatment, suggesting the results were not due to a placebo effect.[40]

Oral administration of 23 mg zinc (sulfate) and 250 mg vitamin C, each twice daily for six weeks, to an unspecified number of patients appeared to reduce the duration and severity of *Herpes simplex* outbreaks during the supplementation period. It was suggested that this treatment be considered for prophylaxis prior to sun exposure for patients who experience sun-induced herpetic outbreaks.[41]

In some studies of patients with AIDS, oral or intravenous zinc supplementation has resulted in clinical improvement, but has also unmasked latent herpetic infections. Therefore, it is recommended that AIDS patients receiving zinc therapy also be treated with acyclovir.[42]

Although the studies using oral zinc supplementation were not placebo-controlled, zinc may be considered as part of an overall immune-enhancing program for patients with recurrent *Herpes simplex* infections. Long-term zinc supplementation should be accompanied by a copper supplement (1-4 mg daily, depending on the zinc dose), in order to prevent zinc-induced copper deficiency.[43]

Vitamin E

In uncontrolled trials, topical application of vitamin E relieved pain and aided in the healing of oral herpetic lesions (gingivostomatitis or herpetic cold sores). In two studies, the affected area was dried and cotton saturated with vitamin E oil (20,000-28,000 IU per ounce) was placed over it for 15 minutes.[44,45] Pain relief occurred within 15 minutes to eight hours, and the lesions regressed more rapidly than usual. In some cases, a single application was beneficial, but large or multiple lesions responded better when treated three times daily for three days. In another study of 50 patients with herpetic cold sores, the content of a vitamin E capsule was applied to the lesions every four hours. Prompt and sustained pain relief occurred and the lesions healed more rapidly than expected.[46]

Adenosine Monophosphate

Adenosine monophosphate (AMP) is a purine nucleotide that is an intermediate in cellular metabolism and nucleic acid synthesis. In studies in mice, parenterally administered AMP inhibited the development of skin lesions induced by inoculation with HSV-1[47] and reduced the reactivation rate of latent HSV-1 infections.[48] However, AMP treatment did not prevent recurrences of vaginal infections in guinea pigs inoculated vaginally with HSV-2.[49] In humans with *Herpes simplex* infections, blood levels of AMP were found to be consistently low.[50]

Thirty-six patients (ages 16-50 years) with recurrent herpes labialis were treated with a series of intramuscular AMP injections.[51] Each injection contained 1.5-2.0 mg AMP per kg body weight and was administered every other day for a total of 9-12 treatments. Prior to the start of treatment, the mean recurrence rate had been 6.3 episodes per year, and 20 patients had been experiencing recurrences for more than five years. After the treatment was begun the lesions healed rapidly. During follow-up periods ranging from one month to over two years, 23 patients (63.9%) remained free of recurrences and nine (25%) were recurrence-free for more than one year. The other 13 patients had only one mild episode each, with lesions restricted to the maculopapular stage and lasting no longer than 2-3 days. The mechanism of action of AMP against *Herpes simplex* is unknown.

This author has administered a series of 10 intramuscular AMP injections (usually 100 mg per injection) to 10 patients with recurrent *Herpes simplex* infections. In most cases, the frequency of recurrences was reduced. The most gratifying response occurred in a 32-year-old woman who had been suffering from recurrent *Herpes simplex* infections for four years. The outbreaks had become progressively more frequent to the point that she was experiencing at least one herpes lesion on some part of her body on most days. Within forty-eight hours after the first of 10 injections, the lesions had essentially disappeared and there was only one recurrence during the next 15 months.

Intramuscular AMP injections occasionally cause transient chest pain. Although this pain is not of cardiac origin, it can be frightening. Chest pain can usually be prevented by injecting half the dose, waiting 20 minutes, and then administering the other half. Care should be taken to ensure the needle is not in a vein, because rapid intravenous injection of adenosine, a related compound, is known to cause cardiac arrhythmias and other side effects.

At the time of this writing, AMP for intramuscular administration is available only through compounding pharmacists. Although this compound was used for more than 40 years with apparent safety, and although it occurs naturally in the body, the U.S. Food and Drug Administration categorizes it as an unapproved drug, and restricts its sale through the usual commercial channels.

Lemon Balm

Extracts of the leaves of lemon balm (*Melissa officinalis*) have been investigated as a topical treatment for *Herpes simplex*. Sixty-six patients with a history of recurrent herpes labialis (at least four episodes per year) were randomly assigned to apply, in double-blind fashion, a standardized lemon balm cream (70:1 extract of leaves, containing 1% Lo-701) or placebo cream to the affected area four times daily for five days. On the second day of therapy, the symptom score was significantly lower in the active-treatment group than in the placebo group (4.03 versus 4.94; p=0.042). For the total symptom score over the five-day period, there was a nonsignificant trend in favor of active treatment (13.3 versus 14.9; p=0.16).[52]

In another randomized, double-blind trial, 116 patients with an acute *Herpes simplex* outbreak applied the same lemon balm cream as in the previous study or a placebo cream. Treatment was begun within 72 hours of the onset of symptoms and administered 2-4 times daily for 5-10 days. Healing was assessed as "very good" by 41 percent of patients in the lemon balm group and by 19 percent in the placebo group (p=0.022).[53]

Lithium

Preliminary evidence suggests that oral or topical lithium is beneficial. Lithium inhibited the replication of HSV-1 and HSV-2 *in vitro* at concentrations that did not inhibit host cell replication.[54] In case reports[55] and observational studies,[56,57] treatment with lithium carbonate for depression or other psychiatric problems was associated with a reduction in the frequency of *Herpes simplex* outbreaks. In contrast, treatment with other antidepressants had no effect on the rate of *Herpes simplex* infections.

An ointment containing eight-percent lithium succinate was evaluated in a double-blind study of 73 patients with recurrent genital *Herpes simplex* infections. The lithium preparation or a placebo was applied topically four times daily for seven days, beginning within 48 hours of the onset of lesions. Compared with placebo, the lithium ointment reduced the median duration of pain (4 versus 7 days; p<0.05), but not the time to complete healing.[58] Although the authors of the study attributed the beneficial effect of the ointment to its lithium content, the product also contained 0.05-percent zinc sulfate, which may have been responsible for all or part of the improvement.

Because of its potential to cause side effects and the absence of controlled trials demonstrating efficacy, oral lithium should not be considered a primary treatment modality for patients with recurrent *Herpes simplex*. Further research is needed to determine whether topical lithium preparations are effective.

Conclusion

There are a number of natural options available for the prevention and treatment of *Herpes simplex* infections. Dietary modifications, although based mainly on anecdotal reports or theoretical grounds, might help prevent recurrences. These

would include restricting refined-sugar intake, identifying and avoiding allergenic foods, and emphasizing foods high in bioavailable lysine. Reducing intake of high-arginine foods may be considered if the clinical history suggests that eating such foods precipitates outbreaks.

Natural remedies that show promise either for prophylaxis or treatment include lysine, vitamin C, zinc, vitamin E, adenosine monophosphate, and lemon balm. Future research should investigate whether using these substances in combination would be more effective than using them individually.

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