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PUŠENJE I KONZUMIRANJE ALKOHOLA KAO FAKTORI RIZIKA KOD 112 ONKOLOŠKIH BOLESNIKA SA DIJAGNOZOM BISFOSFONATNE OSTEONEKROZE VILICA

SMOKING AND ALCOHOL CONSUMPTION AS RISK FACTORS IN 112 ONCOLOGY PATIENTS DIAGNOSED WITH BISPHOSPHONATE-ASSOCIATED OSTEONECROSIS OF THE JAW

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Sažetak

Uvod: Osteonekroza vilica udružena sa bisfosfonatima (OVUB) je komplikacija od velikog medicinskog značaja. Neki od najkontroverznijih apsekata o kojima se najviše diskutovalo jesu faktori rizika, od kojih su neki povezani sa pušenjem i konzumacijom alkohola kod pacijenata kod kojih se osteonekroza pojavila.

Cilj: Proceniti koliki je rizik od nastajanja OVUB oboljenja kod onkoloških pacijenata sa rizičnim zdravstvenim navikama.

Materijal i metode: Sprovedena je Prospektivna epidemiološka studija, je obuhvatila 112 pacijenata sa dijagnostifikovanom osteonekrozom vilice udružene sa bisfosfonatima, sprovedena je na Klinici za maksilofacijalnu hirurgiju Univerzitetske bolnice "Sveti Georgije" u Plovdivu, u Bugarskoj, u periodu od 2016. i 2017. godinu, na osnovu anamneze, kliničkog pregleda i pregleda bolničke dokumentacije. Za statističku analizu korišćen je SPSS program v.24, sa nivoom značajnosti postavljenim na $p < 0,05$.

Rezultati: Preko 2/3 pacijenata bili su pušači (40,18%) ili bivši pušači (25,00%), što ih povezuje sa faktorom rizika -pušenjem. U vreme studije, pušači koji su pušili između 1 cigarete i 9 cigareta i između 10 i 19 cigareta dnevno imali su jednak relativni udeo od 44,22%. Više od polovine pacijenata koji su pušili starosti su između 20 i 39 godina, odnosno bili su sa visokom prosečnom starošću. Većina ispitivanih pacijenata konzumirala je alkohol, najčešće jednom nedeljno ili vikendom (28,57%) ili samo povremeno (26,79%), a 24,11% unosilo je alkohol nekoliko puta nedeljno. Skoro 2/3 ispitanika konzumiralo je piće i sa niskim i sa visokim sadržajem alkohola.

Zaključak: Najveći broj pacijenata bili su pušači/bivši pušači i povremeni konzumenti alkohola, što ih ukazuje da su pušenje i alkohol potencijalni faktori rizika za razvoj bisfosfonatne osteonekroze vilica.

Ključne reči: pušenje, alkohol, rak, bisfosfonati, osteonekroza

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Abstract

Background: Bisphosphonate-associated osteonecrosis of the jaws (BAONJ) is a complication of great medical importance. Some of the most discussed and controversial aspects are the risk factors, some of which are related to patients' smoking and alcohol consumption.

The Aim: To study cancer patients with BAONJ and determine their participation in the mentioned above risky health-related habits.

Material and methods: A prospective epidemiological study of 112 patients diagnosed with bisphosphonate-associated osteonecrosis of the jaw in 2016 and 2017 was conducted at the Clinic of Maxillofacial surgery of University hospital "St. George", Plovdiv, Bulgaria, based on anamnesis, clinical examination, and hospital documentation. SPSS Statistics v.24 was used for statistical analysis, at a significance level $p < 0.05$.

Results: Over 2/3 of the patients were smokers (40.18%) or ex-smokers (25.00%), which linked them with the risk factor of smoking. At the time of the study, patients smoking between 1 and 9 and between 10 and 19 cigarettes a day had equal relative shares of 44.22%. More than half of the patients smoked from the age of 20-39, which we explain by the high average age. The majority of patients studied consumed alcohol, most often once a week or on weekends (28.57%) or only on occasions (26.79%), followed by 24.11% who used alcohol several times per week. Nearly 2/3 drink drinks with both low and high alcohol content.

Conclusion: The highest proportion of patients are smokers / ex-smokers and consume alcoholic beverages occasionally, which links them to these risk potential factors.

Key words: smoking, alcohol, cancer, bisphosphonates, osteonecrosis

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Uvod

Bisfosfonatni lekovi koriste se u lečenju osteoporoze i malignih procesa u koštanoj tkivu¹. Kao rezultat njihove upotrebe, formiraju se lezije u koštanoj tkivu i na oralnoj sluzokoži, poznate kao osteonekroza vilice udružena sa bisfosfonatom (OVUB) – komplikacija od velikog medicinskog značaja. Epidemiološke i kliničke studije sumiraju diskusije različitih grupa specijalista o definiciji, epidemiologiji i faktorima rizika, mehanizmima pojave, klasifikaciji, kliničkim manifestacijama, pristupima lečenju i prevenciji ovog procesa. Jasno je da je ovo izuzetno složen i multifaktorijski proces, koji zahteva pažljivo praćenje i individualni pristup svakom pacijentu. Verovatno su najsporniji i najkontraverziji aspekti faktori rizika²⁻⁴, od kojih su neki povezani sa lošim navikama, poput pušenja i konzumiranja alkohola od strane pacijenata, za koje se pretpostavlja da doprinose bržem i agresivnijem razvoju osteonekroze. Pošto se stanje smatra ireverzibilnim, naponi bi trebalo da budu usmereni ka prevenciji, pre i posle početka terapije bisfosfonatima (BP), što uključuje promene povezane sa zdravijim načinom života.

Materijali i metode

Prospektivna epidemiološka studija, koja je obuhvatila 112 pacijenata sa dijagnostikovanim osteonekrozom vilice udružene sa bisfosfonatima, sprovedena je na Klinici za maksilofacijalnu hirurgiju Univerzitetske bolnice "Sveti Georgije" u Plovdivu, u Bugarskoj, tokom 2016. i 2017. godine, na osnovu anamneze, kliničkog pregleda i uvida u bolničku dokumentaciju. Podaci su uneseni u specijalno napravljen karton za ovu vrstu epidemiološke studije. Za deskriptivnu statistiku, kontinuirane varijabile prikazane su kao srednji i interkvartilni raspon (medijana \pm IKR), a kategorijalne varijabile kao brojevi i procenti. Varijabile su upoređene pomoću dve proporcije z-testa i Pearsonovog hi-kvadrata. Sve statističke analize izvedene su u SPSS program, verzije 24 (IBM Corporation, New York, NY). Vrednost p manja od 0,05 smatrana je statistički značajnom.

Introduction

Bisphosphonate drugs are used in the treatment of the osteoporosis and malignant processes in the bone tissue¹. As a result of their use lesions are formed in bone tissue and oral mucosis, known as bisphosphonate - associated osteonecrosis of the jaws (BAONJ) - a complication of great medical importance. Epidemiological and clinical studies summarize discussions of different groups of specialists on the definition, epidemiology and risk factors, the mechanism of occurrence, classification, clinical manifestations and approaches to treatment and prevention of this process. It is clear that this is an extremely complex and multifactorial process that requires careful monitoring and individual approach to each patient. Arguably of the most discussed and controversial aspects are the risk factors²⁻⁴, some of which are related to bad habits, such as smoking and alcohol consumption of patients, which are assumed to contribute to more rapid and aggressive development of osteonecrosis. As the condition is considered irreversible, efforts should focus on prevention, both before and after the start of BP therapy, which includes changes associated with a healthier lifestyle.

Materials and methods

A prospective epidemiological study of 112 patients diagnosed with bisphosphonate-associated osteonecrosis of the jaw in 2016 and 2017 was conducted in the Clinic of maxillofacial surgery of University hospital "St. George", Plovdiv, Bulgaria, based on anamnesis, clinical examination, and hospital documentation. The data is reflected in a specially created for the purpose epidemiological study card. For descriptive statistics, continuous variables were displayed as the median and interquartile range (median \pm IQR) and categorical variables as counts and percentages. Variables were compared with the use of two proportions z-test and Pearson's chi-square. All statistical analyses were performed with SPSS version 24 (IBM Corporation, New York, NY). A p-value below 0.05 was considered statistically significant.

Rezultati

Srednja starost pacijenata sa OVUB-om bila je 68 godina (IKR = 16), najmlađi pacijent imao je 38 godina, dok je najstariji imao 85 godina. Nije bilo statistički značajne razlike između relativnih proporcija muškaraca (51,79%, n = 58) i žena (48,21%, n = 54) ($p > 0,05$). Onkološke bolesti, kao što su rak dojke (40,18%, n = 45) i rak prostate (37,71%, n = 40) ($p > 0,05$) dominirale su kod pacijenata, a 16,07% (n = 18) pacijenata bilo je sa drugim onkološkim oboljenjima, najčešće bubrežnim ćelijskim karcinomom, 6,25% (n = 7) multiplim mijelomom i 1,79% (n = 2) rakom pluća.

Preko 2/3 pacijenata bili su pušači (40,18%, n = 45) ili bivši pušači (25,00%, n = 28). U vreme sprovođenja studije, sa jednakim relativnim udelom, 44,22% (n = 19) pacijenata pušilo je između 1 cigarete i 9 cigareta i između 10 i 19 cigareta dnevno. Samo su dva pacijenta (4,44%) prestala da puše nakon pojave simptoma / pritužbi. (Slika 1)

Više od polovine pacijenata puši između 20 i 39 godina, što se opravdava visokom srednjom starošću (68 godina). Korisnici nikotina stariji od 40 godina (20,00%, n = 9) i oni koji su pušili od 10 do 19 godina (22,22%, n = 10) imali su sličan relativni udeo ($p > 0,05$). (Slika 2)

Skoro polovina bivših pušača (n = 27) prestala je da puši pre više od 10 godina (25,93, n = 7). Otprilike, četvrtina pacijenata prestala je da puši pre 5 do 9 godina (22,22%, n = 6), a zatim sledi jednak udeo osoba koje su prestale da puše pre 2 do 4 godine (18,52%, n = 5). Nije pronađena statistički značajna razlika između sekcija ($p > 0,05$). (Slika 3)

Većina pacijenata konzumirala je alkohol, najčešće jednom nedeljno ili vikendom (28,57%, n = 32) ili samo povremeno (26,79%, n = 30) ($p > 0,05$), a 24,11% (n = 28) pacijenata konzumiralo je alkoholna pića nekoliko puta nedeljno (Slika 4). Samo 2,68% pacijenata alkohol konzumira svakog dana. Skoro 2/3 pacijenata pije sve vrste alkohola (59,78%, n = 55), dok ostali, sa bliskim relativnim udelom, konzumiraju uglavnom pića sa visokim (19,57%, n = 18) ili pića sa niskim (20,65%, n = 19) sadržajem alkohola ($p > 0,05$).

Utvrđena je statistička veza između vrste raka i pušenja ($\chi^2 = 19,86$, $p < 0,05$) i konzumiranja određene vrste alkohola i raka ($\chi^2 = 45,66$, $p < 0,05$): kod pacijenata sa rakom dojke, bilo je znatno više nepušača od pušača i bivši pušači i oni koji ne konzumiraju alkohol bili su u većem broju od onih koji često i vrlo često konzumiraju alkohol.

Results

The median age of BAONJ patients was 68 years (IQR = 16), with a minimum of 38 years and a maximum of 85 years. There was no statistically significant difference between the relative proportions of men (51.79%, n = 58) and women (48.21%, n = 54) ($p > 0.05$). Oncological diseases breast cancer (40.18%, n = 45) and prostate cancer (37.71%, n = 40) ($p > 0.05$) were predominant in patients, followed by 16.07% (n = 18) with other oncological diseases, most commonly renal cell carcinoma, 6.25% (n = 7) with multiple myeloma, and 1.79% (n = 2) with lung cancer.

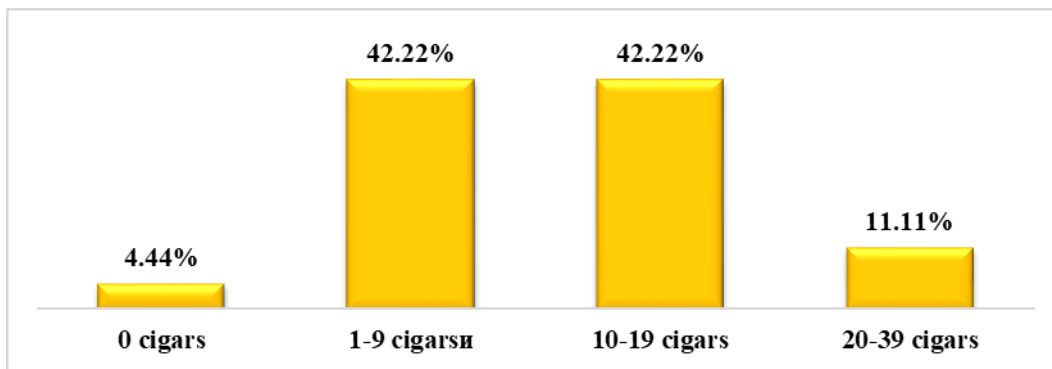
Over 2/3 of the patients were smokers (40.18%, n = 45) or ex-smokers (25.00%, n = 28). At the time of the study, with equal relative shares of 44.22% (n = 19) were the onessmoking between 1 and 9 and between 10 and 19 cigarettes per day. Only two patients (4.44%) stopped smoking after the onset of symptoms/complaints (Figure 1).

More than half of the patients have been smoking for 20-39 years, which we justify by the high median age (68 years). Nicotine users over 40 years (20.00%, n = 9) and those who smoked from 10 to 19 years (22.22%, n = 10) had similar relative shares ($p > 0.05$) (Figure 2).

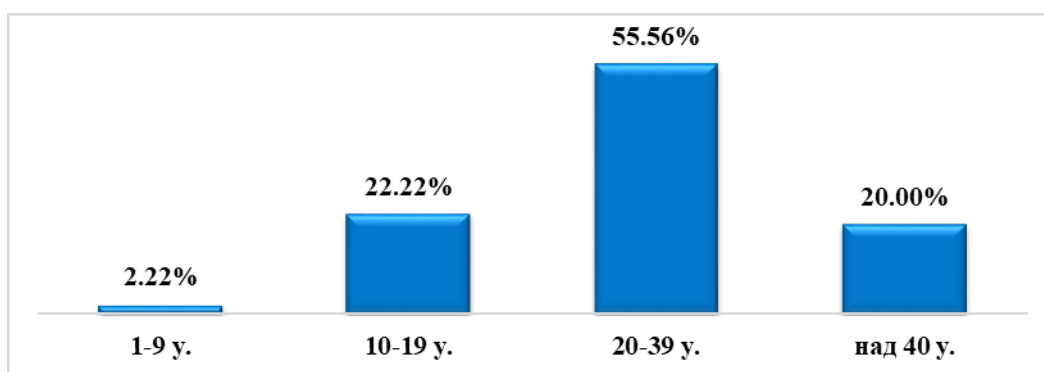
Nearly half of ex-smokers (n = 27) quit smoking more than 10 years ago (25.93, n = 7). About a quarter quit smoking 5-9 years ago (22.22%, n = 6), followed by equal shares of quitters 4 years ago and 2 years ago (18.52%, n = 5). No statistically significant difference was found between the sections ($p > 0.05$) (Figure 3).

The majority of patients studied consumed alcohol, most often once a week or on weekends (28.57%, n = 32) or only on occasions (26.79%, n = 30), ($p > 0.05$), followed by those consuming alcoholic substances several times a week (24.11%, n = 28) (Figure 4). Only 2.68% drank every day. Nearly 2/3 drank all types of alcohol (59.78%, n = 55), while the rest, with close relative shares, consumed mainly drinks with high (19.57%, n = 18) or drinks with low (20.65%, n = 19) alcohol content ($p > 0.05$).

A statistical linkage was found between the type of cancer and smoking ($\chi^2 = 19.86$, $p < 0.05$) and type of cancer and alcohol consumption ($\chi^2 = 45.66$, $p < 0.05$): in breast cancer patients there were significantly more non-smokers than smokers and ex-smokers and there were significantly more nondrinkers than those who consume alcohol often and very often.



Slika 1. Distribucija ispitanih pacijenata prema broju popušenih cigareta u toku 24 sata
Figure 1. Distribution of the studied patients according to the number of cigarettes smoked for 24 hours



Slika 2. Distribucija ispitanih pacijenata u odnosu na vreme trajanja pušenja
Figure 2. Distribution of the studied patients according to the duration of smoking

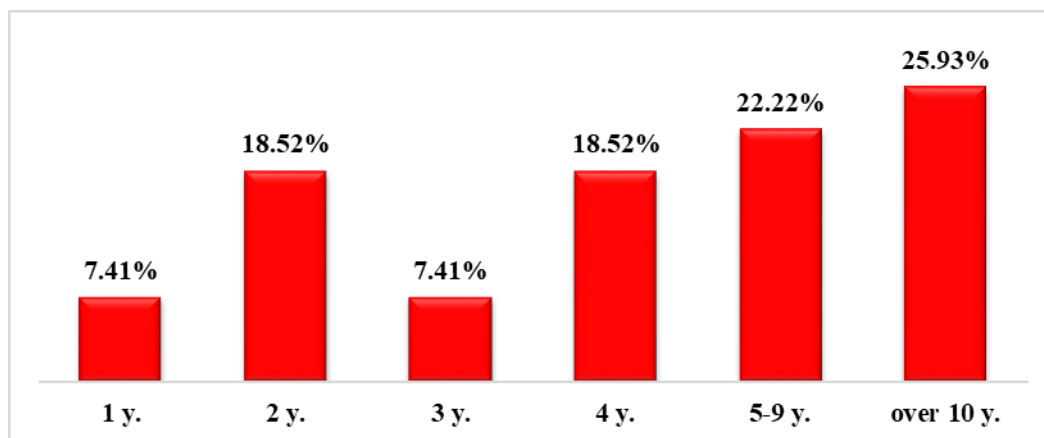
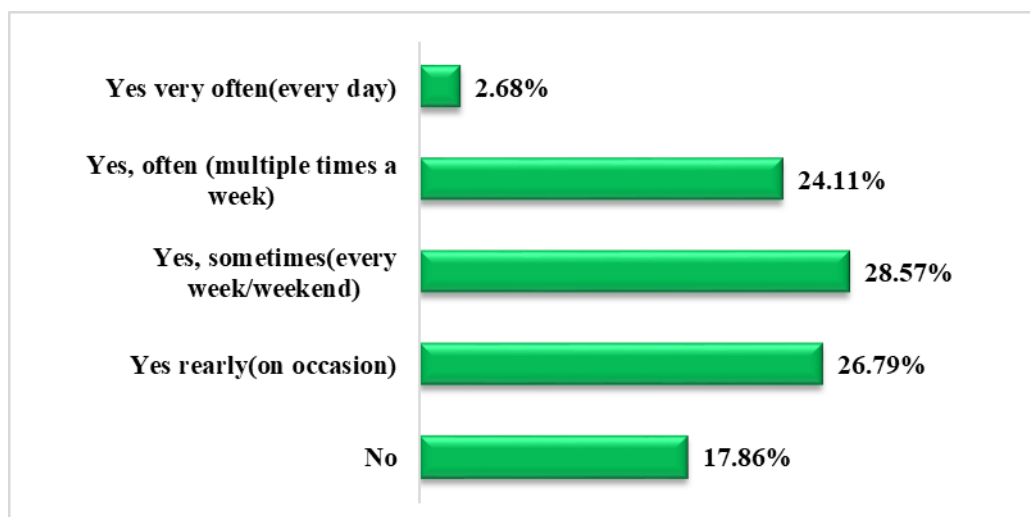


Figure 3. Distribucija bivših pušača po vremenu proteklom od prestanka štetne navike

Slika 3. Distribution of ex-smokers according to the statute of limitations for cessation of the harmful habit



Slika 4. Distribucija ispitanih pacijenata na osnovu količine konzumiranog alkohola
Figure 4. Distribution of the studied patients according to alcohol consumption

Diskusija

Upotreba duvana navodi se kao faktor rizika za OVUB-a²⁻⁶. Upotreba alkohola takođe se navodi, u nekim publikacijama, kao faktor rizika^{3,6}. Utvrđeno je da većina pacijenata sa OVUB-om nedeljno konzumira alkohol, najčešće u umerenim količinama, a više od 2/3 pacijenata bili su pušači ili bivši pušači, ali sve slične informacije o broju konzumiranih cigareta dnevno i trajanju pušenja, kao i detalji o konzumiranju alkohola, nisu pronađeni u drugim studijama na tu temu.

Studija slučaja je otkrila da je većina pacijenata sa osteonekrozom vilice okarakterisana kao pušači⁷. U drugoj studiji kontrole slučaja, gojaznost i pušenje bili su povezani u značajnoj meri sa razvojem osteonekroze vilice (OV)⁵. U Italiji je otkriven niži procenat pojave sa 32 pušača (21,2%) i 11 (7,28%) bivših pušača. U studiji o OVUB-u kod žena sa rakom dojke, 6 žena (21%) bilo je izloženo štetnim efektima duvana⁸. Vatters i dr. pronašli su vezu između pušenja ($p = 0,03$) i OVUB progresije pomoću χ^2 testa⁹. Drugi navode to da istovremena upotreba BP i pušenje mogu produžiti trajanje potpune remisije OVUB lezije¹⁰. Pušenje i dalje može biti zbunjujući faktor, s obzirom na to da pušači imaju goru oralnu higijenu od nepušača. U nedavnoj studiji, samo 2 pacijenta od 146 pacijenata, kod kojih je dijagnostifikovana osteonekroza vilice udružena sa lekovima (OVUL), bili su pušači, možda zbog činjenice da je tokom perioda lečenja zoledronskom kiselinom pacijentima savetovano da prestanu sa pušenjem i konzumacijom alkohola¹¹.

Discussion

Tobacco use is cited as a risk factor for BAONJ²⁻⁶. Alcohol use is also cited in some publications as a risk^{3,6}. We found that the majority of patients with BAONJ most of ten consume alcohol moderately on a weekly basis, and more than 2/3 of patients are smokers or ex-smokers, but any similar information on the number of cigarettes per day and duration of smoking, as well as details on alcohol consumption, were not found in other studies on the topic.

A case-control study also found that most patients with jaw osteonecrosis were smokers⁷. In another case-control study, obesity and smoking were significantly associated with ONJ development⁵. In Italy, they found lower rates, with 32 smoking patients (21.2%) and 11 (7.28%) ex-smokers. In a study of BAONJ in women with breast cancer, 6 (21%) were exposed to the harmful effects of tobacco⁸. Watters et al. found a ratio between smoking ($p = 0.03$) and BAONJ progression by χ^2 test⁹. Others report that concomitant use of BP and smoking may prolong the duration of complete remission of the BAONJ lesion¹⁰. Smoking can still be a confusing factor, given that smokers tend to have poorer oral hygiene than non-smokers. In a recent study, only 2 of the 146 patients diagnosed with medication-related osteonecrosis of the jaws (MRONJ) were smokers, maybe due to the fact that during the treatment period with Zoledronic acid patients were advised to quit smoking and alcohol drinking¹¹.

U studiji sprovedenoj u Kini, koja je obuhvatila 201 pacijenta sa različitim tipovima osteonekroze vilice, 36,7% pacijenata sa OVUL-om bili su pušači. 30% pacijenata sa OVUL-om imalo je naviku konzumiranja alkohola, ali nisu utvrđene statističke razlike između pacijenata sa OVUL-om i drugih grupa pacijenata¹².

Što se tiče konzumiranja alkohola, neke studije povezuju alkoholizam i zloupotrebu alkohola sa osteonekrozom, ali dalje informacije nisu dostupne u naučnoj literaturi¹³⁻¹⁶.

Međutim, smernice za prevenciju OVUB-a/OVUL-a i dalje uključuju kontrolu faktora rizika, kao što su pušenje i alkohol¹⁷ i ograničavanje ili prestanak rizičnog ponašanja za oralno zdravlje, poput pušenja i upotrebe droga i alkohola. Kada postoji rizik, ove smernice odmah se preporučuju, zbog rizika od razvoja OVUB-a¹⁸⁻²⁰, čak iako za neka istraživanja nisu klinički potkrepljena²¹.

Zaključak

U ovoj studiji, koja je obuhvatila 112 pacijenata obolelih od raka, kojima je dijagnostifikovan OVUB, najveći procenat pacijenata bili su pušači / bivši pušači, koji povremeno konzumiraju alkoholna pića, što ih povezuje sa ovim potencijalnim faktorima rizika. Takođe, smernice za sprečavanje OVUB-a/OVUL-a i dalje preporučuju ograničavanje ili prestanak rizičnog ponašanja, radi oralnog zdravlja, kao što su pušenje i upotreba droga i alkohola. Uprkos tome, pušenje, a naročito konzumiranje alkohola i dalje su kontroverzni faktori rizika, pa bi trebalo sprovesti detaljnije studije, kako bi se utvrdilo njihovo pravo učešće u razvoju ovog ozbiljnog stanja.

Sukobi interesa

Nema sukoba interesa za otkrivanje.

Zahvalnice

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In a study in China with 201 patients with different types of osteonecrosis of the jaw, 36.7% of MRONJ patients were smokers. Thirty percent of MRONJ patients had drinking habits, but no statistical differences between MRONJ and other groups were found¹².

As for alcohol consumption, some studies link alcoholism and alcohol abuse to osteonecrosis, but no further information is available in the scientific literature¹³⁻¹⁶.

However, the guidelines for prevention of BAONJ/MRONJ continue to involve controlling the risk factors such as smoking and alcohol¹⁷ and limiting or ceasing oral health risk behaviors such as smoking and drug and alcohol use are promptly recommended when at risk for development of BAONJ¹⁸⁻²⁰ even if for some researchers it is not evidence-based²¹.

Conclusions

In our study of 112 cancer patients diagnosed with BAONJ, the highest proportion of patients are smokers/ex-smokers and consume alcoholic beverages occasionally, which links them to these potential risk factors. Also, guidelines for prevention of BAONJ/MRONJ continue to recommend limiting or ceasing oral health risk behaviors such as smoking and drug and alcohol use. In spite of that, smoking and especially alcohol consumption are still controversial risk factors, and more in-depth studies should be conducted to determine their true involvement with the development of this serious condition.

Conflicts of Interest

There are no conflicts of interest to disclose.

Acknowledgments

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