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Isotretinoin May Decrease the Risk of Periodontitis and the Risk of CMV-Or of HPV-Infection

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Abstract

Background: Isotretinoin helps to control acne which is partly due to Cutibacterium acnes infection.

Objective: Assess whether Isotretinoin may also help to control other types of infections which may directly or indirectly be associated with biofilms containing Cutibacterium acnes such as periodontitis, herpetic infections or HPV-infections.

Methods: All relevant medical and biological data were collected during routine consultations for Small Intestinal Bowel Overgrowth from 2021 March 1st to 2024 March 1st.

Results: 729 patients older than 34 and younger than 65 years of age were included. 63 patients reported a previous treatment with isotretinoin (Iso) and were compared with the control group (666 patients, C group).

Iso group presented with less periodontitis (15.9 versus 44.3%; p<0.001), less medical history of zona (4.8 versus 8.0%; p<0.001) and less positive serology against cytomegalovirus (27.0 versus 49.7%; p<0.001) than the C group. Previous HPV-infection was investigated in women. Iso is associated with a decreased percentage of periodontitis (21.4 versus 47.5%; p<0.001) and of HPV-infection (2.4 versus 18.1%; p<0.001).

Conclusion: Previous therapy with Iso is associated with a decreased risk of periodontitis, and of CMV or HPV-infection.

Keywords: Isotretinoin; periodontitis; CMV-infection; HPV-infection; herpes virus

List of Abbreviations: AKT: activating receptor tyrosine kinases; BMI: Body Mass Index; CA: Cutibacterium acnes; C group: control group; CMV: cytomegalovirus; EBV: Epstein Barr Virus; HPV: Human Papillomavirus; Iso: isotretinoin, mTOR: mechanistic target of rapamycin; PA: propionic acid; PI3K: phosphoinositide 3-kinase; PO: Periodontitis; Small Chain Fatty Acids: Small Chain Fatty Acids; Small Intestinal Bowel Overgrowth: SIBO

Introduction

Medical attention is currently focussed on periodontitis (PO) which is a frequent disease associated with several severe systemic diseases [1].Anaerobic bacteria such as Porphyromonas gingivalis [2] and herpetic viruses such as herpes simplex 1/2, Epstein Barr Virus (EBV) or cytomegalovirus (CMV) [3] have been involved in the occurrence of PO. Human Papillomavirus (HPV) is also frequently found in the gum of patients with PO [4]. Cutibacterium acnes (CA) is implicated in acne [5] and may integrate invasive biofilms, especially periodontal abscesses [6].

Iso has been used for decades and is still used to control severe acne [7]. However, its mechanisms of action remain unclear. Iso is not known to possess antibiotic or antiviral properties, especially against herpes virus, CA or anaerobic oral bacteria. We investigated whether Iso could have an impact on the occurrence of PO and its possible causes. We particularly focussed on CMV because it can be a key factor of immunity [8]. We also investigated exhaled Small Chain Fatty Acids (SCFA) which are good markers of dysbiosis and inflammation and display bidirectional relationship with the oral microbiome [9].

Material and Methods

This work is a descriptive retrospective epidemiological study. Data were collected during the normal course of routine gastroenterological consultations for Small Intestinal Bowel Overgrowth (SIBO), from 2021 March 1st to 2024 March 1st.There was no hypothesis testing before data collection, no data collection beyond that which is part of routine clinical practice, no scheduled data analysis before data collection. This retrospective analysis of Case Series cannot therefore be qualified as "research" and does not requires approval from ethics boards designed to protect humans involved in clinical research, according to the International Committee of Medical Journal Editors (ICMJE). French legislation does not require the consent of an Institutional Review Board in such epidemiological studies.

Inclusion Criteria: Patients consulting for SIBO and who previously underwent a serology for CMV-infection. Patients were followed at least two years by the same gastroenterologist who provides consistent, though personalized, dietary advice as well as dental and oral health guidance. No tobacco use for at least 10 years or total smoking less than 10 pack-years. Patients are followed by their dentists at least every year and do not present with untreated tooth cavity. For patients belonging to the Iso group, Iso should have been taken for at least 6 months at the usual range (0.5 to 1 mg/kg and per day), at least 10 years before the inclusion. Patients should be older than 34 and younger than 65 years of age. Patients signed a written consent for the possible retrospective use of the collected data.

Exclusion Criteria: Recent tobacco use or total smoking above 10 pack-years. Patients with diabetes (controlled or uncontrolled) were excluded. Patients treated with cyclosporine, phenytoin or calcium inhibitors [10]. Patients with neglected tooth cavities. Lack of signed consent for possible retrospective epidemiological use of data; incomplete information on CMV-serology or Iso use.

Gas Measurement: The patient comes after at least 10 hours of fasting. He /she inhales room air and hold his/her breath for 20 seconds. He/she exhales the air of the lungs in a first neutral plastic bag (1.3 litre) and afterwards he/she exhales at least 100 ml (expected to belong to the expiratory reserve volume) in a small neutral plastic bag (Contralco®; Gignac; France; www.contralco.com).

E-VOCs from the second bag are then immediately measured by the X-pid 9500®, an ambulatory gas chromatograph associated with photoionization detection technology [Dräger; Lubeck; Germany; www.draeger.com › Products › Multi-Gas-Detectors]. X-pid 9500® detects Volatile Organic Compounds (VOCs) concentrations as low as 50 ppb. Acetic acid is detected between 4.4 to 4.7 seconds, propionic acid is detected between 4.7 to 5.0 seconds and butyric acid is detected between 7.8 to 8.1 seconds.

X-pid 9500® does not detect hydrogen and is therefore not suitable for the detection of SIBO related to sugar-malabsorption. X-pid 9500® was used after breath holding and only after fasting, not after sugar intake.

The air of the first bag is analysed by the Dräger X-am® 8000. We routinely use the Dräger X-am® 8000 [Dräger; Lubeck; Germany; www.draeger.com › Products › Multi-Gas-Detectors] to measure hydrogen before and two hours after the intake of lactulose in order to diagnose SIBO related to sugar-malabsorption. Results are published separately. Both devices are easily portable and equipped with powerful pumps. The setup is basic and similar for both devices. It requires only a short neutral tube to connect the bag and the device.

Statistics: Comparisons of percentages or means used two-sample t-tests. Yates correction was used for small samples. Because of the large number of tests necessary for this specific analysis the threshold of statistical significance was set to $p<0.001$. Identified statistical differences only concern few percentages: mainly CMV, zona, HPV, PO. We therefore did not calculate confidence intervals and effect sizes which require means and standard deviations. It is therefore not possible to provide a clear understanding of the magnitude of the observed effects of Iso.

Control Group: All eligible consulting patients were pre-included in the study and no case was discarded except when at least one exclusion criteria was identified. As a consequence no recruitment or selection bias is expected. The control group is equal to the total number of included patients minus the Iso group. Classical demographic data will be compared. The control group appears appropriate.

Results

This descriptive observational epidemiological study includes 729 patients. 63 received Iso (Iso group) for at least 6 months and 666 belong to the control group (C group). 66.7% were female in the Iso group and 73.5% in the control group. All patients were Caucasian. The mean age of patients is 45.6 +/- 8.8 for the Iso group and 49.2 +/- 10.2 in the C group ($p<0.01$). In both groups, the minimal age is 34 and the maximal age is 65 years of age according to inclusion criteria. This population sample appears appropriate for the occurrence of periodontitis. The two groups appear comparable regarding, age, gender, BMI and exhaled-SCFA. See table 1 for details. PO (44.3% versus 15.9%), positive CMV serology (49.7% versus 27.0%) as well as a medical history of zona (8.0% versus 4.8%) were more frequent in the control group.

Table 1: Demographic data and percentages of periodontitis or flares of herpes simplex or zona, or cytomegalovirus infection in isotretinoin or control groups. Results of SCFA detection in exhaled-breath are expressed in percentages. The number of patients is given in parenthesis

	Gender% of female	**Agein years**	**BMI**	**Periodontitis%**	**CMV%**	**HerpesSimplex 1/2%**	**Zona%**	**Exhaled SCFA**		
								Acetic acid %	**Propionic acid %**	Butyric acid %
Iso (63)	**66.6**	**45.6+/-8.8**	**22.0+/-3.4**	**15.9**	**27.0**	**36.5**	**4.8**	**38.1**	**41.3**	42.9
Control (666)	73.5	49.2+/-10.2	22.6+/-4.9	44.3	49.7	37.8	8.0	30.9	30.9	56.3
P values	>0.05	<0.01	>0.05	<0.001	<0.001	>0.05	<0.001	>0.05	<0.05	>0.05
Iso CMV+ (17)	94.1	46.9+/-10.2	22.1+/-3.2	35.3	100%	41.2	11.8	17.6	11.8	47.1
Control CMV+ (331)	78.1	50.3+/-10.6	22.7+/-4.6	57.7	100%	45.5	12.4	32.8	32.8	57.7
P values	>0.05	>0.05	>0.05	>0.05	NA	>0.05	>0.05	>0.05	<0.01	>0.05

Iso CMV- (46)	56.5	45.2+/-8.5	21.9+/-3.98	8.7	0%	34.8	2.2	45.7	52.2	41.3
ControlCMV- (335)	72.0	48.4+/-9.8	22.2+/-3.6	34.8	0%	34.8	8.3	31.8	53.8	46.2
P values	>0.05	>0.05	>0.05	<0.001	NA	>0.05	<0.001	<0.01	>0.05	>0.05
Iso CMV+ (17)	94.1	46.9+/-10.2	22.1+/-3.2	35.3	100%	41.2	12.4	17.6	11.8	47.1
Iso CMV- (46)	56.5	45.2+/-8.5	21.9+/-3.98	8.7	0%	34.8	2.2	45.7	52.2	41.3
P values	<0.05	>0.05	>0.05	<0.001	NA	>0.05	<0.001	<0.05	<0.001	>0.05
Control CMV+ (331)	78.1	50.3+/-10.6	22.7+/-4.6	57.7	100%	45.5	12.4	32.8	32.8	57.7
Control CMV- (335)	72.0	48.4+/-9.8	22.2+/-3.6	34.8	0%	34.8	8.3	31.8	53.8	46.2
P values	>0.05	>0.05	>0.05	<0.001	NA	<0.001	<0.001	>0.05	<0.001	<0.01

Flares of herpes simplex1/2 were similar in Iso group and C. group. Iso is associated with a reduced risk of PO only in CMV-negative patients (8.7% versus 34.8%; p<0.001), whilst previous infection with CMV suppresses the association between Iso and PO (35.3 versus 57.7; p<0.05). CMV infection is associated with an increased risk of PO whether patients receive Iso (35.3 versus 8.7%; p<0.001) or not (57.7% versus 34.8%; p<0.001). The same relationship is observed for zona.

CMV infection is associated with an increased risk of herpes simplex 1/2 in the control group (45.5 versus 34.8%; p<0.001) and with a marked decrease in exhaled-propionic acid (PA) (11.8 versus 52.2% in the Iso group; 32.8 versus 53.8% in the control group).

We focussed on female patients, since the prevalence of HPV infection can be evaluated because of regular HPV-screening. See table 2. A medical history of HPV is less frequently observed in patients who received Iso (2.4% versus 18.1%; p<0.001). In female patients, Iso is associated with a decreased risk of PO (21.4% versus 47.5%; p<0.001). The frequencies of herpes simplex flares, previous CMV-infection or reactivation of varicella/zona are similar between the Iso group and the C group. In female patients HPV-negative, Iso is associated with a decreased risk of PO (36.6 versus 50.3%; p<0.001) or zona (4.9 versus 10.8%; p<0.001).

In female patients treated with Iso, periodontitis (37.5% versus 11.5%; p<0.001) or zona (12.5 versus 3.8%; p<0.001) are more frequent in CMV-positive patients. Exhaled-propionic acid was less frequently detected (12.5 versus 61.5%; p<0.001) in CMV-positive patients.

In the C group, CMV infection was associated with increased rates of periodontitis (55.6 versus 38.5%; p<0.001), zona (13.0 versus 8.3%; p<0.001, herpetic flares (50.0 versus 36.5%; p<0.001), HPV infection (22.2 versus 13.5%; p<0.001). Exhaled-propionic acid was less frequently detected (31.5 versus 49.0%; p<0.001) in CMV-positive patients. No difference has been observed between the patients with or without HPV in the control group. Lack of power precludes any analysis between Iso group HPV+ and Iso group HPV-.

Table 2: Demographic data and percentages of periodontitis or flares of herpes simplex or zona, or cytomegalovirus infection in isotretinoin or control groups in women. Results of SCFA detection in exhaled-breath are expressed in percentages. The number of patients is given in parenthesis.

	Agein years	**BMI**	**Periodonditis%**	**CMV%**	**HerpesSimplex 1/2%**	**Zona%**	**HPV%**	**Exhaled SCFA**		
								Acetic acid %	**Propionic acid %**	Butyric acid %
Iso (42)	46.9+/-9.1	21.3+/-3.3	21.4	38.1	38.1	7.1	2.4	40.5	42.9	42.9
Control (540)	49.8+/-10.1	21.9+/-3.9	47.5	52.9	43.6	10.8	18.1	31.9	31.9	52.9
P values	>0.05	>0.05	<0.001	>0.05	>0.05	>0.05	<0.001	>0.05	<0.05	>0.05
IsoHPV- (41)	46.8+/-9.2	21.1+/-3.1	22.0	36.6	39.0	4.9	0%	41.5	43.5	41.5
Control HPV- (396)	51.3+/-10.1	21.8+/-3.85	47.3	50.3	41.3	10.8	0%	31.7	31.1	53.3
P values	>0.05	>0.05	<0.001	>0.05	>0.05	<0.001	NA	>0.05	>0.05	>0.05
Iso CMV+ (16)	48.8+/-9.9	22.1+/-4.0	37.5	100	43.8	12.5	6.3(1 case)	18.8	12.5	50.0
IsoCMV- (26)	44.2+/-8.3	20.8+/-2.7	11.5	0	34.6	3.8	0%	53.8	61.5	38.5
P values	>0.05	>0.05	<0.001	NA	>0.05	<0.001	NA	<0.01	<0.001	>0.05
Control CMV+ (235)	50.5+/-10.7	22.0+/-4.2	55.6	100	5.0	13.0	22.2	30.6	31.5	56.5
Control CMV- (305)	49.5+/-10.2	21.8+/-3.6	38.5	0	36.5	8.3	13.5	33.3	49.0	51.0
P values	>0.05	>0.05	<0.001	NA	<0.001	<0.001	<0.001	>0.05	<0.001	>0.05
ControlHPV+ (98)	49.8 +/- 10.7	22.4 +/- 4.3	48.6	64.9	54.1	10.8	100	32.4	35.1	51.4
ControlHPV- (396)	51.3+/-10.1	21.8+/-3.85	47.3	50.3	41.3	10.8	0%	31.7	31.1	53.3
P values	>0.05	>0.05	>0.05	<0.05	>0.05	>0.05	NA	>0.05	>0.05	>0.05
IsoHPV+ (1)	52	28.7	0	100	0	100	100	0	0	100
ControlHPV+ (98)	49.8 +/- 10.7	22.4 +/- 4.3	48.6	64.9	54.1	10.8	100	32.4	35.1	51.4
P values	the low number of cases in the Iso HPV+ group precludes any adequate statistical analysis									

We concluded from table 1 firstly that Iso (potential positive effect) and CMV infection (potential negative effect) are two key factors associated with PO and zona. Iso is associated with a lower prevalence of CMV-infection. Secondly that Iso is associated with a decreased rate of PO in CMV-negative patients. However, CMV infection prevents the beneficial preventive effect of Iso – if any – regarding PO or zona. Eventually and incidentally previous infection with CMV may favour the occurrence of herpes simplex recurrence. CMV was associated with a decreased diversity of the gut biota leading to less detection of exhaled-PA.

We concluded from table 2 firstly that Iso is associated with a decreased frequency of HPV-infection.Secondly that Iso is associated with a decreased rate of PO in patients HPV-negative. Incidentally, HPV is probably only a bystander in PO.

Discussion

Risk factors for PO are poor home dental care, old age, smoking, diabetes type 2/metabolic syndrome (frequently associated with gastroesophageal reflux), diet or some medications [10]. The Iso group and the control group were homogenous regarding the main parameters: dental care, smoking, body mass index, diabetes, age, gender, medication or food complements intake.

It is the first time that Iso is associated with a drastic decrease of PO. This observational study does not enable to discuss any possible causal relationship. We will therefore focus only on published knowledge that could link the known properties of Iso to a reduced risk of PO.

Iso's Immunoregulatory and Anti-Inflammatory Properties

Iso possesses anti-inflammatory and immunomodulatory properties by reducing monocyte TLR-2 expression and minimizing the inflammatory cytokine response [11]. Iso significantly decreases TNF, IL-4, IL-17 and IFN-γ levels in patients with acne, although T helper differentiation does not appears to be modified [12]. Iso may also decrease dyslipidemia, a new identified factor of skin inflammation [13].

Iso May Inhibit PI3K-AKT-mTOR Pathway (mTOR)

Acne is associated with occidental diet, high sugar consumption and mTOR activation [14]. Iso efficacy in Hidradenitis suppurativa is attributed to mTOR inhibition [15]. The unifying mechanism of Iso-induced adverse effects is the apoptosis of stems cells which involves neural crest cells (explaining teratogenicity), hippocampal neurones (depression), epidermal keratinocytes and mucosa cells (muco-cutaneous side-effects), hair follicle cells (telegenic effluvium), intestinal epithelial cells (inflammatory bowel disease), skeletal muscle cells (myalgia and release of creatine kinase) or hepatocytes (release of transaminases and very low-density lipoproteins). Apoptosis induced by mTOR inhibition may explain the pharmacological mode of action and the adverse event profile of Iso, including its teratogenicity [16]. Iso is also associated with a decreased rate of colonic polyps [17]. All these unexpected, "adverse" or favourable effects of Iso may be explained by the inhibition of mTOR.

Iso is Probably Not Reducing Propionic Acid Synthesis

PA is a small chain fatty acid produced by many CA species and contributes to their Pathogenicity [18]. One could expect that any skin reduction of PA synthesis by CA may reduce acne. However, PA increases immunity and inhibits the mTOR pathway [19]. Therefore the efficacy or the adverse event profile of Iso does not speak in favour of any action against the production of PA. There is no published data on the effect of Iso on PA synthesis.

Major Role of Previous CMV Infection

Our work confirms that CMV is probably a key factor for the occurrence of PO [3]. It also shows that previous CMV-infection prevents any beneficial effect – if any causal relationship exists - of Iso on PO. This fact has never been published before. CMV is known to favour epigenetic immunologic or global aging [20].

Early-life CMV infection is associated with a decreased beta-diversity of the gut microbiota [21]. Our work confirms that CMV is associated with a decreased production of PA and therefore a decreased diversity. It is however not possible to speculate whether CMV infection is the cause or the consequence of poor microbial diversity. A decreased diversity of the gut microbiota and low immunity may explain the increased rates of HPV, herpetic, flares ou zona. It may also explain more frequent PO.If Iso mainly modulates mTOR pathway whereas CMV mainly influences immunity or biodiversity it is logical to observe that these two factors act independently and therefore that Iso cannot prevent the consequences of CMV infection.

However, CMV alone may explain the occurrence of PO and cannot be prevented by mTOR inhibition. One can also speculate that Iso is not able to fully inhibit mTOR in 100% of cases; especially in CMV-positive patients. CMV activates the mTOR pathway in order to favour its own replication [22]. Failure of mTOR inhibition by Iso in case of CMV infection may explain the occurrence of PO. Conversely, actual inhibition of mTOR by Iso may explain a decrease rate of CMV infection in the Iso group.

HPV Infection: A Probable By-Stander

Gynaecological HPV is probably triggered by local inflammatory anaerobic biofilms [23]. The same is probably true for oral HPV. CMV-induced immunosuppression is not expected to favour gynaecological HPV-infection [24]. In our work, female patients treated with Iso present with a drastic decreased rate of HPV. Those without HPV present with a decreased rate of PO.Those with previous CMV-infection present with a higher risk of PO, HPV, herpetic flares or zona, and a lower level of exhaled PA.

No difference has been observed between the patients with or without HPV in the control group. HPV may only be an opportunistic bystander of CMV-induced immunosuppression or severe inflammation induced by a biofilm containing CA and anaerobic bacteria.

Global Hypothesis

We suggest that PO may mainly rely on two independent mechanisms. Firstly viral infection, especially CMV and secondly an inappropriate diet associated with a metabolic syndrome which is known to trigger the mTOR pathway. Adequate inhibition of mTOR may decrease inflammation and partly control CMV infection. When mTOR is not adequately inhibited by Iso, CMV is able to replicate and PO is not attenuated. It is also possible that CMV infection may hinder the Iso-induced inhibition of mTOR. In patients CMV-, inhibition of mTOR pathway alone could be able to reduce PO. As a consequence, adequate treatment of PO should simultaneously conjugate anti-CMV and anti-mTOR therapy, in addition to good oral health: which means local control of anaerobic bacteria.

Limitations of the Study

The retrospective design of the study precludes any causal relationship conclusion. Populations were not randomized and the two groups may be different, leading to some biases. Inclusion and exclusion criteria took all published causes of periodontitis into consideration. However, unknown biases may still remain and alter our conclusions.Declarative information regarding, herpes simplex flares, gynaecological HPV or zona may be inaccurate. However under-reporting concerns both groups. Additional risk factors could have been forgotten and may be under-reported in the Iso group. However all main risks factors have been taken into account and both group appears similar with regard to the risk of PO.

Oral testing by polymerase chain reaction for HPV or CMV replication or for detection of CA or anaerobic bacteria involved in PO has not been performed. However, this work does not intend to identify the replication of viruses or of bacteria at the time of a routine consultation, however to assess whether Iso taken at least 10 years before may have modified the local or general parameters (ex: inflammation, biofilm, local immunity, viral replication, …) and consequently decrease the occurrence of PO one to three decades after its discontinuation. Replication or not at the time of the consultation does not appear to be a relevant parameter.

The mechanism of action of Iso remains unclear and this retrospective study cannot explain how Iso may reduce the occurrence of PO. Since PO may be the cause of many severe systemic diseases, prospective studies involving Iso or other mTOR inhibitors should include PO in there design, at least as a secondary point in order to answer the issue of a possible causal relationship between Iso treatment and a decreased risk of PO and therefore improve the management of oral diseases.

Application of this New Knowledge for Routine Practice

In practice, the biofilm containing Porphyromonas gingivalis and Fusobacterium nucleatum could be easily identified with a blue lamp during an outpatient consultation [25]. The biofilm containing CA could be easily identified with a Wood lamp [26]. CMV serology is an inexpensive test and HPV detection is currently a well-established routine screening in women.We suggest that at risk patients (oral CA and Porphyromonas/Fusobacterium plus CMV positive serology +/- gynaecological HPV detection) be identified and then treated with innocuous therapy used on a long term basis.

Such innocuous and inexpensive therapies are currently available. For example, hydrogen peroxide may be useful against anaerobic bacteria involved in periodontitis [27]. Coriolus versicolor is currently successfully used against HPV [28]. Coriolus versicolor is also efficacious against CMV in mice [29]. Polyphenols or lectins might be useful to inhibit mTOR [30].

Conclusion

Patients treated with Iso more than 6 months present with less PO or HPV-infection 2 to 5 decades afterwards. We suggest that the blockade of mTOR in stem-cells may partly explain this finding. CMV-infection appears to be an independent factor of PO. HPV-infection is less frequent in female patients who received Iso. It would appear that HPV is only an opportunistic agent in PO.

Studies should be performed to further investigate the association of anaerobic bacterial control, CMV control and m-TOR inhibition against PO which is currently a frequent worldwide disease with recognized severe systemic consequences looking for preventive actions.

References

1. Pai SI, Matheus HR, Guastaldi FPS (2023) Effects of periodontitis on cancer outcomes in the era of immunotherapy. Lancet Healthy Longev, 4: e166-e175.

2. Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent RL Jr (1998) Microbial complexes in subgingival plaque. J Clin Periodontol, 25: 134-44.

3. Picolo M, de Araújo Nobre MA, Salvado F, Barroso H (2023) Association of Herpesvirus and Periodontitis: A Clinical and Laboratorial Case-Control Study. Eur J Dent, 17: 1300-8.

4. Shigeishi H, Sugiyama M, Ohta K (2021) Relationship between the prevalence of oral human papillomavirus DNA and periodontal disease (Review). Biomed Rep, 14: 40.

5. Dessinioti C, Katsambas A (2024) The Microbiome and Acne: Perspectives for Treatment. Dermatol Ther (Heidelb), 14: 31-44.

6. Ergün E, Toraman E, Barış Ö, Budak H, Demir T (2023) Quantitative investigation of the bacterial content of periodontal abscess samples by real-time PCR. J Microbiol Methods, 213: 106826.

7. Eichenfield DZ, Sprague J, Eichenfield LF (2021) Management of Acne Vulgaris: A Review. JAMA, 326: 2055-67.

8. Saint-André V, Charbit B, Biton A, Rouilly V, Possémé C et al. (2024) Smoking changes adaptive immunity with persistent effects. Nature, 626: 827–835.

9. Leonov GE, Varaeva YR, Livantsova EN, Starodubova AV (2023) The Complicated Relationship of Short-Chain Fatty Acids and Oral Microbiome: A Narrative Review. Biomedicines, 11: 2749.

10. Darby I (2022) Risk factors for periodontitis & peri-implantitis. Periodontol 2000, 90: 9-12.

11. Dispenza MC, Wolpert EB, Gilliland KL, Dai JP, Cong Z et al. (2012) Systemic isotretinoin therapy normalizes exaggerated TLR-2-mediated innate immune responses in acne patients. J Invest Dermatol, 132: 2198-205.

12. Karadag AS, Ertugrul DT, Bilgili SG, Takci Z et al. (2012) Immunoregulatory effects of isotretinoin in patients with acne. Br J Dermatol, 167: 433-5.

13. Ali MA, El Taieb MA, Hegazy EM, Ibrahim HM, Mohamed AA et al. (2023) Evaluation of the Effect of Oral Isotretinoin on the Level of Serum YKL40 in Acne Vulgaris Patients: A Cross-Sectional Case-Control. Clin Cosmet Investig Dermatol, 16: 3241-8.

14. Melnik BC, Zouboulis CC (2013) Potential role of FoxO1 and mTORC1 in the pathogenesis of Western diet-induced acne.Exp Dermatol. 22: 311-5.

15. De Vita V, Melnik BC (2017) The Magnitude of mTORC1 Signalling May Predict the Response to Isotretinoin Treatment in Patients with Hidradenitis Suppurativa. Dermatology, 233: 399-400.

16. Melnik BC (2017) Apoptosis May Explain the Pharmacological Mode of Action and Adverse Effects of Isotretinoin, Including Teratogenicity. Acta Derm Venereol, 2: 173-81.

17. Donatini B, Le Blaye I (2022) Exhaled Volatile Organic Compounds in Patients with Colonic Polyps. J Case Rep Stud, 10: 301.

18. Tax G, Urbán E, Palotás Z, Puskás R, Kónya Z et al. (2016) Propionic Acid Produced by Propionibacterium acnes Strains Contributes to Their Pathogenicity. Acta Derm Venereol, 96: 43-9.

19. Chen D, Qiu YB, Gao ZQ, Wu YX, Wan BB et al. (2020) Sodium Propionate Attenuates the Lipopolysaccharide-Induced Epithelial-Mesenchymal Transition via the PI3K/Akt/mTOR Signaling Pathway. J Agric Food Chem, 68: 6554-63.

20. Kananen L, Nevalainen T, Jylhävä J, Marttila S, Hervonen A et al. (2015) Cytomegalovirus infection accelerates epigenetic aging. Exp Gerontol, 72: 227-9.

21. Sbihi H, Simmons KE, Sears MR, Moraes TJ, Becker AB et al. (2022) Early-life cytomegalovirus infection is associated with gut microbiota perturbations and increased risk of atopy. Pediatr Allergy Immunol, 33: e13658.

22. Miller MJ, Akter D, Mahmud J, Chan GC (2024) Human cytomegalovirus modulates mTORC1 to redirect mRNA translation within quiescently infected monocytes. J Virol, 98: e0188823.

23. Loonen AJM, Verhagen F, Luijten-de Vrije I, Lentjes-Beer M, Huijsmans CJ et al. (2024) Vaginal dysbiosis seems associated with hrHPV infection in women attending the Dutch Cervical Cancer Screening Program. Front Cell Infect Microbiol, 14: 1330844.

24. Zhang H, Cai S, Xia Y, Lin Y, Zhou G et al. (2023) Association between human herpesvirus infection and cervical carcinoma: a systematic review and meta-analysis. Virol J, 20: 288.

25. Lee MA, Kang SM, Kim SY, Kim JS, Kim JB et al. (2018) Fluorescence change of Fusobacterium nucleatum due to Porphyromonas gingivalis. J Microbiol, 56: 628-33.

26. Shu M, Kuo S, Wang Y, Jiang Y, Liu YT et al. (2013) Porphyrin metabolisms in human skin commensal Propionibacterium acnes bacteria: potential application to monitor human radiation risk. Curr Med Chem, 20: 562-8.

27. Hossainian N, Slot DE, Afennich F, Van der Weijden GA (2011) The effects of hydrogen peroxide mouthwashes on the prevention of plaque and gingival inflammation: a systematic review. Int J Dent Hyg, 9: 171-81.

28. Rokos T, Pribulova T, Kozubik E, Biringer K, Holubekova V et al. (2023) Exploring the Bioactive Mycocompounds (Fungal Compounds) of Selected Medicinal Mushrooms and Their Potentials against HPV Infection and Associated Cancer in Humans. Life (Basel), 13: 244.

29. Okada M, Minamishima Y (1987) The efficacy of biological response modifiers against murine cytomegalovirus infection in normal and immunodeficient mice. Microbiol Immunol, 31: 45-57.

30. Wang G, Ge L, Liu T, Zheng Z, Chen L (2023) The therapeutic potential of arctigenin against multiple human diseases: A mechanistic review. Phytomedicine, 110: 154647.