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Impact of Cholesterol Disorders and their Pharmacotherapy on Oral Health and Oral Healthcare: A Narrative Review

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Abstract

Hypercholesterolemia (HC) or dyslipidemia is a common metabolic disorder estimated by WHO to affect 39% of the population globally. Some oral diseases or conditions, such as gingivitis or periodontitis, lichen planus, and recurrent aphthous ulceration, are believed to be more common among hypercholesteremic patients. HC may adversely affect the prognosis of dental implants, promote periapical periodontitis, and increase pulp chamber calcification, while hypocholesterolemia may be linked to oral cancer or potentially malignant disorders. Statins, mainly atorvastatin, prescribed for managing HC have antimicrobial effects and have been suggested as a promising pulp capping agent in vital pulp therapy. It also promotes periodontal regeneration, wound healing, improves oral cancer prognosis, and increases dental implant success rate. It may aid in managing minor recurrent aphthous ulcers and arthritis in TMJs. Adverse oral effects of statin therapy include increasing pulp calcification, lichenoid eruption, and xerostomia. The ability of simvastatin to reduce the osteoclastic, and increase osteoblastic activity of bone is rendering the patients susceptible to medication-related osteonecrosis of jaws. General dental practitioners and oral health workers should be aware of the oral manifestations of HC and statin therapy for better and safer management of their dental patients.

Keywords: dyslipidemia, hypercholesterolemia, oral features, statin.

INTRODUCTION

Despite the absence of a clear universally accepted definition for hypercholesterolemia (HC), it is widely defined as an elevation of total cholesterol and/or low-density lipoprotein cholesterol in the blood. The US National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) defined HC as total cholesterol >200mg/dL (>5.2mmol/L) [1]. Dyslipidemia is characterized by plasma hypertriglyceridemia, increased triglyceride-rich lipoproteins including very low-density lipoproteins, and intermediate-density lipoproteins, with low high-density lipoprotein cholesterol levels [2]. Therefore, the terms HC and dyslipidemia are commonly used interchangeably [2]. The

epidemiologic studies showed prominent ethnic and geographic variations in the prevalence of HC ranging from 16% in Ethiopia to 96% in Pakistan [3]. The World Health Organization in 2008 estimated the overall global prevalence of HC as 39%[4], while in the USA approximately 47% of the population has HC [5] which also affects 44.3% of Jordanian populations aged between 18-90 years [6]. HC is a significant health concern since it is considered a major risk factor for stroke and atherosclerotic cardiovascular diseases such as hypertension and myocardial infarction [7].

Statins are considered the cornerstone in the medicinal management of HC due to their ability to reduce cholesterol biosynthesis in the liver and intestine, in addition to their ability to modulate lipid metabolism derived from their inhibitory effect upon 3-hydroxy-3-methylglutaryl coenzyme A (AHMG-CoA) reductase. Independent of their hypolipidemic properties, statins are known for having several pleiotropic effects including antioxidative, antiinflammatory, immunomodulatory, and antimicrobial properties [8].

Due to the high prevalence of HC and subsequent statin use, it is likely for the general dental practitioner to deal daily with hypercholesteremic patients who are on statin therapy. Reviewing the literature reveals that the information on oral manifestations associated with HC / dyslipidemia and statins, and their effect on oral health and dental treatment is scarce. This research aims to give an overview of the oral manifestations associated with cholesterol disorders and the effect of statin therapy on oral tissues and various dental treatments to increase the awareness of dental practitioners and oral health care workers of this issue for better and safer management of patients.

To prepare this review, a systematic electronic search of the Medline, SCOPUS, Web of Science, and Google Scholar databases using a combination of the following search terms, in titles and abstracts, was conducted: hypercholesterolemia, dyslipidemia, statin, oral manifestations, periodontitis, gingivitis, dental implant, antimicrobial or adverse effects. The literature was searched from January to March 2023. Search was conducted for English literature published between 1/1/1985-1/6/2023

Adverse effects of HC to oral health

Gingivitis and periodontitis

Broadly, periodontitis is a multifactorial inflammatory noncommunicable microbial disease causing the destruction of connective tissue and bone supporting the tooth structure. It is estimated to rank sixth among the most common human disease, and in its severe form affects 10% to 44.7% of the adult population worldwide [9].

There is mounting information on the relationship between HC, statin therapy, and periodontal health, but most of this information was derived from observational studies. Health surveys described a positive correlation between HC / dyslipidemia and gingivitis or periodontitis [10, 11] and teeth loss [12], also noticed that the severity of periodontitis correlates positively with the severity of dyslipidemia [13]. The finding that treatment of periodontitis can reduce the patient's plasma cholesterol level lends support to the theory that lipid metabolism may be altered by the periodontal disease [14].

The correlation between HC and periodontitis may be explained by the systemic inflammatory alteration induced by HC, resulting in high levels of

proinflammatory cytokines which alters the host immune response [11]. In addition, HC may cause adverse morphological and functional alterations in the gingival arterial wall which could facilitate periodontitis [15]. Taking into consideration that dyslipidemia may be evident in up to 95% of type 2 diabetic patients [16], oral health workers should pay attention to the interplay between dyslipidemia, hyperglycemia, and periodontal disease[11].

The mainstay of clinical treatment for periodontitis is root debridement for plaque (biofilm) removal, in addition to local or systemic application of antibiotics to reduce bacterial load at deep periodontal pockets and root furcation areas. Statin has recently evolved as a promising agent in periodontal regeneration and therapy. Local delivery of atorvastatin or simvastatin, in addition to scaling and root planning, resulted in a significant reduction in probing depth and relative periodontal attachment level in patients with chronic periodontitis and infra bony defects, with a superior effect for atorvastatin [17]. More clinical research is needed in this area to establish the role of statins in periodontal therapy.

Oral cancer and potentially malignant disorders

Although this review is concerned mainly with the HC, hypocholesterolemia has been repeatedly accused of playing a role in the progression of several body cancers [18]. In recent years, low levels of serum cholesterol have been observed in association with oral cancer and potentially malignant disorders compared to otherwise healthy subjects [19-22], also a significant decrease in serum cholesterol in diagnosed oral cancer patients when compared to patients with potentially malignant disorders [21, 22]. The reduction in serum cholesterol values may be even evident before the clinical detection of oral cancer, which may point to a possible relation to the carcinogenesis process [21]. These findings lead to the hypothesis that a reduction in serum cholesterol levels below normal may constitute an early predictor or prognostic factor in oral potentially malignant disorders and malignant lesions [21]. Accordingly, dental patients with below normal serum cholesterol levels should be examined thoroughly for the possibility of oral potentially malignant disorders or even malignancy. Moreover, patients with oral potentially malignant disorders or malignancies should have their serum cholesterol level assessed, in addition to the other investigations. However, whether hypocholesterolemia should be counted as a potentially malignant disorder is not determined yet. Detailed studies are needed to explore the relationship of serum cholesterol to various potentially malignant lesions, any correlation with the severity of epithelial dysplasia in these lesions in addition to any intercorrelation with the etiologic factors of oral cancer. For instance, chronic alcohol consumption can impair cholesterol synthesis, which is known also to promote cancer progression [23].

Few theories were postulated to explain the reduction in serum cholesterol levels in cancer patients [23]. The widely accepted theory suggests that the rapid proliferation of malignant cells requires a high amount of cholesterol for cell membrane biogenesis and other cellular functions, which drains serum cholesterol. Another theory assumes that certain malignant cell types have an elevated low-density lipoprotein receptor activity, which theoretically can lead to hypocholesterolemia [24].

The relationship of statin to oral cancer was explored by the experimental study of

Mehibel et al. [25] where a group of mice were given daily oral doses of simvastatin two weeks before laboratory induction of oropharyngeal cancer. These mice showed a significant reduction in tumor growth compared to untreated mice, which suggests that simvastatin antagonized tumor metabolic reprogramming. Tissue culture studies showed that atorvastatin can increase cell migration, oxidative stress, and angiogenesis in oral squamous cell carcinomas and can inhibit metastasis [26] and tumor cell proliferation [27]. Clinically, some observational studies described an inverse relationship between statin therapy and the incidence of oral cancer [28] or the survival rate of cancer patients [29].

Mucositis is an early complication and a significant morbidity of cancer chemotherapy. An animal study pointed to the ability of atorvastatin to reduce oral mucositis following chemotherapy for oral cancer. Histopathological and immunohistochemistry tests of the cheek pouch mucosa showed that intraperitoneal injection of atorvastatin (10mg/kg) prevented mucosal damage and inflammation associated with 5 fluorouracil-induced oral mucositis [30]. On the contrary, a recent clinical trial did not find a benefit from a 10mg atorvastatin daily tablet, taken during chemotherapy sessions, in reducing fluorouracil-induced mucositis [31]. Whether higher doses of atorvastatin will induce any protective effect is worth investigating.

Oral lichen planus (OLP) and lichenoid drug eruption

Lichen planus (LP) is a chronic immunologically-mediated disease with debatable etiology, but cell-mediated immunity is considered a major aspect of its pathogenesis. The full spectrum of LP affects the skin, mucosae, nails, and scalp, but OLP is more persistent and protracted when compared to the skin counterpart, and is claimed to have a relatively low malignant transformation rate if any at all [32].

The association of dyslipidemia and cutaneous LP has been long recognized, but the relationship to OLP was noticed only a few decades ago [33]. Later, several cross-sectional clinical studies reported evidence of a higher prevalence of dyslipidemia among OLP patients [34-36]. Aniyan et al. [35] assumed that the chronic inflammation induced in OLP may cause discrepancies in lipid and carbohydrate metabolisms leading to HC.

OLP induces more impairment in lipid metabolism and consequently higher atherogenic indexes compared to cutaneous LP patients [34, 36], which should urge patients and physicians to apply early protective measures against the development of cardiovascular disease in OLP patients.

Oral lichenoid drug eruption and idiopathic OLP share similar clinical and histopathologic features but the former has an underlying causative agent (e.g. adverse effect of medications). Similar to OLP, higher levels of plasma cholesterol and other constituents of the blood lipid profile were reported in patients with oral lichenoid eruption [37].

Interestingly, cutaneous lichenoid eruptions were reported in an elderly patient secondary to atorvastatin [38] and pravastatin therapy [39]. The recurrence of the lichenoid eruptions following rechallenging with statin therapy gives support to the theory that the lichenoid eruption was due to therapy rather than being induced by the HC state. However, up to the author's knowledge, stain-induced oral lichenoid eruption may not have been reported yet.

Oral ulcerations

Recurrent aphthous ulcer (RAU) is an ubiquitous immunologically-mediated mucosal disorder characterized by recurrent painful episodes of oral ulcerations affecting up to 25% of the population [40]. The immune regulatory characteristic of cholesterol stimulated the investigators to explore a possible relationship between HC and RAU. Few clinical studies concluded that a higher level of cholesterol was associated with RAU [41, 42], but evidence for a cause-effect relationship is still lacking.

In a randomized clinical trial, topical atorvastatin has effectively reduced the pain, size, and healing time of minor RAU, presumably due to the known oxidative stress reduction, anti-inflammatory, immune modulation, and analgesic effects of statin [43]. Should these results be confirmed this may open the door for the emergence of a new potential agent for the management of RAU.

On the contrary, some case reports described patients with painful non-specific recurrent oral ulcerations emerging in patients on atorvastatin [44] and rosuvastatin therapy [45], which disappeared after the cessation of statins.

Xerostomia

Historically, Cheraskin and Ringsdorf [46] surveyed oral symptoms in a group of elderly patients and noticed that the concentration of serum cholesterol was significantly higher in the patients with xerostomia. At that time, no explanation was given for this presumed association, and it was not clear whether the xerostomic patients were on statin therapy for their high cholesterol or on other xerogenic drugs.

A comparative morphometrical study of minor salivary glands in xerostomic patients with dyslipidemia and control subjects with normal lipid levels reported morphological changes in minor salivary glands of dyslipidemia patients [47]. Again it was not clear whether the patients were on lipid-lowering therapy and whether the changes were due to the dyslipidemia state or its therapy. However, the reported remarkable improvement in xerostomia after cessation of the statin suggests that it could have been a side effect of the statin therapy [48].

The available information on the relationship between statin therapy or HC and xerostomia is inconclusive and elusive. More clinical research is needed to precisely clarify if the reported xerostomia was a consequence of HC or due to statin therapy.

Dental implant

Several laboratory and clinical studies demonstrated a negative impact of HC and dyslipidemia on the prognosis of dental implants [49-51] through several adverse effects [52]. HC and dyslipidemia can increase implant marginal bone loss and peri-implantitis [50, 51], decrease the bone formation and strength around the fixture [53], and increase the peri-implant bone graft failure rate [49] leading to implant loss.

The mechanisms by which HC adversely affects the prognosis of dental implants seem to be multifactorial. Some epidemiologic studies have demonstrated a strong association between HC and osteoporosis [54], which has been counted as a risk factor in dental implantology [55]. High cholesterol levels and other lipids can affect the differentiation and activation of osteoclasts and osteoblasts in a way not in favor of osseointegration, where the differentiation of osteoblasts is inhibited [56] and osteoclast is promoted [57].

Whether controlling HC by statin therapy would improve the success rate of dental implants was the field of several animal

studies. Atorvastatin injected intra-peritoneally in an animal model of dyslipidemia increased both the quality and quantity of peri-implant bone formation and boosted implant osseointegration [58], and the same effects were observed with topical application of fluvastatin [59].

It is believed that the titanium oxide layer on the dental implant surface enhances osseointegration around the dental implant [60]. Sun et al. [52] explained how oxidized lipids around the titanium implant retards osseointegration in a hyperlipidemia environment. When a titanium implant is fixed in a hyperlipidemic patient, titanium oxidizes low-density lipoproteins in the blood to a certain extent to form oxidized low-density lipoprotein. The latter enhances the activity of osteoclasts and promotes bone resorption. In addition, it induces local inflammation as well as oxidative stress around the fixture, which retards osseointegration.

Standardized studies are needed to clarify the role of statins on osseointegration taking into consideration the systemic health of the implant patients and other confounders that may affect the prognosis of the dental implant.

Restorative and endodontic treatment

Animal studies have shown that HC can promote apical periodontitis and peri-apical bone resorption in peri-apically-infected teeth, which may jeopardize the prognosis of endodontic treatment [61].

Prolonged statin therapy has contradicting effects on endodontic treatment. In one hand, it can enhance periapical healing in cases of peri-apical periodontitis following endodontic treatment [62], while on the other hand, statin therapy may be a hurdle in the way of successful endodontic treatment by increasing the possibility of pulp chamber calcification [63].

In vital pulp therapy, a laboratory study suggested simvastatin as a promising pulp capping agent due to its suppressing effect on lipopolysaccharide-induced inflammatory cytokine, cell adhesion molecules, and NF-κB transcription factors in human dental pulp cells [64]. However, more clinical data are needed to support this finding.

Fordyce's granules (FG)

FG are ectopic sebaceous glands clinically detected as yellowish to whitish spots and most commonly observed on buccal mucosa and vermilion border in up to 50% of normal people, with variable geographic prevalence, therefore, they are widely considered as a normal variation of the oral mucosa [65]. In one cross-sectional study, individuals with elevated lipid profiles tended to have a higher number of FG [66], whereas another study could not find a relationship between FG and HC or hypertriglyceridemia [67]. In a more recent study, subjects of blood group AB+ showed the highest mean of both FG number and serum cholesterol level [68]. Although it is known that subjects with high levels of dyslipidemia may exhibit extra vascular lipid deposits (e.g., Xanthoma), FG are sebaceous glands and distinct from lipid deposition. Given the scarcity of information, the relationship of FG to HC is considered equivocal and may be coincidental. Nevertheless, the lack of clinical significance of FG explains the rarity of studies in this field.

Antimicrobial effect of statins

Many clinical surveys and epidemiological studies described a strong inverse relationship between total serum cholesterol and several systemic infections such as hepatitis B, respiratory, gastrointestinal, and urinary tract infections [69]. Apart from gingivitis and periodontitis,

information regarding oral infections is rare.

In vitro studies have provided evidence for the antimicrobial activity of statins against most dental plaque bacteria, including *Streptococcus mutans*, and the periodontal pathogens *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*. Statins also demonstrate antiviral properties against hepatitis B virus, hepatitis C virus, human cytomegalovirus, and have antifungal properties against *Candida* species, *Aspergillus fumigatus*, and *Zygomycetes* species [70].

Candida species are widely spreading opportunistic fungi that constitute part of the oral microflora in many normal individuals. Statin therapy seemed to give some protection against oral *Candida* colonization, where oral *Candida* prevalence and colony count were significantly lower in the HC patients treated with statin compared to HC patients who were not on statin therapy [71]. When statins were combined with several clinically used antifungal agents in the treatment of invasive candidiasis, they acted synergistically and resulted in substantial decreases in the therapeutic doses of antifungal agents [72]. Whether statin combined with antifungal agents can aid in controlling recalcitrant oral candidiasis warrants investigations.

Statins and tissue healing and repair

Stains have been proven clinically to accelerate soft tissue wounds and bone healing and repair following surgery. Chauhan et al. [73] implanted 10mg simvastatin, with foam gel as a carrier, in the socket of a surgically extracted mandibular third molar of 30 patients, but only foam gel in the extraction socket of control subjects. The two groups were reviewed for 3 months and reported a significantly faster regeneration of socket bone of the simvastatin group compared to the control group. Later, Deepanjali et al. [74] repeated the same experiment but on 15 patients with bilateral surgical extraction of mandibular third molars, where one side served as the study side while the other was a control, and concluded the same result.

In soft tissue surgery, the application of a mixture of 10mg simvastatin and chitosan gel (a hemostatic and antibacterial agent) three times daily for 2 weeks on free gingival grafts resulted in a significant acceleration of wound healing and reduction of postoperative pain [75].

Statins and temporomandibular joint (TMJ) disease

Animal studies have shown that intra-articular simvastatin injections had a role in the treatment of experimentally induced arthritis in TMJs by reducing inflammation [76] and preserving normal condylar bone growth [77]. However, clinical human studies are still awaited.

Statins and orthodontic treatment

Mandibular advancement devices are appliances used to force the propulsory and elevatory muscles of the mandible to exercise by making the jaw move forward. Since myalgia, the side effect of statin appears more often during exercise, statin users may experience more muscular pain or tenderness while using these devices [78].

Adverse effects of statins

Despite statins being well tolerated by the majority of patients, liver and muscle toxicity are their major adverse effects, especially if administered in conjunction with other inhibitors of cytochrome P450 or other inhibitors of statins metabolism such as azole antifungals which are common medication prescribed for oral candidiasis [79]. In the United States, approximately 48.6% of the population over the age of 40 are on statin

therapy [80]. Despite the wide use of statins, the reported adverse oral effects of statins are generally rare and described mainly in sporadic case reports. Cruz et al. [48] in their preliminary observational study of patients who were on statin therapy and referred for management of oral symptoms reported xerostomia in 88.5%, mucosal paresthesia in 67.7%, and dysguasia in 53.8% of the referred patients, and the majority of these adverse effects resolved after cessation of statin therapy. Reviewing the literature revealed case reports of angioedema on the face, tongue, and lips [81], recurrent ulcerative/ keratotic lesions on the tongue [44], and cheilitis [82] as adverse oral effects of statin therapy.

Statins and medication-related osteonecrosis of the jaw (MRONJ)

MRONJ is a known side effect of antiresorptive or antiangiogenic medications. The antiresorptive effect of bisphosphonates is achieved by blocking the function of osteoclast and increasing apoptosis, which subsequently leads to a reduction in bone resorption and remodeling [83]. Osteonecrosis of the jaw has been reported in association with long-term use of high doses of simvastatin (40mg) [84, 85]. This adverse effect may be attributed to the ability of simvastatin to reduce osteoclastic and increase osteoblastic activity of bone [83], rendering the patients susceptible to MRONJ.

CONCLUSION

Taking detailed medical history, including HC, is an essential step in proper dental patient management. The treating physician should be alert to the presence of HC or hypocholesterolemia states. In addition to cardiovascular disease, hypercholesterolemic patients are more susceptible to several oral symptoms and adverse effects, and uncontrolled HC may complicate dental treatments. The oral cavity of hypocholesterolemic patients should be examined thoroughly for the possibility of potentially malignant disorder or even malignancy.

Similarly, statin therapy has several oral adverse effects but may improve the prognosis of several dental treatments. Most of the information regarding the oral implications of HC and statin therapy was derived from cross-sectional surveys and laboratory or animal studies. The promising pleiotropic effects of statins should stimulate more clinically oriented studies to explore the potential oral and dental applications of statins.

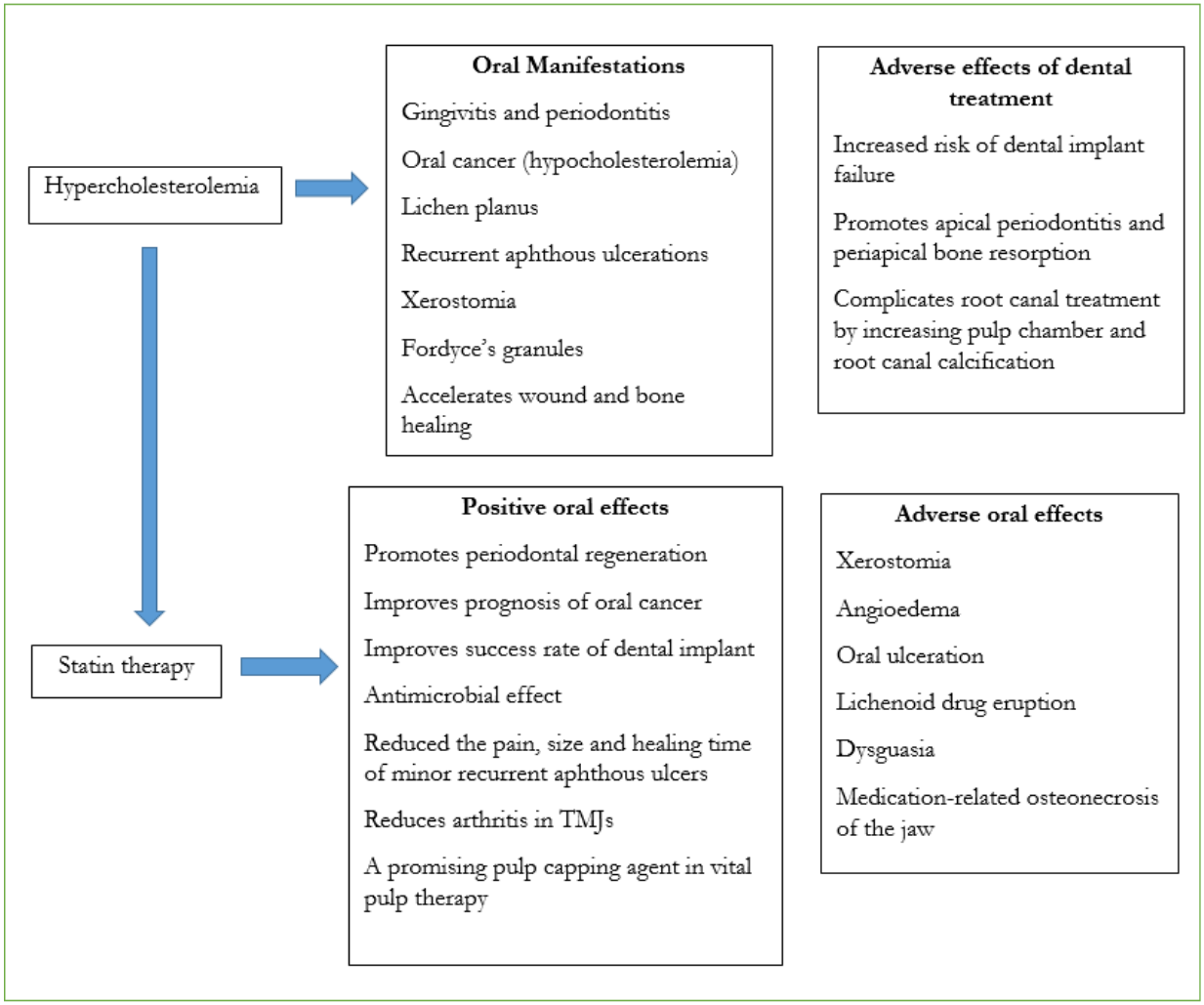

Figure 1: The impact of cholesterol disorders and statin therapy on the oral cavity and dental health care.

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تأثير اضطرابات كوليسترول الدم وعلاجها الدوائي على صحة الفم والعناية بصحة الفم و الأسنان: مراجعة سردية

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الملخص

فرط كوليسترول الدم هو إضطراب إستقلابي شائع , و تقدر منظمة الصحة العالمية أنه يؤثر على 39٪ من السكان على مستوى العالم. يثعتقد أن بعض أمراض الفم ، مثل التهاب اللثة أو التهاب رباط دواعم الأسنان ، والحزاز المسطح ، والتقرح القلاعي المتكرر ، أكثر شيوعاً بين مرضى فرط كوليسترول الدم كما و يؤثرسلبا على زراعة الأسنان ، ويعزز التهاب دواعم السن الذروي ، ويزيد من تكلس حجرة اللب السني، بينما قد يرتبط نقص كوليسترول الدم بسرطان الفم أو الافات الفموية محتملة الخباثة. إن العقاقير المخفضة للكوليسترول ، وخاصة أتورفاستاتين ، لها تأثيرات مضادة للميكروبات وقد تم اقتراحها كعامل يزيد في إنجاح علاج اللب السني الحيوي. كما أنه يعزز تجديد الأربطة الداعمة للجذور ، والتئام الجروح ، ويحسن إنذار و مآل سرطان الفم ، ويزيد من معدل نجاح زراعة الأسنان. كما قد يساعد في تدبير القرح القلاعية المتكررة والتهاب المفصل الفكي الصدغي. تشمل الآثار الفموية الضارة للعلاج بالستاتين زيادة تكلس حجرة اللب السني ، و ظهورالتهاب الفم الحزازي الشكل ، وجفاف الفم. إن قدرة دواء سيمفاستاتين على تقليل نشاط الخلايا الناقضة للعظم و تحفيز الخلايا البانية للعظم تجعل المرضى عرضة لنخر عظم الفك المرتبط بالأدوية. لذلك, يجب أن يكون ممارسو طب الأسنان العامون, والعاملون في مجال صحة الفم و الأسنان على دراية بالمظاهر الفموية المصاحبة لفرط كوليسترول الدم و تأثير الستاتينات على صحة الفم من أجل تدبير صحي و سني أفضل وأكثر أمانا لمرضى الفم و الأسنان.

الكلمات الدالة: شذوذ استقلاب الشحميات, فرط كوليستيرول الدم, المظاهر الفموية, ستاتين.