Universidad Europea

GRADUATION PROJECT

Degree in Dentistry

CROSS-SECTIONAL STUDY OF RECURRENT HERPES LABIALIS

Madrid, academic year 2022/2023

Identification number: 134

ABSTRACT:

Introduction:
Recurrent herpes labialis is a common disease transmitted through infected bodily secretions during asymptomatic and symptomatic viral shedding periods . The symptoms include burning, stinging, itching, pain, pruritus, and paresthesia, with sudden appearance of vesicular lesions on an inflammatory base.

Objective: Investigate effectiveness of treatments for recurrent herpes labialis in university students, assess prophylactic treatment usage, identify triggers and association with dental procedures, COVID-19, age, family history, and gender differences.

Methodology: A cross sectional study complemented with a bibliographical review was realized in between November 2022 and April 2023 over 100 subjects.

Results: 27% positive for herpes labialis, with outbreaks reported annually (72%), every 6 months (24%), or monthly (4%). Triggers include physical/emotional stress (85.2%), hormonal changes (37%), sun exposure (29.6%), cold weather (18.5%), mouth/lip trauma (14.8%), respiratory illness (7.4%), Covid-19 (7.4%), and dental interventions (7.4%). Age of first infection: 33% at 12-18 years, 18.5% at 19-24 years, 14.8% at 24-30 years, 14.8% at >30 years, 11.1% at 6-11 years, and 7.4% at 2-6 years. 59.3% have infected family members. 55.6% use treatment, with 65.4% using antiviral cream, 23.1% oral antivirals, 11.5% indifferent cream, and smaller percentages using patch, toothpaste, laser, or essential oil. 88.9% find treatment effective. Prophylaxis measures: 38.5% take medication, 30.8% sometimes, and 30.8% do not. Gender breakdown: 65% female, 35% male.

Conclusion : Recurrent herpes labialis has effective treatments (topical antiviral creams, oral antivirals) for pain relief and lesion disappearance. Etiologic factors include physiological, emotional stress, and hormonal changes. Recurrence is common (yearly to twice a year). Dental treatments and SARS-CoV-2 virus may trigger symptoms. Family history and age of contamination (12-18 years old, 19-24 years old, 24-30+ years old) are correlated. Women are more prone to recurrent outbreaks than men.

Key words: recurrent herpes labialis ; treatment; evolution; pharmacology; etiology ; epidemiology .

RESUMEN :

Introducción :

El herpes labial recurrente es una enfermedad común transmitida a través de secreciones corporales infectadas durante períodos de eliminación viral asintomática y sintomática. Los síntomas incluyen sensación de ardor, picazón, dolor, prurito y parestesia, con la aparición repentina de lesiones vesiculares en una base inflamatoria.

Objetivo: Investigar la efectividad de los tratamientos para el herpes labial recurrente en estudiantes universitarios, evaluar el uso de tratamientos profilácticos, identificar los desencadenantes y la asociación con procedimientos dentales, COVID-19, edad, antecedentes familiares y diferencias de género.

Metodología: Se realizó un estudio transversal complementado con una revisión bibliográfica entre noviembre de 2022 y abril de 2023 sobre 100 sujetos.

Resultados: El 27% dio positivo para herpes labial, con brotes reportados anualmente (72%), cada 6 meses (24%) o mensualmente (4%). Los desencadenantes incluyen estrés físico/ emocional (85,2%), cambios hormonales (37%), exposición al sol (29,6%), clima frío (18,5%), traumatismo en la boca/labio (14,8%), enfermedades respiratorias (7,4%), Covid-19 (7,4%) e intervenciones dentales (7,4%). Edad de la primera infección: 33% entre 12-18 años, 18,5% entre 19-24 años, 14,8% entre 24-30 años, 14,8% >30 años, 11,1% entre 6-11 años y 7,4% entre 2-6 años. El 59,3% tiene familiares infectados. El 55,6% utiliza tratamiento, con un 65,4% que utiliza crema antiviral tópica, 23,1% antivirales orales, 11,5% crema indiferente, y porcentajes más pequeños que utilizan parches, pasta de dientes, láser o aceite esencial. El 88,9% encuentra efectivo el tratamiento. Medidas de profilaxis: el 38,5% toma medicación, el 30,8% a veces y el 30,8% no lo hace. Distribución por género: 65% mujeres, 35% hombres.

Conclusión : El herpes labial recurrente tiene tratamientos efectivos (cremas antivirales tópicas, antivirales orales) para el alivio del dolor y la desaparición de las lesiones. Los factores etiológicos incluyen cambios fisiológicos, estrés emocional y cambios hormonales. La recurrencia es común (anualmente o dos veces al año). Los tratamientos dentales y el virus del SARS-CoV-2 pueden desencadenar síntomas. Los antecedentes familiares y la edad de contaminación (12-18 años, 19-24 años, 24-30+ años) están correlacionados. Las mujeres son más propensas a tener brotes recurrentes que los hombres.

Palabras clave: herpes labial recurrente; tratamiento; evolución; farmacología; etiología ; epidemiología

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1. INTRODUCTION

1.1. History and definition of recurrent herpes labialis

As a highly prevalent disease, herpes simplex virus-1 (HSV-1) continues to affect millions of people.

Herpes Virus Infections have been widespread among humans as early as ancient Greek times. Father of medicine Hippocrates is one of the first to have described the cutaneous spreading of herpes simplex lesions . In fact the greek word "herpes" means "to creep or crawl" as a referral to the specific communicable and contagious nature of the herpetic skin lesions.(1) However , the human transmission form from one person to another of HSV-1 was only identified in 1893 by Léon Émile Vidal. (1)

Whilst the past century , HSV research flourished . Histopathological studies demarcated the multinucleated giant cells correlated with the herpes virus infection. In 1919, Lowenstein confirmed experimentally the infectious nature of HSV by passing it onto rabbits, and found it to be sensitive to alcohol and higher temperatures . Schneweiss classified viruses in 1962 based on their serological properties, identifying two distinct types that were later found to belong to the Alphaherpesvirinae subfamily along with the varicella-zoster virus. These viruses are characterized by their ability to establish neurotropic latency, often resulting in mucosal or skin lesions following reactivation in sensory nerves. The International Committee on Taxonomy of Viruses has formally designated the two herpes simplex virus strains as Human herpesvirus (HHV) 1 and 2, which fall under the Simplexvirus genus. (2) During the 1920s and 1930s, researchers extensively investigated the natural history of HSV and found that the virus contaminate not just the skin but also the central nervous system. In the 1930s, extensive studies were conducted on host immune responses to HSV, leading to the identification of one of its key features - latency. In recent years, research efforts have focused on antiviral research, identifying differences between HSV strains, and exploring the use of HSV vectors for the development of vaccines. (1)

Recurrent herpes labialis is mainly transmitted through exposure to infected bodily secretions such as saliva. Asymptomatic and symptomatic periods of viral shedding can cause transmission of the disease. An associated gingivostomatitis may also occur with pharyngintis (3). Inoculating the virus results in it entering the trigeminal nerve and remaining chronic and latent in the trigeminal ganglion for the rest of one's life. (4)

Although the virus may remain latent indefinitely, 20% to 40% of those infected by HSV-1 will experience reactivation as recurrent herpes labialis (RHL) when exposed to triggers such as fever, trauma, sunlight, menstruation, or emotional stress.(5) Recurrences can also result from dental extractions(6). In the early stages of mucocutaneous manifestations, HSV-1 replicates in the basal layer of the mucosa.(3) Symptoms such as burning, stinging, itching, pain ,pruritus and paresthesia outbreak within the first to sixth hour after the onset of prodromal symptoms.(7,8)

The appearance of the disease is usually sudden, with specific vesicular lesions superimposed on an inflammatory erythematous base.(7)

After about 24 hours the lesions are demonstrated by particular characteristics such as erythema, papules and blisters.(4,7) The lesions of RHL undergo a process of crusting, regeneration, and re-epithelialization without leaving behind any scars, usually taking 1-2 weeks to complete.(5) The diagnosis of RHL is primarily based on the location, clinical appearance, and patient history of the lesions. (6,9). Recurrences typically befall at the site of primary infection or adjacent areas around the verimillion border of the lip. The frequency and severity of it relies on several factors, such as the immunocompetency and stress of the host.(7) Patients may have a know or unknown specific trigger (6,9). Recurrences vary as once a month or more infrequently as once or twice a year (5,7,10,11). Dehydration that necessitates the use of intravenous fluids is the most prevalent complication, although there is also a possibility of secondary bacterial infection (5).The lesions are painful and often cause torment to the individual (12).

1.2. Epidemiology

Herpes simplex viruses are a prevalent form of human infection that has been studied by testing various populations for the presence of antibodies to measure the frequency of HSV occurrence. Globally, approximately 90% of individuals have either one or both of the herpes simplex viruses. HSV-1 is the more predominant virus, with 65% of people in the United States exhibiting antibodies to HSV-1. In Europe, the epidemiology is comparable, as around 50% of the population have antibodies to HSV-1. Meanwhile, in emerging countries , HSV-1 is nearly ubiquitous and typically contracted during early childhood through intimate contact with family members. Beyond childhood, the prevalence of HSV-1 infection marginally increases with age. HSV-1 infection rates are higher in women than men.(13) In the US, African-Americans and Asians have a higher prevalence of HSV-1 infection compared to Caucasians. Although the majority of HSV-1 infections occur orally and without any noticeable symptoms, studies indicate that in developed countries, the attainment of the virus is typically deferred until adolescence or young adulthood, rather than during early childhood. (5)

HSV can cause both mucocutaneous and systemic diseases. The factors that contribute to the variability in clinical presentation are not well perceived , but the clinical manifestations of HSV infections are believed to be mainly influenced by the host's immune system.(5) Neonates are the most intensely impacted and generally obtain the affliction at the time of birth by contact with infected genital discharge. Severe or fatal HSV infections are rare in adults, but pregnant women are at a higher risk.(5) HSV infections are typically limited to the skin and mucous membranes in the majority of individuals. However, in individuals with weakened immune systems, HSV infections can be more severe, either due to underlying conditions (such as HIV or lupus), immunosuppressive treatments, organ transplantation, or prolonged skin diseases like eczema. Some HSV-related syndromes, such as HSV uveitis, have significant immunopathological constituants and can be treated with immunosuppressive therapy (5)

About 30% of individuals with serologic evidence of HSV-1 have recurrent herpes labialis . Amid those, 40% will have more than one outbreak per year.

Prominent triggers of HSV-1 reactivation include facial injury, operations, pyrexia and exposure to sunlight . HSV labialis lesions were frequently conjoined with pneumococcal pneumonia and thought to be encouraged by the swift upsurged in core temperature. (5)

Table 1: Comparaison of primo-infection with HSV-1 and recurrent herpes labialis according to prevalence , affected age group , gender , risk factors and clinical expressions .

	Prevalence	Affected age group	Gender prevalence	Risk factors	Clinical expression
HSV-1	65% (US)	Childhood-adulthood	Higher in women	Childhood exposure, immune suppression, UV light, stress/illness	Oral infections (mostly asymptomatic), mucocutaneous and systemic disease in immunocompromised individuals
Recurrent herpes labialis	30% of HSV-1 positive individuals	N/A	N/A	Triggers include facial trauma, surgery, fever, and UV light	Mostly confined to skin and mucosa, but can be severe in immunocompromised individuals

1.3. Classification of Herpes Simplex Virus

There are several different ways to classify herpes labialis. Some common classifications include:

Primary vs. recurrent: Primary herpes labialis refers to the first time a person is infected with the virus. Recurrent herpes labialis refers to outbreaks of cold sores that occur after the initial infection.

Type of HSV: Herpes labialis can be induced by either HSV-1 or HSV-2.

Severity: Cold sores can range in severity from mild to severe, depending on the number and size of the blisters and the extent of the inflammation.
Location: Cold sores can occur anywhere on the face, but the typical location for these lesions to appear is in the vicinity of the mouth, specifically on the lips, and on the nose.
Duration: Cold sores can last for several days to a week or more, depending on the individual and the severity of the infection.
It should be emphasize that the specific classification of herpes labialis may vary depending on the individual and the specific characteristics of their infection.

Herpes labialis : HSV-1 is the main cause of herpes, with only a few known cases caused by HSV-2. HSV-1 primo- infections often occur during childhood and may not present symptoms. However, when symptoms do occur, they may manifest as gingivostomatitis, which includes symptoms such as fever, sore throat, bad breath, loss of appetite, swollen lymph nodes, and painful lesions on the buccal mucosa, gums, tongue, and pharynx. Recurrent herpes labialis lesions, also known as "cold sores" or "fever blisters", typically appear on the vermillion border of the lip.(13,14) (as seen in figure 1)

Figure 1 : Ulcers that form after the vesicles break with herpes labialis (A). Recurrent herpes simplex virus type 1 in the crusting stage seen at the vermilion border (B). (15)

Herpetic willow : Marked by the development of painful vesicular lesions in the area surrounding the nails or fingers. (13) (as seen in figure 2)

Figure 2 : Severely painful herpetic whitlow with large vesicles on the thumb. (14)

Infections of the eye : dendritic ulceration can be seen on the conjunctiva and cornea. An HSV infection may also lead to other eye conditions, such as blepharitis/dermatitis, conjunctivitis, dendritic epithelial keratitis, and corneal ulceration (8) (as seen in figure 3)

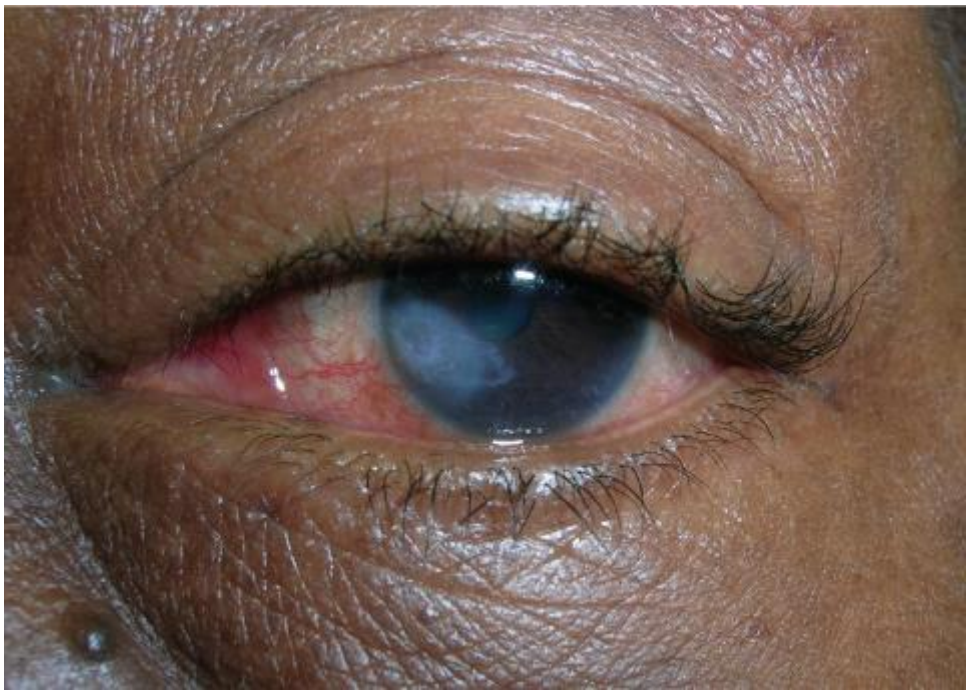

Figure 3 : Herpetic keratitis with corneal clouding in a 56-year-old woman. Copyright © Richard P. Usatine, MD

Encephalitis : Serious infections of the central nervous system can affect children and adolescents and may result from primary or dormant HSV-1 infection. HSV encephalitis typically affects one temporal lobe, causing focal neurological symptoms and swelling. If left untreated, the disease can be fatal, with a mortality rate of 70%. (13)

Genital herpes : It is a sexually transmitted infection caused primarily by HSV-2, although in developed countries, HSV-1 has become equally frequent in primary genital infections. The primary form of genital herpes is delineated by the emergence of several bilateral genital ulcers that are painful and usually resolve within 12 days without scarring. Patients may also experience enlarged sore lymph nodes, fever, malaise, and myalgia. In rare cases, the disease may cause aseptic meningitis with symptoms such as migraines and neck rigidity. Recurrent genital herpes is typically milder, with no systemic symptoms, and lasts for a shorter duration. Prodromal paresthesias in the perineum, genitalia, or buttocks often precede the formation of aggregated lesions on the external genitalia, which heal within 2-5 days without scarring.(13,15)

Neonatal herpes : Neonatal herpes can arise when a newborn is exposed to HSV while being delivered (8). It is a highly serious disease that can result in neurological complications and a significant mortality rate. The clinical presentation of the disease is diverse and can be categorized into three groups: disseminated disease affecting multiple internal organs such as the lungs, liver, adrenal glands, skin, eyes, and brain,central nervous system disease with listlessness and seizures and disease limited to the skin, eyes, and/or mouth (SEM) . (13) Neonatal herpes is rare, occurring in an estimated 10 out of every 100 000 births globally. The risk for neonatal herpes is superlative when the mother acquires HSV for the first time during the third trimester.(7,8)

Herpes gladatorium: Cutaneous HSV-1 infections manifested on the lateral neck, side of the face, and forearms within 4 to 11 days after exposure (as seen in figure 4).This condition is widespreaded among certain athletes, such as wrestlers. To preclude transmission to others, athletes should not participate in contact sports until all herpes lesions have entered the dry crust stage. (3,7,15)

Figure 4 : Herpes gladatorium on arm (17)

1.4. Stages of Herpes Labialis:

Stage 1 : Is called the prodrome phase : formerly , a sensation of prickling, itching, or burning felt beneath the skin around the mouth or at the base of the nose. Further symptoms include : lethargy, fatigue, fever , sore or enlarged lymph nodes.(16)During this stage ,there is no visible vesicle. Population with recurrent herpes labialis may manifest milder symptoms. It is recommended to initiate treatment at the appearance of these signs . Therapy for herpes labialis can entail oral or topical medications. (16)

Stage 2: If no medication was employed , a fluid-filled blister will probably develop around 1 to 2 days after the initial symptoms.(16) (as shown in figure 5)

Stage 3: Is called the ulcer or “weeping stage”. Arise around day 4, involves the blister tearing up and releasing its fluid. The blister’s fluid is highly contagious , and the transmission rate is important. (16)

Stage 4 : From day 5 to 8, the sore will dry out and develop a crust in yellow or brown color. Eventually, the crust will flake off. Extra care measures need to be implemented during this stage , as the the scab can crack or fracture.(16)

Stage 5: The last phase of a cold sore is the period of recovery.. Commonly herpes labialis lesions will not leave a scar.(16)

Figure 5 : The five stages of cold sores (16)

1.5. Histopathology of herpes labialis:

The examination of HSV infection under a microscope shows the degeneration of keratinocytes and the existence of giant cells with multiple nuclei. Cowdry A inclusions, which are pink-stained nuclear inclusions, can also be seen in multinucleated keratinocytes and in other herpesviruses such as varicella-zoster virus and cytomegalovirus. While there is no distinctive histological indication for HSV-1 infection, it is essential to consider the clinical symptoms during histopathological analysis. (3)

1.6. Pathophysiology of recurrent herpes labialis :

HSV infects and multiplies in neurons, additionally in cells found in the skin's demris and epidermis. Upon contact, the virus travels from the skin to the

sensory dorsal root ganglion, where it enters a dormant state. Oral HSV-1 infections can reactivate from the trigeminal sensory ganglia, affecting various mucosal areas including the face, mouth, lips, throat, and eyes.(14)After 2 to 20 days ,primo-infection manifests itself after close or personal involvement with an infected person. The virus is spread effortlessly by for example touching items on which the virus may be present such as bath linens , shaving blades , cutlery, or other goods that are commonly shared.(10)

The transmission typically involves mucous membranes and skin that is either open or has been damaged. Research on herpes labialis has revealed that the virus is shed for an average of 60 hours when detected through polymerase chain reaction (PCR) and 48 hours when detected through culture. (14)

The highest concentration of viral DNA was detected at 48 hours after the onset of symptoms, and no virus was found beyond 96 hours (14) Various triggers, such as stress, fever, exposure to sunlight, extreme temperatures, UV radiation, weakened immune system, or physical injury, can lead to recurrent infections. (10,16) The virus remains inactive for an indeterminate period of time. Recurrent oral HSV-1 infections typically occur between 1 and 6 times a year, with milder and shorter-lasting symptoms compared to the initial herpes labialis episode.(8)

The probability of reactivating an HSV infection varies depending on the type of virus (HSV-1 or HSV-2) and the anatomical location (sacral or trigeminal). According to a study, the average monthly recurrence rates were 0.33 for genital HSV-2 infections, 0.12 for oral HSV-1 infections, 0.020 for genital HSV-1 infections, and 0.001 for oral HSV-2 infections. These findings indicate that the likelihood of recurrences is higher for oral HSV-1 and genital HSV-2 infections. (14)

1.7. Diagnosis of herpes labialis:

The diagnosis of HSV-1 infection is usually empiric , based on clinical signs and on the patient's personal history. Nonetheless, if the lesions do not have a distinct HSV pattern, additional diagnostic methods such as viral culture, PCR, serology, direct fluorescent antibody testing, or Tzanck test can be used to

confirm the diagnosis. (14) If possible, it is recommended to obtain a viral culture from vesicles. This is because the vesicles exhibit the most substantial viral load during the initial 24 to 48 hours after their onset. (89% positive).(14)
PCR is a highly sensitive method for diagnosing HSV infection in the laboratory, and it is particularly useful identifying silent viral shedding. Air-dried specimens can undergo direct fluorescent antibody testing, which can identify 80% of true cases of HSV infection, in contrast to culture findings. After several weeks of infection, type-specific immunoglobulin G antibodies to HSV develop and persist indefinitely. Although the Tzanck test can be performed in an office setting by scraping the floor of a herpetic vesicle, staining the specimen, and searching for multinucleated giant cells, it is difficult to perform accurately without specific mentoring. (14)

1.7.1.Differential diagnosis of herpes labialis:

Aphthous stomatitis, Stevens-Johnson syndrome, erythema multiforme (EM) major, and herpangina are among the conditions that can be considered as differential diagnoses for orolabial HSV-1 infection. These conditions can be differentiated from orolabial herpes based on the patient's medical history and the results of a physical examination. Herpetic whitlow, on the other hand, can be differentiated from blistering dactylitis and acute or chronic paronychia through a similar diagnostic process. (3)

Table 2 : Differential diagnosis of Herpes simplex type 1 infection (14)

Table 1. Differential Diagnosis of Herpes Simplex Virus Type 1 Infection

Condition	*Identifying features*	*Diagnosis*	*Treatment*
Acute paronychia	Localized bacterial abscess in a nail fold; has white pus rather than the clear fluid often seen in herpetic whitlow (Figure 6[8]), although the fluid in herpetic whitlow also can become white (Figure 7)	Clinical appearance; can be confirmed with a Gram stain or bacterial culture	Incision and drainage
Aphthous ulcers	Similar to the ulcers in the mouth that occur in primary herpetic gingivostomatitis; these ulcers are painful, but the patient is afebrile and not otherwise ill The cause remains unknown, but these are not viral	Clinical appearance; herpes simplex virus culture will be negative	Self-limited, usually no treatment necessary; topical steroids, if needed
Behçet syndrome	Produces ulcerative disease around the mouth and genitals	Clinical constellation of recurrent oral and genital aphthous-type ulcers; refer to ophthalmologist to look for characteristic eye findings	Tetracycline and topical steroids; may need prednisone and immunosuppressive agents
Herpangina	Oral infection with small ulcers caused by Coxsackie virus; ulcers characteristically seen on the soft palate Seen in children ages three to 10 years	Clinical presentation	Treat symptoms only
Herpes gestationis (pemphigoid gestationis)	Rare blistering eruption that occurs during the second or third trimester of pregnancy; bullae may be seen around the umbilicus, but can occur anywhere on the body (Figure 9)	Skin biopsy to confirm clinical suspicion	Prednisone
Herpes zoster (shingles)	Painful clusters of blisters on a red base in a dermatomal distribution	Presence of dermatomal distribution and painful prodrome; direct fluorescent antibody testing of skin scraping can be done	If diagnosed early, may treat with oral acyclovir (Zovirax), valacyclovir (Valtrex), or famciclovir (Famvir)
Pemphigus vulgaris	Rare bullous disease that can present with oral ulcers, cutaneous bullae, and erosions	Skin biopsy to confirm clinical suspicion	Oral prednisone and refer to dermatologist immediately
Varicella	Caused by a virus in the herpes family; widespread vesiculopustular lesions more concentrated on the face, scalp, and trunk	Its widespread distribution helps to differentiate it from herpes simplex virus; direct fluorescent antibody testing of skin scraping can be done	If diagnosed early, may treat with oral acyclovir

1.8. Known trigger factors of Recurrent herpes labialis:

Herpes labialis and its recurrency are often triggered by numerous factors. These various stimulis can awake latent HSV-1 . The most common triggers are closely related to stress , menstruation in women, fever, sun exposure , extremes in temperatures , UV radiation , a compromised immune system, injury and trauma (14). Some triggers are less known and are additionally related to the field of dentistry such as post dental extraction or root scaling/ planing treatment (6). Also since 2020 , COVID Sars and its correlation with the reactivation of HSV-1 has been studied.(17–19)

Stress: The herpes virus can become difficult to control for the body as stress can compromise the immune system. When the immune system is weakened,

the virus is more likely to become reactivated, leading to an outbreak of cold sores.

Illness: Illness, especially those that involve a fever or a compromised immune system, can also trigger an outbreak of cold sores. This is because the virus is more likely to become active again when the body is experiencing stress or when the immune system is compromised.

Exposure to sunlight or cold temperatures: Exposure to sunlight or cold temperatures can also trigger an outbreak of cold sores. This is because these environmental factors can irritate and damage the skin, making it more susceptible to infection.

Menstruation in women:

Hormonal fluctuations: During menstruation, a woman's body experiences changes in hormone levels, particularly a drop in estrogen. These hormonal fluctuations may affect the immune system and increase the risk of recurrent herpes outbreaks.

Stress: Menstruation can be a stressful time for many women, and stress is known to be a common trigger for herpes outbreaks.

Iron deficiency: Menstruation can also cause a temporary drop in iron levels, which can lead to anemia. Iron deficiency can weaken the immune system and make it more susceptible to infections, including herpes.

Physical irritation: Using tampons or pads during menstruation can cause irritation of the genital area, which may make it more susceptible to herpes outbreaks.

Trauma : such as a cut or scrape on the skin, can allow the herpes simplex virus (HSV) to enter the body and cause an outbreak of cold sores. When the skin is damaged, it becomes more susceptible to infection. If the HSV virus is present on the skin or in the saliva, it can enter the body through the damaged skin and cause an outbreak.

Dental extraction :
Stress: Dental procedures can be stressful, and stress can weaken the immune system and increase the risk of cold sores.
Trauma: The surgical procedure itself may cause trauma to the skin, increasing the risk of cold sores.
Local anesthesia: Local anesthesia, which is used to numb the area during the procedure, can sometimes cause irritation or inflammation of the skin, increasing the risk of cold sores.

Immunosuppression: Some people may be immunosuppressed due to underlying health conditions or medications, which can increase the risk of cold sores.

It's important to note that not everyone who has a dental extraction will develop cold sores. The risk of developing cold sores after a dental extraction is higher if a person has previously had an HSV infection or if their immune system is compromised. If you have a history of cold sores and are planning to have a dental extraction, it may be a good idea to talk to your dentist or healthcare provider about ways to minimize the risk of an outbreak.

Not all triggers will affect everyone in the same way, and some people may be more susceptible to outbreaks than others. In addition, the specific triggers that activate the herpes virus can vary from person to person, so it's important to pay attention to your own individual triggers and try to avoid them as much as possible.

1.9. Treatments and profilaxis:

A study involving 46 patients with herpes labialis found that prompt treatment with zinc oxide and glycine cream (the cream should be applied every two hours during the day, beginning treatment promptly upon the onset of initial symptoms appear and should be continued until the symptoms disappear completely) shortened the time until recovery (5.0 vs 6.5 days) compared to the individuals who were given indifferent cream. In another study of 79 patients,

after a period of five days, it was discovered that 50% of those who received zinc sulfate (1%) gel and applied it in a similar way were free of symptoms, compared to only 35% in the placebo group who experienced relief. (20,22)

	Time until recovery	Percentage symptom-free after 5 days
Zinc oxide + glycine cream	5.0 days	N/A
Placebo	6.5 days	35%
Zinc sulfate (1%) gel	N/A	50%

Table 3: Comparaison of different zinc topical creams versus placebo for treatment of herpes labialis

Anesthetic cream: In a placebo-controlled crossover study involving seven patients, the application of cream containing lidocaine and prilocaine (25 mg of each per 1 g) resulted in a reduction of the mean duration of substantial symptoms (2.1 vs 5.1 days) additionally, the duration of outbreaks was also reduced (2.6 vs 7.3 days). (20,22)

Table 4 : Comparaison of anesthetic cream (lidocaine and prilocaine) versus placebo for the treatment of herpes labialis

	Mean duration of substancial symptoms	Mean duration of eruptions
Anesthetic cream	2.1 days	2.6 days
Placebo	5.1 days	7.3 days

Antiviral cream : Acyclovir cream (Zovirax, Valeant Pharmaceuticals North America Inc. , 5 times daily for 5 days) (11) were analyzed in 10 studies (number of patients per study varied from 3015 to 67316). Treatment in each study initiated in the first stage (prodromal) . No reduction in the the length or intensity of discomfort were noticed as per the accounts of the patients .Nevertheless , a decrease in recovery time in eight of the studies, varying from 0.5 (4.3 vs 4.816) to 2.5 (5.7 vs 8.315) days was recognised. In two other studies involving 53,425 and 220,926 patients, Denavir cream (Penciclovir cream) (11) showed similar effects. One of these studies also reported a decrease in pain duration (3.5 vs. 4.1 days). However, Penciclovir cream must be applied every 2 hours during the day, which makes it less convenient than Acyclovir cream. (20) Docosanol cream (Abreva, GlaxoSmithKline) is the only FDA-approved non-prescription ointment for RHL. (11)

Medication	Dose	Duration of Treatment	Results
Antiviral cream	Acyclovir cream (5 times daily for 5 days)	5 days	Decrease in recovery time in 8 of 10 studies, ranging from 0.5 to 2.5 days
Antiviral cream	Penciclovir cream (applied every 2 hours during the day)	Until symptoms disappear	Decrease in recovery time in 2 of 2 studies, reduction in duration of pain in 1 study
Antiviral cream	Docosanol cream	Until symptoms disappear	FDA-approved non-prescription ointment for herpes labialis

Table 5: Comparaison of different antiviral creams (acyclovir , penciclovir , docanosol) for the treatment of herpes labialis

Oral antiviral medication: 5 studies have assessed the effectiveness of oral antiviral medications for the treatment of herpes labialis . One study involving 149 patients found that oral acyclovir (200 mg taken 5 times daily for 5 days) had no impact on how long the pain lasts or the process of recovery. However, a separate study involving 174 patients found that a higher dose of acyclovir (400 mg taken 5 times daily for 5 days) led to a decrease in the length of symptoms. (8.1 versus 12.5 days). Two other studies involving 1524 and 1627 patients, respectively, examined the effectiveness of valacyclovir using two different regimens: a one-day regimen (2000 mg taken twice daily) and a two days regimen (2000 mg taken twice on the first day and 1000 mg taken twice on the second day). The results showed that the 1-day regimen was more effective, reducing the duration of symptoms by one day (4 versus 5 days) compared to the two days regimen, which was less effective (4.5 versus 5 days).

Another study was conducted to evaluate the effectiveness of two famciclovir treatment regimens in 701 patients. The patients in the famciclovir groups received either a unique 1500 mg dose or 750 mg taken twice daily for 1 day. The results showed that both famciclovir regimens were more effective than the placebo group, with patients experiencing a reduced duration for the first

lesions to heal, as measured by the median time. (single dose: 4.4 days; 750 mg twice daily: 4.0 days; placebo: 6.2 days).

All of the investigations were conducted when therapy was incorporated during the early prodromal stage.(22) The active compounds in these antiviral medications selectively target and interfere with the synthesis of viral DNA by inhibiting viral DNA polymerase, which is particularly effective against HSV-1 and HSV-2. These oral medications are generally well-tolerated, although they may cause gastrointestinal side effects or headaches. They have a good margin of safety and tolerability because they are selectively converted to active compounds only within infected cells.(7)

Table 6: Comparaison between different oral antiviral medications according to their dosages , duration of treatment and their results .

Medication	Dose	Duration of Treatment	Results
Acyclovir	200 mg taken 5 times daily for 5 days	5 days	No impact on duration of pain or recovery
Acyclovir	400 mg taken 5 times daily for 5 days	5 days	Decrease in duration of symptoms (8.1 vs 12.5 days)
Valacyclovir	2000 mg taken twice daily	1 day	1-day reduction in duration of symptoms (4.0 vs 5.0 days)
Valacyclovir	2000 mg taken twice on first day, 1000 mg taken twice on second day	2 days	Lesser efficacy (4.5 vs 5.0 days)
Famciclovir	Single 1500 mg dose	1 day	Shorter median time until first lesions healed (4.4 days)
Famciclovir	750 mg taken twice daily for 1 day	1 day	Shorter median time until first lesions healed (4.0 days)
Placebo	-	-	6.2 days until first lesions healed

Heat application: A novel device, shaped like a lipstick and named Herpotherm or Hotkiss, is available in the market, which can be used to treat the prodromal symptoms of herpes labialis by applying it to the affected area. Within seconds of application, it heats up to 50°C. It is believed that this elevated temperature can stop the virus from multiplying and the development of blisters. However, there are no published randomized research studies verifying the efficacy of this therapy.(20,22)

There are certain self-care methods that individuals can utilize to alleviate their symptoms, such as: cleaning the blisters with antiseptic soap and water can aid in limiting the virus from spreading to different body parts. The application of ice to the blisters can help alleviate the discomfort. Refraining from consuming hot beverages and spicy or salty foods. Cool water gargling can be done to ease discomfort . Rinsing the mouth with a saltwater solution as a mouthwash. Using analgesic medications like paracetamol or ibuprofen to alleviate pain .(10)

Table 7 : Antiviral agents for herpes labialis : a comparison (21)

TABLE 1

Antiviral agents for herpes labialis: A comparison

	DRUG	REGIMEN (OR PLACEBO)	N	OUTCOME (VS PLACEBO)	
				HEALING TIME	PAIN DURATION
Oral	Valacyclovir*	2 g twice daily for 1 day	603	1.3 days (95% CI, –1.9 to –0.7) (4.8 vs 6.1 days)[1]	
			615	1.3 days (95% CI, –1.8 to –0.7) (5.1 vs 6.4 days)[1]	
	Acyclovir	400 mg 5 times a day for 5 days	174		1.3 days (2.5 vs 3.8 days)[2]
Topical	Penciclovir*1%	Every 2 hours during waking hours for 4 days	3057	31% (HR=1.31; 95% CI, 1.20–1.42)[3]	28% (HR=1.28; 95% CI , 1.17–1.39)[3]
			1573	0.7 days (4.8 vs 5.5)[3]	0.6 days (3.5 vs 4.1)[3]
	Acyclovir 5%	5 times a day for 4 days	689	0.5 days (4.3 vs 4.8) (HR=1.23; 95% CI, 1.06–1.44)[4]	0.3 days (2.9 vs 3.2 days, HR=1.20; 95% CI, 1.03–1.40)[4]
	Docosanol* 10% (available OTC)	5 times daily	737	0.7 days (95% CI, 0.08–0.92 days) (4.1 vs 4.8 days)[5]	0.56 days (95% CI, 0.125–0.69 days) (2.18 vs 2.74 days)[5]

* FDA approved

CI, confidence interval; , decrease; HR, hazard ratio.

For patients presenting recurrent herpes labialis and are aware of their conditions and its triggers ,profilaxis is advised in some cases . In certain patients important sun exposure can induce to HSV-1 reactivation: diverse modus operandi treatments have been assessed to prevent these recurrences, including zinc-based sunscreen products and topical and oral antiviral therapies, although no studies have directly compared any of these strategies. It is advised for patients with HSV-1 triggered by sunlight to use sunscreen. A placebo-controlled crossover trial of 38 patients found that after ultraviolet (UV) light exposure, herpes labialis appeared in 27 patients (71 %) treated with placebo with an average time to HSV recurrence of 2.9 days . Versus, no lesions evolved, although 1 in 35 patients shed virus was observed at the UV light exposure site, when sunscreen was employed before the UV light exposure .The use of prophylactic antiviral therapy for the sole purpose of preventing recurrences due to sunlight is not recommended , since there are conflicting data on the benefit of antiviral therapy in this context. (7)

TABLE 2

Valacyclovir and sunscreen: Helpful in preventing a herpes labialis outbreak

DRUG	REGIMEN	N	OUTCOME (VS PLACEBO)
Valacyclovir (oral)	500 mg daily	98	24% ; attack rate, 38% vs 62%; NNT=4[6]
Sunscreen	Various	19	Attack rate, 0% vs 71%; NNT=1[7]
Sunscreen	Various	19	Attack rate, 5% vs 58%; NNT=2[8]

, decrease; NNT, number needed to treat

Table 8: Comparaison of valacyclovir and sunscreen helpful in preventing a herpes labialis outbreak (21)

Prophylactic treatment: In the setting of surgical procedures HSV reactivation can be observed when trigeminal nerve root decompression, facial dermabrasion, and ablative laser resurfacing are performed . The risk of

recurrent oral herpes has been reported to be as high as 50-70% in some outlines. Given the high risk of HSV reactivation associated with these procedures, we customarily administer antiviral prophylaxis around the time of surgery, even to those without a known history of HSV.(7)

Before dental treatment that include surgery , root scaling or planning ,warm saline mouthwash, analgesics, antibiotics, and lubricating cream for the angle of mouth without antiviral prescription is favored. Preventive mesures 24 hours before the dental treatments are to be taken and continued for two days afterwards.(6) In a study on patients who were given valacyclovir before dental procedures, it was found that 11.3% of the patients in the treatment group developed clinical lesions, compared to 20.6% of those who received a placebo. This indicates a 46% decrease in the incidence of visible lesions. (22)

Oral antiviral therapy has been privileged : studies have demonstrated that oral valacyclovir, prescribed either as 500 mg twice a day for 5 days or 1 g once a day for 5 days, is as effective as acyclovir in decreasing the length of the outbreak, the amount of viral shedding, and the time required for healing. Furthermore, a 3-day regimen of valacyclovir (500 mg twice a day) is equally effective as a 5-day treatment. The effectiveness of famciclovir at different dosages (125 mg, 250 mg, or 500 mg taken twice daily for 5 days) differs, but there is no apparent benefit to taking a higher dosage as no dose-dependent advantages have been observed among the various courses of therapy .The recommended quantity of medication is the lowest, 125 mg twice a day, as it provides a 50% decrease in overall risk in the incidence of recent wounds compared to a placebo. Additionally, the treated group experienced a decrease in duration of at least 12 hours in lesion-related irritation and painful sensations. (22)

Supressive therapy : While the majority of patients with HSV infections don’t necessitate chronic suppressive therpay , patients who have intense pain or deformity, challenges with swallowing, or a prolonged duration of the condition of the disease and those with frequent recurrences are suitable for CST. About 5% to 10% of individuals with labial herpes suffer from recurrent outbreaks of at least six per year. Recurrences of any frequency can have a detrimental impact

on a patient's quality of life. Therefore, for those who are psychologically affected by the illness, CST is a reasonable option. An option to minimize the transmission of potential harm to uninfected partners is the use of long-term prophylactic therapy for genital herpes caused by HSV-2.

The efficacy of acyclovir and valacyclovir as continuous suppressive therapy (CST) for the prevention of recurrent herpes labialis has been established in clinical trials. A study from the 1990s found that oral acyclovir (400 mg taken twice daily) was efficient in reducing the number of patients experiencing recurrent cold sores by 41% and the total number of outbreaks by 53% over a 4-month period compared to placebo. According to another study, taking valacyclovir prophylaxis at a dose of 500 mg once a day produced a score of 60% of the treated group being healthy, versus 38% of the placebo group. The median time to the initial relapse was 13.1 weeks in the treatment group, analogous to to 9.6 weeks in the control group. In a crossover study, valacyclovir given as reactive therapy administered at irregular intervals (2 doses of 2 grams taken 12 hours apart) was compared to CST (1 gram taken once daily) for 6 months. The chronic suppressive therapy was found to substantially lowered the rate of recurrences and the intensity of pain scores. (24)

While there have been no randomized controlled trials conducted to specifically gauge the efficiency of continuous famciclovir usage in preventing recurring cold sores, studies have shown that short-term prophylactic use of famciclovir (250 or 500 mg taken two times daily for 10 days, starting 24 hours prior to the intervention) has reduced the frequency of outbreaks. This suggests that long-term famciclovir treatment could be effective and beneficial in preventing recurring cold sores. (24)

Table 9: Comparaison between different oral antivirals in continuous supressive therapy according to the duration of treatment and their results.

Medication	Dose	Duration of Treatment	Results
Acyclovir	400 mg taken twice daily	4 months	41% reduction in number of patients with recurrent cold sores, 53% decrease in total number of outbreaks
Valacyclovir	500 mg taken once daily	4 months	60% of treatment group remained disease-free, median duration to first recurrence of 13.1 weeks
Valacyclovir	2 doses of 2 grams taken 12 hours apart (intermittent reactive therapy) or 1 gram taken once daily (CST)	6 months	CST significantly reduced frequency of recurrences and pain severity scores
Famciclovir	250 or 500 mg taken twice daily for 10 days starting 1 day before a procedure	10 days	Reduced frequency of outbreaks, suggesting long-term treatment may be effective

1.10.Justification :

Recurrent herpes labialis is a condition that impacts a significant portion of the global population. The present work aim is to do an overview of what is the recurrent herpes labialis in order to gain a better understanding of the disease, on how to treat and prevent it focusing on the minor recurrent herpes labialis which is the most common form and to review the different treatments as well as their efficiency through a cross-sectional study together with the bibliography.

2. OBJECTIVES :

Primary :

To study the most frequently used treatment and their efficacy among the students .

To determine the use and efficacy of prophylactic treatment in cases of recurrent herpes labialis.

Secondary :

To describe most common triggers for herpes labialis amid students of the university.

To determine the possible correlation between dental intervention and recurrent herpes labialis .

To ascertain any correlation between COVID –Sars and recurrent herpes labialis among the students , as stated in recent studies .

To know the frequency of recurrent herpes labialis .

To ascertain whether or not the condition is related to age and if there are any correlations with the entourage such as family members.

To notice if there are any differences by gender among the affected population.

3. MATERIAL AND METHODS :

Design:

A cross sectional study was sonducted over UEM students from 3rd year to 5th year in dentistry degree from November 2022 to April 2023.

An online survey was designed to collect the data using the platform Microsoft forms approved by the UEM ethics committee with the code CIPI/23.174.

- Inclusion criteria:

- Keywords: recurrent herpes labialis, treatment, oral, evolution, pharmacology, etiology, triggers, dental intervention, covid .

- Sources: medline, publine, ncbi, biblioteca CRAI, personal experience.

- By the mean of an online survey, a cross sectional study was conducted on a
- YOUNG POPULATION (UEM dentistry students) ranging from 19 to 30 years old with mixed ethnicity.

- Articles and documents published from 1991 to 2022.

- Minor form of recurrent herpes labialis has been mainly focused on since
- it is the most frequent type.

- Exclusion criteria:

- Articles and documents published before 1991.
- Including “major” form of recurrent herpes labialis in the cross-sectional study. The main focus will be on the “minor” form.

4. RESULTS:

A cross sectional study was performed over a total of 100 subjects , 73 % were healthy and 27% were positive to herpes labialis . They had to answer 10 questions . Here are the results for each questions of the survey .

For the question 1 : « To which gender do you identify yourself ? »

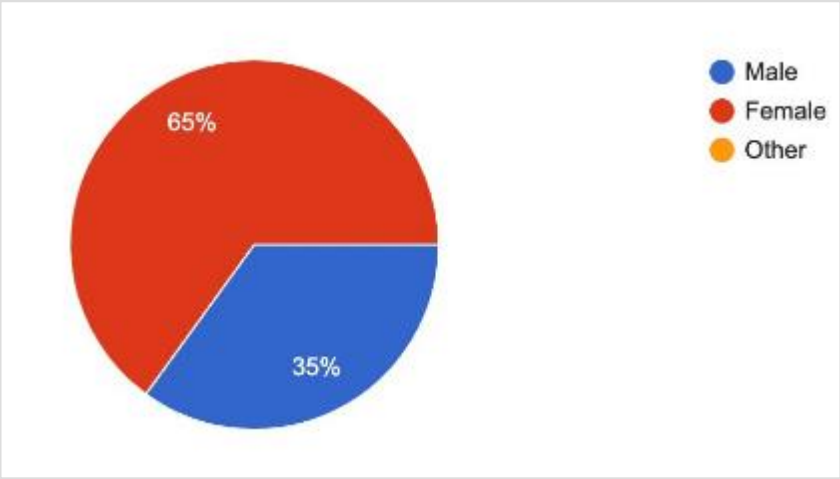

Figure Graphic for question 1 .

65 % have answered identify themselves as female gender and 35% of male gender .

For the question 2 : « Do you sometimes experience herpes labialis ? (aka lip coldsores) »

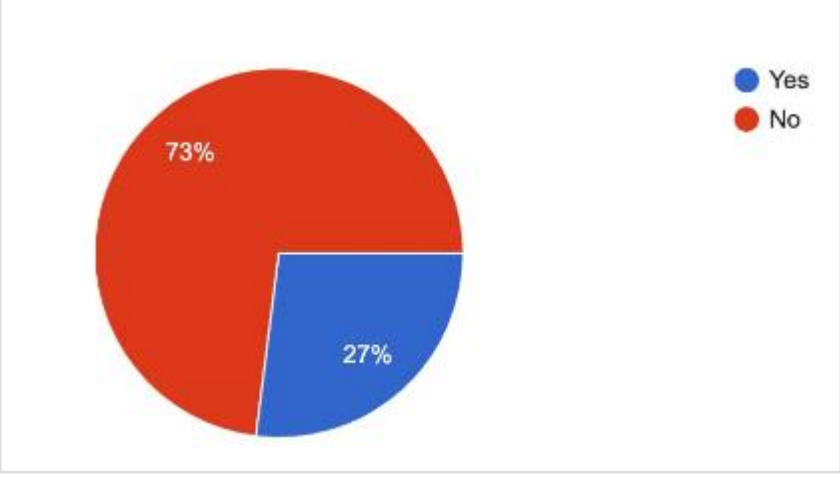

Figure Graphic for question 2 .

73% have answered that they never experienced herpes labialis and 27% have answered positively .

For the question 3 : « If yes , how frequently do you experience herpes labialis ? »

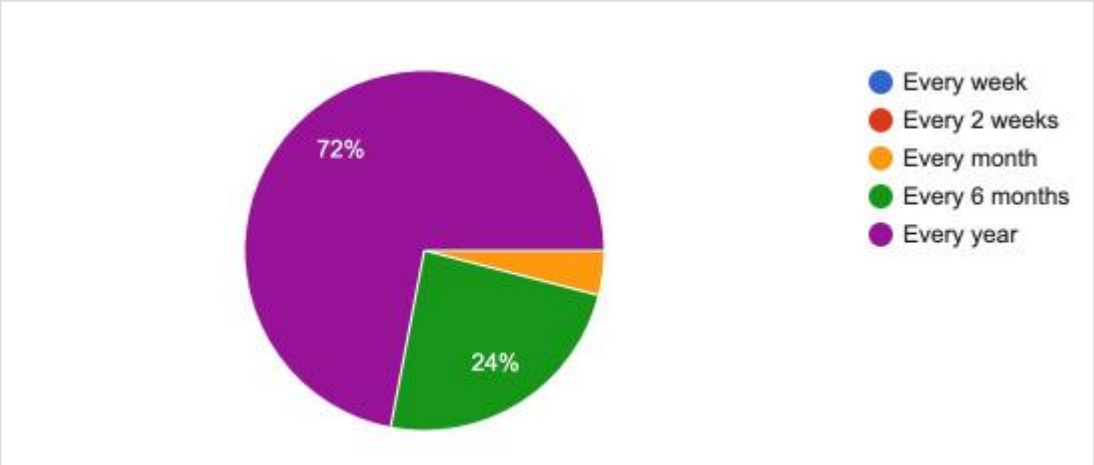

Figure Graphic for question 3.

72 % (18) answered every year , 24% (6) answered every 6 months and 4 % (1) every month .

For the question 4 : « Around what age did your first herpes labialis start happening ? »

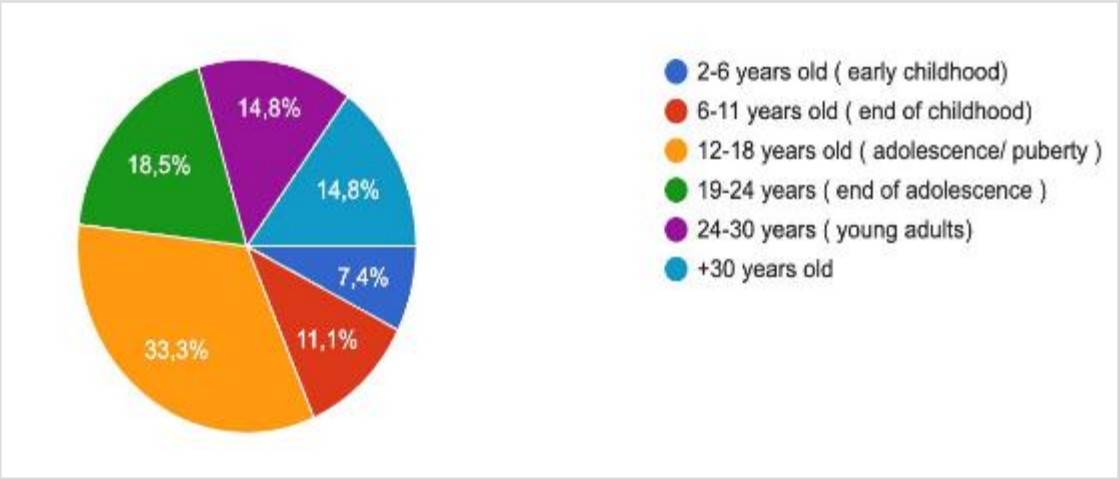

Figure Graphic for question 4 .

33,3 % (9) answered around the age of 12-18 years old (adolescence / puberty), 18,5% (5) answered around the age of 19-24 years old (end of adolescence) , 14,8% (4) answered around the age of 24-30 years old (young adults) , 14,8% (4) answered around the age of +30 years old , 11,1% (3) answered around the age of 6-11 years old (end of childhood) and 7,4% (2) answered around the age of 2-6 years old (early childhood) .

For the question 5 : « Does any close members of your family presents herpes labialis ? »

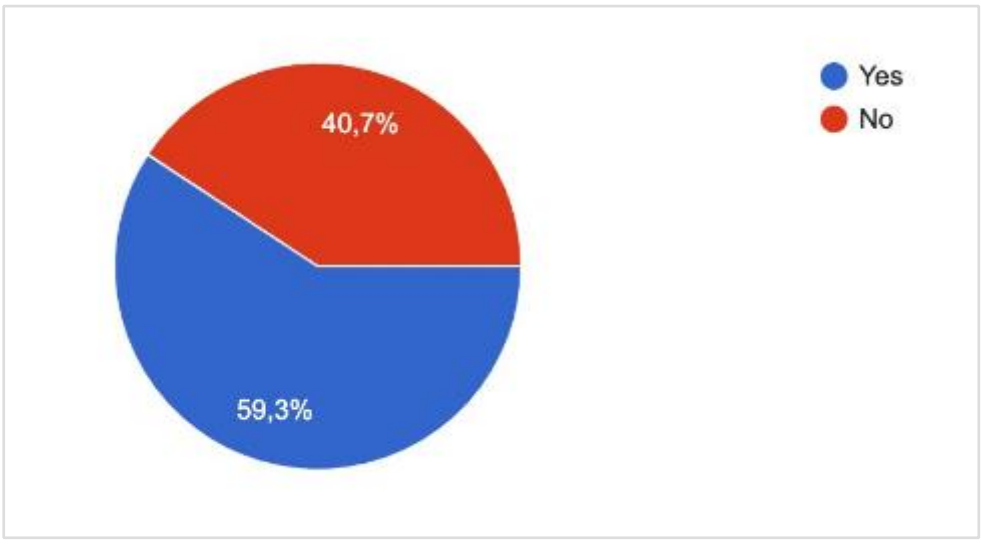

Figure Graphic for question 5 .

59,3% (16) answered yes and 40,7% (11) answered no .

For the question 6 : « In your opinion , what do you think are the main causes of herpes labialis ? (Choose one or more) »

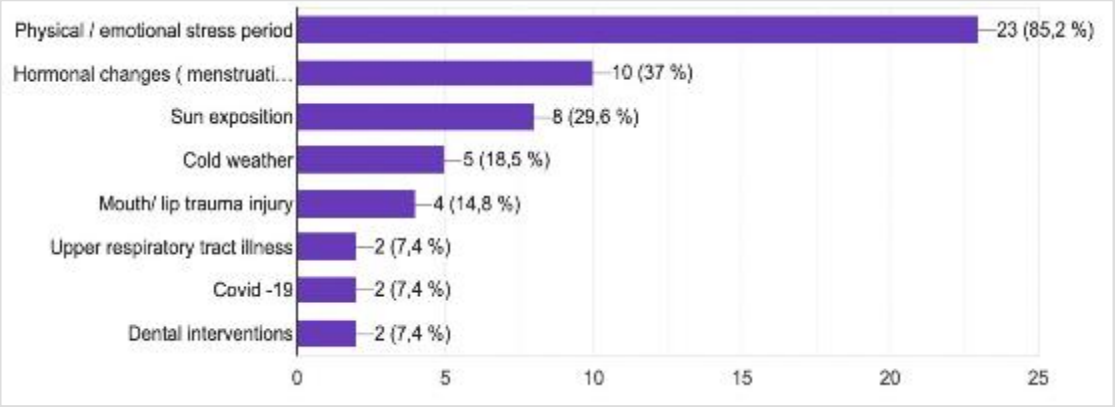

Figure Graphic for question 6 .

23 (85,2%) answered that is was due to a physical/ emotional stress period , 10 (37%) due to hormonal changes (menstruation) , 8 (29,6%) due to sun exposition , 5 (18,5%) due to cold weather , 4 (14,8%) due to mouth/ lip trauma injury , 2 (7,4%) due to upper respiratory tract illness , 2 (7,4%) due to Covid-19 and 2 (7,4%) due to dental interventions .

For the question 7 : « When you experience herpes labialis do you use any treatment(s) ? »

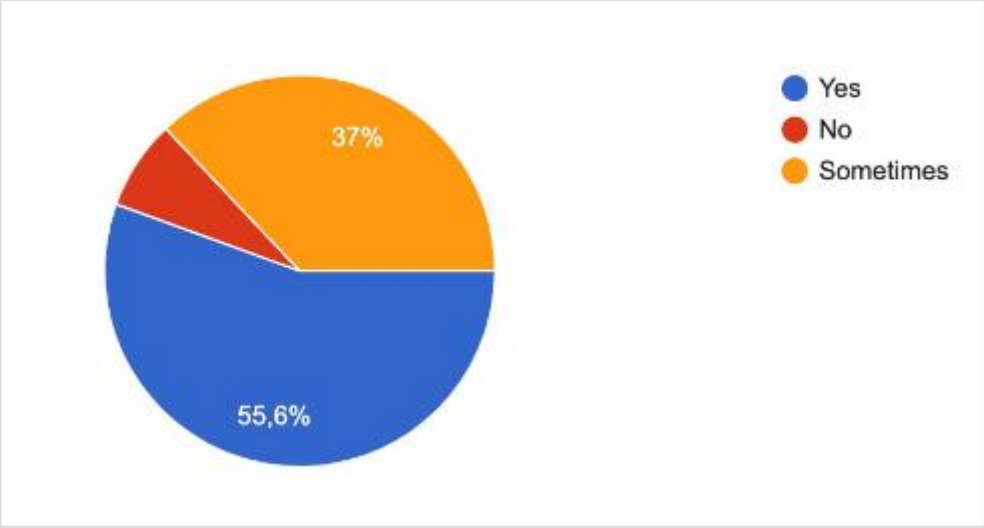

Figure Graphic for question 7 .

55,6% (15) answered yes , 37% (10) answered sometimes and 7,4% (2) answered no .

For the question 8 : « If yes, what treatment do you use ? »

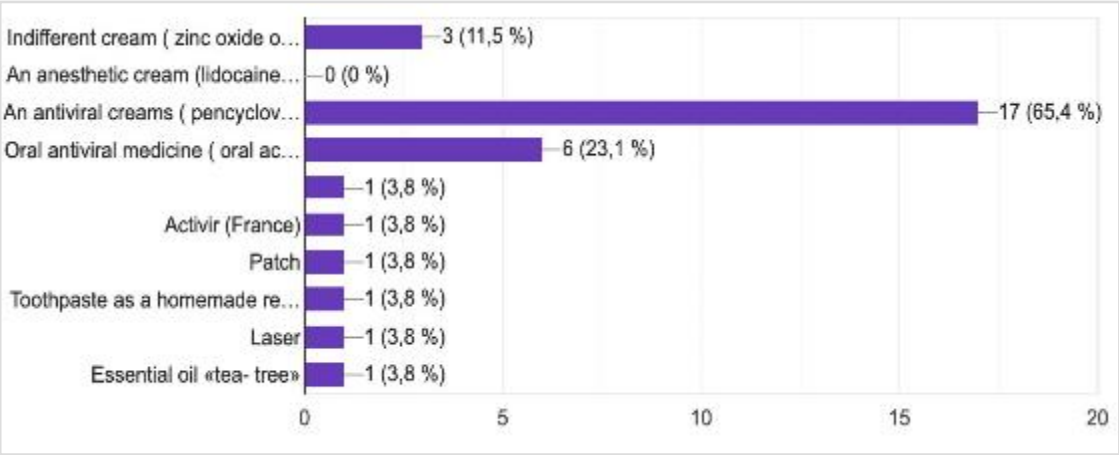

Figure Graphic for question 8 .

17 (65,4%) use antiviral cream (pencyclovir or acyclovir) , 6 (23,1%) use oral antiviral medicine (oral acyclovir or valacyclovir or famicyclovir) , 3 (11,5%) use indifferent cream (zinc oxide or zinc sulfate) , 1 (3,8%) use a patch (hydrocolloid) , 1 (3,8%) use toothpaste « as a homemade remedy » , 1 (3,8%) use laser and 1 (3,8%) use « tea-tree » essential oil .

For the question 9: « Does the herpes labialis disappear faster with treatment ? »

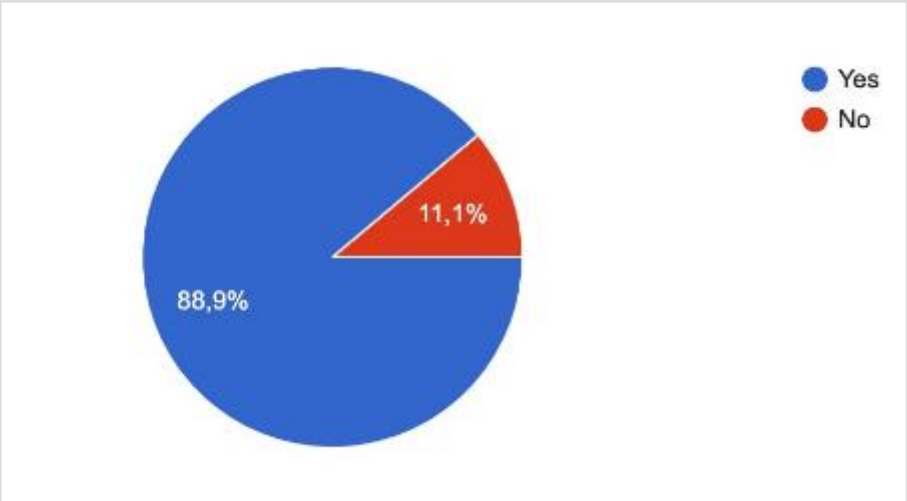

Figure Graphic for question 9.

88,9% (24) answered yes and 11,1% (3) answered no .

For the question 10 : « Does taking the treatment as a profilaxis (before the apparition of symptoms) help ? »

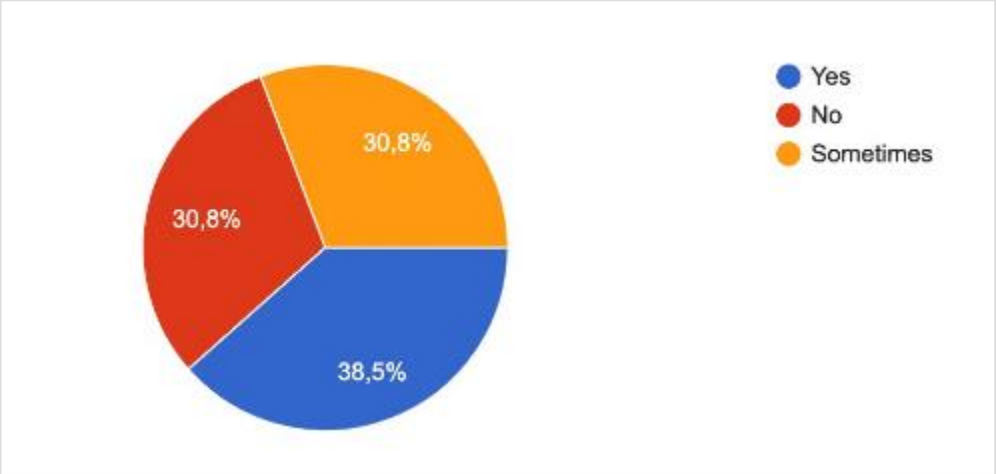

Figure Graphic for question 10 .

38,5% (10) answered yes , 30,8% (8) answered no and 30,8% answered sometimes .

5. DISCUSSION :

A cross sectional study was realized over a total of 100 subjects, where 73 % were healthy and 27% were positive to RHL , by the mean of an online survey. The healthy group was excluded in the results since they were not relevant in the pursue of this study. The RHL subjects had then to answer a total of 8 questions.

There are multiple existing treatments for RHL, the most widely used being pharmacological treatments. The subjects were asked if they were taking any treatments for RHL 55,6% responded positively and 37% responded seeking and using treatments sometimes .

As stated previously, there are several avelable options for RHL therapy. A total of 4 treatments were suggested to the group of subjects that answered positively to question 2 : indifferent cream (zinc oxide or zinc sulfate) , anesthethic creams (lidocaine or prilocaine) , antiviral creams (pencyclovir or acyclovir), oral antiviral medicine (oral acyclovir, valacyclovir,or famicyclovir) .They were instructed to choose from a variety of treatment options to use when experiencing herpes labialis , and could also write down their personal treatment of choice . 65,4% answered using a antiviral cream , 23,1% oral antiviral medicine and 11,5% an indifferent cream such as zinc oxide .

23,1% of the subjects answered using oral antiviral medicine . According to Spruance and al. (2003), the use of high doses of Valaciclovir for a short duration (2 grams orally twice a day for 1 day) has been shown to reduce the time it takes for lesions to heal and alleviate pain or provided relief from discomfort when compared to a placebo, and the episode duration was reduced by around one day (23)

For the 11,5% whom answered usind and indifferent cream such as zinc oxide to treat their herpes labialis , in accordance with “A randomized clinical trial on the treatment of oral herpes with topical zinc oxide/glycine” by H R Godfrey, N J Godfrey ,J C Godfrey , D Riley , it has been shown that the patients who received the treatment with zinc oxide cream recovered faster (in 5.0 days)

compared to those who were given a placebo (took 6.5 days to recover). The cream was given every two hours throughout the daytime hours commencing as soon as the initial symptoms were detected and continuing until resolution of symptoms. In a separate investigation, the effectiveness of applying zinc sulfate (1%) gel in a similar manner was evaluated in 79 patients. Results revealed that after five days, 50% of the patients who underwent treatment were asymptomatic .(24,25)

3,8% of the subjects answered unsing tea-tree oil as a topical treatment for herpes labialis . According to a correspondance in the Journal of Antimicrobial Chemotherpay (2001) , , out of the 19 patients who received tea tree oil treatment in the study , only one patient did not develop clinical RHL . After treatment with tea tree oil, the mean time to re-epithelialization was 9 days, which was faster than the 12.5 days it took for those who received a placebo. Although tea tree oil treatment slightly decreased the median duration of culture positivity compared to the placebo group, the median duration of PCR validation was still 6 days for both groups, and the median time for scabbing was 4 days. The viral tires appeared lower in the tea tree oil group than in the placebo group at days 3 and 4 after onset, but these differences did not reach statistical significance. (26) .

Furthermore the subjects that answered the question if herpes labialis disappeared faster when using a treatment , 88,9% said yes and 11,1% said no.

As mentionned in “Topical and systemic therapies for Oral and Perioral Herpes Simplex Virus Infections” from Eric T. Stoopler and Ramesh Balasubramenlam , the use of topical antiviral medications has been shown to be effective in reducing the time it takes for RHL lesions to heal, particularly when they are applied during the prodromal phase.(27)

However in consonnance with the uptake of oral antiviral, early treatment with Valaciclovir does not seem to increase the chances of aborting a clinical recurrence before the development of cold sore lesions, as found by Chosidow et al. (2003) and Spruance et al. (2003). Meanwhile, Valaciclovir, administered

as a 500 mg dose once daily, has been proven to yield positive outcomes in preventing the recurrence of herpes labialis. During four months of suppressive therapy, almost two-thirds of patients who received treatment remained recurrence-free, in comparison to approximately one-third of those who received a placebo, as indicated by Baker and Eisen (2003) and Baker et al. (2000). (26)

As reported in our survey , 38,5% of the subjects think that taking a prophylaxis treatment help , 30,8% sometimes and 30,8% that it doesn't help. It is recommended to seek treatment at the prodromal stage before the appearance of lesions to limit tissue damage and potential secondary complications. Topical treatments are not proven to be effective for pain relief or faster healing compared to placebo. Most cases of herpes labialis are self-limiting, and antiviral treatment is not recommended for mild to moderate cases unless the patient has a history of invasive treatment that has caused an outbreak. Oral antiviral treatment should only be initiated at the onset of prodromal symptoms and is only necessary for severe or persistent cases in otherwise healthy individuals. (28)

In our survey in the quest to know what are the most common triggers for recurrent herpes labialis , the subjects answered a percentage of 85,2% due to physical/ emotional stress period . There are multiple reports supporting the theory that psychological stress can impact the interactions among physiological systems, and this modulation of the immune system due to stress may lead to consequences for health. Additionally, some studies have found a correlation between the resurgence of dormant HSV infections on the lips or eyes and stress-triggering life circumstances. Among others , according to Shmidt and al . (2003) individuals who frequently experience oral HSV infections tend to have experienced distressing life circumstances, such as the loss of a loved one, challenges in their relationships, or problems related to their occupation . (29)

The second most prevalent trigger in our survey is hormonal changes (menstruation) with 37% of answers . In a study conducted by Usha Balan,

Nitin Gonsalves, Maji Jose, KL Girish in The Journal of Contemporary Dental Practice, a comprehensive medical examination was conducted on 40 female volunteers, which included an oral examination. The results showed that 5% of the participants had a history of recurrent herpes labialis. According to Segal et al, the occurrence of herpes labialis is influenced by the interaction between changes in the menstrual cycle and other factors such as trauma, fever, and sunburn. Complaints, like the occurrence of recurrent herpetic lesions in females during their regular menstrual cycle is believed to be linked to the influence of female sex hormones levels like estrogen and progesterone . (30)

The third most common trigger which was elected by the subjects is sun exposition up to 29,6%. In a research study conducted in Hyogo Prefecture, Japan, the researchers investigated the impact of solar UV radiation (UVR) exposure on the occurrence and recurrence of herpes simplex virus 1 (HSV-1) infections among patients. About 10.4% of the study population reported sun-induced HSV-1 flare-up. However, the percentage increased to 19.7% among patients diagnosed during the prime of summer , to 28% amidst patients under 30 years of age detected during the same period of time , and up to 40% with a recurrent infection. These results indicate that solar UVR may play a significant function in the development of recurrent HSV-1. (31).

Sun exposure has been linked to the reactivation of HSV [herpes simplex virus] according to previous studies . The sudden exposure to sunlight has been identified as a cause for 30% of reactivation cases and axon migration to the skin. (32)

To the question if dental interventions could be a trigger to recurrent herpes labialis , 7,4% of the subjects experienced symptoms post dental interventions. It is still debatable if dental interventions are directly related to herpes labialis or the recurrence of it . However in the article Severe herpes simplex virus type –I infections after dental procedures by Lara El Hayderi, Laurent Raty, Valerie Failla, Marie Caucanas, Dilshad Paurobally, Arjen F. Nikkels (2001) , seven cases of severe herpes simplex virus (HSV) infections that were related to dental extractions. However, the role of dental injury in causing these infections should be interpreted with caution. All of the patients had a prior history of

recurrent herpes labialis (RHL), and none of them had experienced RHL after dental fillings or at the time of extraction. Notably, all of the recurrences began at the same location as the previous episodes. While dental extraction is often blamed as the cause of these infections, HSV may also affect fixed prosthodontic tissue. In one study, it was observed that among 20 patients with a previous history of recurrent herpes labialis (RHL), 4 experienced RHL following dental extraction. In contrast, no cases of recurrence were noted in 19 patients without a history of RHL. However, a larger study involving 3818 extractions did not find any cases of herpes simplex virus (HSV) infection. Another study of 48 patients who underwent third molar extraction revealed a low frequency of HSV-1 positive , which was not noticeably different from a control group who underwent standard procedures. There may be multiple factors that contribute to the activation of the herpes simplex virus (HSV) during dental procedures. Firstly, research has shown that fear and stress related to dental procedures can increase the shedding of HSV without causing any noticeable symptoms. (33)

We wanted to know if there was any parallel between being infected with SARS-CoV-2 and trigger factors for recurrent herpes labialis. In our survey 7,4% answered positively .According to an article in the journal Microorganisms from 2021, the risk associated with super-infection and viral reactivation is limited and recent studies suggest that Herpesviridae reactivations may be more common in COVID-19 patients in ICU wards. There are also case reports of Herpesviridae clinical manifestations in non-ICU COVID-19 patients. In the research it has been found that nearly approximately 33% of patients with severe or critical SARS-CoV-2 pneumonia encountered the reawakening of herpes simplex virus type 1 (HSV-1), with 62% of them showing symptoms. There is limited literature on this topic, but a study by Balc'h et al. showed that almost half of SARS-CoV-2 pneumonia patients on mechanical ventilation for more than a week had at least one viral pulmonary re-activation, with Herpesviridae being the most common. There have also been some small case series reports on herpetic skin lesions, but without an evaluation of plasma PCR. (34) For now it has been shown that patients experiencing severe

COVID with complications and already with a past history of recurrent herpes labialis are more likely to endure a relapse . Since SARS-CoV-2 is considerably new in the medical world, further reasearch must be conducted regarding the correlation between it and recurrent herpes labialis.

We are talking about recurrent herpes labialis, but wanted to see what was considered frequent among our subjects. 72% (18) of our subjects answered experiencing a relapse once a year, 24% (6) every 6 months and 4% (1) every month. According to the prospective study Prevalence of recurrent herpes labialis in Western Maharashtra (2021), around 25% of recurrences may heal before any blister formation occurs. The frequency of relapses decreases beyond the age of 35 years. Most patients in the presented study had two recurrent herpes labialis episodes, while some had just one recurrence in the past year. These findings are consistent with previous studies reporting that over 50% of patients experience at least two recurrences per year. (35)

To know if recurrent herpes labialis had any interelation with having close family members with also a past history of recurrent herpes labialis, we asked our subjects to choose a given age gap where their first herpes labialis occured and if wether they had any close family members with herpes labialis . 59,3% of our subjects answered positively to having a close family members with herpes labialis. As seen in a cross sectional study of recurrent herpes labialis for the American Journal of Epidemiology , the correlation between recurrent herpes labialis and several factors including family history . Age-adjusted odds ratios were used to estimate the risk of recurrent herpes labialis associated with the disease in various first-degree family members, which were as follows: mother 3.30 , father 3.80 , sister(s) 3.93 and brother(s) 6.81. (36) HSV infection can be transmitted to newborns from their mothers during birth if the mother is infected, or through oral contact with caregivers after birth, but this occurrence is uncommon in developped countries, as it corroborate with our survey where only 7,4% answered having been infected with HSV-1 between the age of 2-4 .
In our survey the highest percentage of 33,3% includes the subjects that presented herpes labialis in their adolescence/puberty years (12-18 years old) , it then lessens uproportionally according to the age groups, 18,5% for age

19-24 , 14,8% for the group 24-30 years old , 14,8% for the age group 30+ . According to the research article on Global and Regional Estimates of Prevalent and Incident Herpes Simplex Virus Type 1 Infections, in 2012, the worldwide occurrence of HSV-1 infection among individuals aged 0-49 was estimated to be 67%, with a higher prevalence seen in older age groups. HSV-1 infection appeared to plateau during adolescence in Africa and Southeast Asia, and during early adulthood in the Eastern Mediterranean. However, in America, Europe, and Western Pacific, the prevalence continued to rise throughout adulthood and plateaued much later, if at all.(37)

Lastly we wanted to know if women were more prone to developp recurrent herpes labialis througout their lives. We saw precedently that woman were exposed to hormonal changes at different stages during their lifetimes , puberty , menstruations , menopause , etc... 65% of our survey were women versus 35% of men. The two most answered triggers were physical/emotional stress and menstruation . Physical and emotional stress could also occur more to women due to their monthly period. The findings of a 2021 study shows that RHL was most commonly found in the 30-39 age group and was more prevalent in females than males. These results are consistent with the findings of Mathew et al.'s study, which reported a higher prevalence of recurrent herpes labialis in the 21-40 age group and a higher incidence among females than males (0.9% and 0.4%, respectively).(35)

6. CONCLUSION :

- In the present study the most frequently used treatments are topical antiviral creams followed by oral antivirals , and are effective according to the results .
- Less than half of the questionned people use a treatment as a prophylaxis.
- There are various triggers that have been identified. The most common triggers among the university students in the study appear to be physical or emotional stress , hormonal changes such as menstruation in women and sun exposure.
- There is a correlation between dental treatments and appearances of symptoms , specifically with dental extraction , although the numbers in the study are low and usually appears in patients with past medical history of recurrent herpes labialis .
- In our study less than 10% answered having a outbreak due to Covid.

- The frequency of the disease is purely individual , though more than the majority of the students answered having an outbreak once a year or twice a year .

- There seems to be a correlation between herpes labialis and close family members. The greater part of students answered having a close family member presenting the condition . The pic age of contamination is between 12-18 years old , followed by 19-24 years old and 24-30+ years old . Only a few were contaminated during childhood.
- Women are more likely to experience recurrent outbreaks than men. The exact reason for this difference is unclear, but hormonal changes during the menstrual cycle, pregnancy, and menopause may play a role.

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