Stress assessment in patients with medication-related osteonecrosis of the jaw[1]

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Abstract: Objectives: Medication-related osteonecrosis of the jaw (MRONJ) has become increasingly common due to the widespread use of antiresorptive drugs in cancer and osteoporosis treatment. Cancer diagnosis and treatment, particularly with concurrent serious illnesses, impose significant stress on patients. There is well-documented evidence linking cancer progression with stress, suggesting that psychosocial factors may influence disease development. This study aimed to evaluate stress levels in MRONJ patients, defining their physical, psychological, and behavioral responses, and exploring correlations between stress levels and socio-demographic factors (gender, age, education, residence).

Methods: A total of 82 MRONJ patients at various stages of the disease, with different primary cancer types, completed a validated stress symptom checklist (SSCL). Additionally, they provided socio-demographic information, including gender, age, residence, education, occupation, type of cancer, MRONJ phase, and necrosis location.

Results: The majority of MRONJ patients experienced high to very high stress levels, irrespective of sex, age, primary diagnosis, or MRONJ stage. Stress level data indicated that 5% had moderate stress, 35.5% had high stress, and 60% experienced very high stress. Anxiety was the most common psychological symptom (92.7%), followed by temper flare-ups (74.4%), restlessness (69%), irritability (63.4%), and depression (61%). The study highlighted the significant impact of prolonged stress on both general health and cancer progression in MRONJ patients.

Conclusion: The findings underline the need for preventive strategies to mitigate stress in cancer patients at risk of MRONJ. Integrating stress-reduction practices in treatment plans could potentially benefit overall patient health and improve treatment outcomes.

Keywords: carcinoma, cancer; depression; quality of life; MRONJ; stress; Stress Symptom Checklist (SSCL); well-being

Introduction

High levels of stress cause many diseases related to this construct, such as mental disorders, suicidal behavior, various psychodynamic, and psychopathological dysfunctions (Lo Castro, 2006; Schlebusch, 2004).

The diagnosis of cancer is a profoundly stressful event in life and is clearly associated with an increase in distress among the general population (Spiegel, 1997).

Cancer covers a group of over 300 subtypes of the disease and is characterized by uncontrolled growth and spread of abnormal cells. This disease is recognized as a major public health problem worldwide.

According to the National Cancer Registry[2], the number of registered new cases of malignant neoplasms is nearly

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35,200 as of year 2015 (used as an year of reference).

MRONJ prevention is of great importance not only for the quality of life of patients. With the increasing use of intravenous bisphosphonates in oncological conditions, osteonecrosis of the jaw is now a more common and often devastating complication, which at an advanced stage significantly affects the quality of life (Sayaseng, Vernon, 2018).

MRONJ was first described in 2003 by Marx. It is caused by drugs that belong to the group of bisphosphonates and/or monoclonal antibodies. They block osteoclast activity and thus stop bone resorption. They are used to treat bone metastases - most commonly breast cancer and prostate cancer, as well as multiple myeloma and osteoporosis. Despite the various options for the treatment of osteonecrosis, it remains a huge problem in clinical practice.

The incidence of osteonecrosis of the jaw in patients with intravenous bisphosphonate treatment has been increasing since 2015. Between 2016 and 2015, an incidence increase of 5.15% was observed. Between 2017-2015, it is already 8.75%. Studies show that their number only in the first 6 months of 2018 is 3543 and if this frequency of new cases is maintained, the number of MRONJ in 2018 alone will be almost doubled compared to 2015 (Tsolov et al 2019)

Cancer patients are at significant risk of developing anxiety and depression because they are under tremendous psychological distress. Mehnert et al. (2020); Hartung, Tim Julian et al (2017).

The development of mental disorders due to stress can happen not only to cancer patients, but also to their family members (Ahmet et al, 2014). According to the National Cancer Institute (NCI)[3] anxiety and depression are the most common diseases. Breast cancer diagnosis and treatment can be a very stressful problem both during and after treatment (Maeda, 2008). As a result, in recent years, attention has been focused on the rapidly increasing number of psychiatric problems in cancer patients, with the goal of improving their quality of life (Ahmet et al, 2014).

Since antiquity, people have speculated about the role of psychosocial factors in the development and progression of cancer. In fact, epidemiological and clinical studies over the past 40 years have provided convincing evidence of links between chronic stress, depression and social isolation, and cancer progression.

The "multilayered structure of stress" becomes obvious by the effect of the individual's adaptation to internal/external stressors on his/her "psysiological, psychological and behavioral reactions", which explains why the term (stress) is so difficult to define and hence there are different definitions in the fields of psychology, biology, physiology, pharmacology, and internal medicine, and cultural research and anthropology (Cannon, 1942).

Stress reactions include a person's previous experience, perceptions, and assessments of the stressful event. The importance of evaluation - that is, the importance that an event has for an individual - is emphasized in the transactional model of stress. The initial assessment refers to the importance that the stressor has for a particular person. The secondary assessment occurs in response to a person's awareness that something can be done about an event or situation, and the re-assessment is the result of changes in the person's initial assessment due to a changed situation (Adams, 1980; Schlebusch, 2000).

Since the physical, psychological and behavioral symptoms of human reactions can overlap when stress is present, it becomes very important to ensure, that stress can be distinguished from anxiety and depression by appropriate stress scales, as it has been proven by Lovibond and Lovibond (1995).

Given the above, the main study aims to examine the validity of SSCL by analyzing stress interactions. Schlebusch

[2] *https://www.sbaloncology.bg/index.php/bg/%D1%81%D1%82%D1%80%D1%83%D0%BA%D1%82%D1%83%D1%80%D0%B0/%D0%BD%D0%B0%D1%86%D0%B8%D0%BE%D0%BD%D0%B0%D0%BB%D0%B5%D0%BD-%D1%80%D0%B0%D0%BA%D0%BE%D0%B2-%D1%80%D0%B5%D0%B3%D0%B8%D1%81%D1%82%D1%8A%D1%80.html*

[3] *https://www.cancer.gov/about-cancer/treatment/side-effects/fatigue/fatigue-pdq*

(2004) reported that current indications are that SSCL is effective in measuring nonpathological stress in the general population.

Thus, we could define the presence of stress, prevent its possible impact on the development of tumor cells through timely therapy and indirectly support the treatment of cancer.

Patients and Methods

The study on stress levels was conducted by researchers with an interest in the diagnosis and treatment of MRONJ, improving mental health and lifestyle. All patients, who participated, provided informed consent.

The questionnaires were collected between January 2024 and February 2024. They were reviewed and entered into a final database using an additional input process. The data extracted for this analysis.

In order to carry out the study, all patients were presented as follows:

(1) Questionnaire related to socio-demographic factors: personal data, such as gender, age, education, education, profession, MRONJ phase and the place where the necrosis occurred (upper or lower jaw)
(2) SSCL to quantify subjects' non-pathological stress (Bourne, 2010)

The sample of the study included 82 patients, with an equal number of men and women. All are patients of the Clinic of Maxillofacial Surgery, "St. George" University Hospital.

In this study no control group was envisaged.

The assessment tool used to assess stress levels in the present study is a checklist of common signs and symptoms of stress (Bourne, 2010). All patients were asked to complete an additional questionnaire for socio-demographic data: (1) sex, age, place of residence, education, occupation, and type of cancer (2) disease data: MRONJ phase, necrosis site (upper/lower jaw)

A preliminary, pilot study was carried out (regardless of the sample in the study) involving 17 patients who participated voluntarily. The aim was to check for appropriate clarity, mood, tone, and ease of understanding for patients, as well as if there are any difficulties with the filling of the test forms. Ambiguous or unclear terms were corrected, which prevented the possible difficulties in assessing the scale in the actual study.

Instruments

SSCL provides operational measures to quantify subjects **non-pathological stress** responses and addresses variables based on response rather than incentives. In this sense, SSCL functions as a stand-alone tool that measures stress-related variables involving three categories (dimensions) of the overall matrix of human stress behavior. This measurement approach is common in anxiety, depression, and related rating scales (APA, 2000b; McDowell & Newell, 1996). SSCL is designed for comprehensive coverage, psychometric stability

SSCL is intended to measure stress levels (or stress intensity) and not as a diagnostic tool in psychopathology.

It measures symptoms that are manifestations or reported states of stress. It cannot be used to identify stress-related psychological and/or medical disorders (i.e., pathological stress), as occurs, for example, in PTSD, ASD, and AD (Kaplan & Sadock, 1995).

SSCL analyzes stress using an approach based on the biopsychosocial model, from which it follows that the structure of the stress questionnaire corresponds to the theoretical framework of this study. SSCL is a 52-point dichotomous questionnaire divided into the following sections: physical reactions (29 elements) and psychological reactions (23 elements) and behavioral reactions.

SSCL measures the level of stress based on the number of symptoms that have occurred often enough in the last month. A high score means a high level of stress. A total score of 21 or higher on the two sub-scales indicates an overall level of dysfunctional stress for that person.

Translation

A stress symptom checklist (SSCL) was used for the present study (Bourne, 2010). It includes analysis of physical, psychological, and behavioral responses to stress. A straightforward and reverse translation of the SSCL was made, and the translators were independent of each other and did not suspect that they were translating each others work.

Statistical analysis

The data analysis was performed with the statistical software IBM SPSS version 27 (2020).

Stress was described through the mean value and standard deviation (SD) and as an ordinal variable including the following stress levels: low (0 to 7), moderate (8 to 14), high (15 to 21) and very high (> 22). The Chi-square test was used to compare stress levels to different target subsections of the studied sample (including sex, age, MRONJ phase, and primary diagnosis). The independent-samples Kruskal-Wallis test was used when more than 25% of the cells had an expected count of less than 5. The mean stress level was compared through an independent samples t-test and Welch one-way ANOVA. Categorical and ordinal data were presented as frequencies and percentages. All statistical tests were two-tailed with level of significance alpha = 0.05 ($p < 0.05$).

Results

The study sample included 82 patients, with an equal number of men and women. The age ranged between 41 to 90 years, with the majority of the patients being between 61 to 80 years old. Medication-related osteonecrosis of the jaw (MRONJ) was more frequent in the lower jaw (68.30%), with the majority of the patients in phrase 2 (37.80%) and phase 3 (56.10%). Among the primary diagnosis, breast cancer was the most frequent (46.30%), followed by prostate cancer (32.90%). The other types of primary cancers were less frequent and were subsequently put together in one group to aid the statistical analysis (**Table 1**).

Table 1. Characteristics of the patients.

Variables	Number (%)
Sex	
• men	41 (50%)
• women	41 (50%)
Age	
• 41 to 50 years	5 (6.10%)
• 51 to 60 years	7 (8.50%)
• 61 to 70 years	23 (28.00%)
• 71 to 80 years	33 (40.20%)
• 81 to 90 years	14 (17.10%)
Jaw affected by MRONJ	
• upper jaw	26 (31.70%)

• lower jaw	56 (68.30%)
MRONJ phase	
• 1st	1 (1.20%)
• 2nd	31 (37.80%)
• 3rd	46 (56.10%)
• 4th	4 (4.90%)
Primary diagnosis	
• breast cancer	38 (46.30%)
• prostate cancer	27 (32.90%)
• renal cancer	6 (7.30%)
• colorectal carcinoma	4 (4.90%)
• melanoma	3 (3.70%)
• testicular cancer	2 (2.40%)
• ovarian cancer	1 (1.20%)
• uterine cancer	1 (1.20%)

The individual stress scores ranged between 12 and 32 points, with a mean score of 22.10±4.44. Based on their stress scores, 5% of the patients were associated with moderate stress level; 35.50% with high stress level; 60.00% with very high stress level. The distribution of stress levels across the different subsections did not show significant differences: sex ($p = 0.973$); age ($p = 0.063$); MRONJ phases ($p = 0.899$); primary diagnosis ($p = 0.167$). The mean test scores were very similar across the target subsections, except for the patients diagnosed with phase 4 MRONJ who had the highest mean score of 24.50 ±5.0 and were all categorized into the very high stress level (> 22). However, the small number of patients ($n = 4$) does not allow any generalizations beyond these descriptive observations (**Table 2**).

Table 2: Stress levels for the whole sample and target subsections.

Variables	Stress levels (n,%)				Stress score	
	Moderate (8-14)	High (15-21)	Very high (> 22)	p	Mean (±SD)	p
Total	4 (5.0%)	29 (35.5%)	49 (60.0%)	na	22.1±4.4	
Sex						
• men	2 (5.0%)	15 (36.5%)	24 (58.5%)	0.973χ^2	22.5±4.9	0.402^t
• women	2 (5.0%)	14 (34.0%)	25 (61.0%)		21.7±3.9	
Age						
• 41 to 50 years	1 (25.0%)	3 (10.3%)	1 (2.0%)		19.0±5.0	
• 51 to 60 years	0 (0.0%)	5 (17.2%)	2 (4.0%)		20.2±2.4	

• 61 to 70 years	0 (0.0%)	10 (34.5%)	13 (27.0%)	0.063^{KW}	22.0±5.2	0.129^{WA}
• 71 to 80 years	2 (50.0%)	6 (20.7%)	25 (51.0%)		23.4±2.9	
• 81 to 90 years	1 (25.0%)	5 (17.3%)	8 (16.0%)		21.2±4.4	
Jaw affected by MRON						
• upper jaw	1 (3.8%)	10 (38.5%)	15 (57.7%)	0.899 χ^2	22.1±4.1	0.980^{t}
• lower jaw	3 (5.4%)	19 (33.9%)	34 (60.7%)		22.0±4.6	
MRONJ phase						
• 1st	0	1	0	0.161^{KW}	na	0.423^{WA}
• 2nd	2 (6.5%)	13 (42.0%)	16 (51.5%)		21.4±4.5	
• 3rd	2 (4.4%)	15 (32.6%)	29 (63.0%)		22.5±4.3	
• 4th	0 (0.0%)	0 (0.0%)	4 (100%)		24.5±5.0	
Primary diagnosis						
• breast cancer	2 (5.0%)	11 (29.0%)	25 (66.0%)	0.167^{KW}	22.0±3.7	0.504^{WA}
• prostate cancer	0 (0.0%)	10 (37.0%)	17 (63.0%)		22.9±4.6	
• other cancers	2 (12.0%)	8 (47.0%)	7 (41.0%)		21.1±5.4	

$\chi2$ – Chi-square test; KW – Kruskal-Wallis test; t- independent-samples t-test; WA – Welch ANOVA

Stress symptoms with frequency over 70%

Out of 29 physical symptoms in the *Stress Symptom Checklist*, nine showed frequencies over 70% (**Figure 1**). Backaches were reported by 97.60% (n = 80); jaw tension and headaches by 79 (n = 96.30%); weight change by 93.90% (n = 77); neck pain and tight muscles by 90.20% (n = 74); other pain by 85.40% (n = 70); muscle cramps by 78.00% (n = 64) and appetite change by 73.20% (n = 60). The remaining 20 physical symptoms were experienced by less than 50% of the patients as some of them had very low frequency, including: cold hands/feet (3.7%); diarrhea (3.7%); allergies (1.2%); teeth grinding (1.2%); digestive upsets (14.6%); constipation (8.5%); hypoglycemia (6.1%); colds (2.4%); overeating (4.9%).

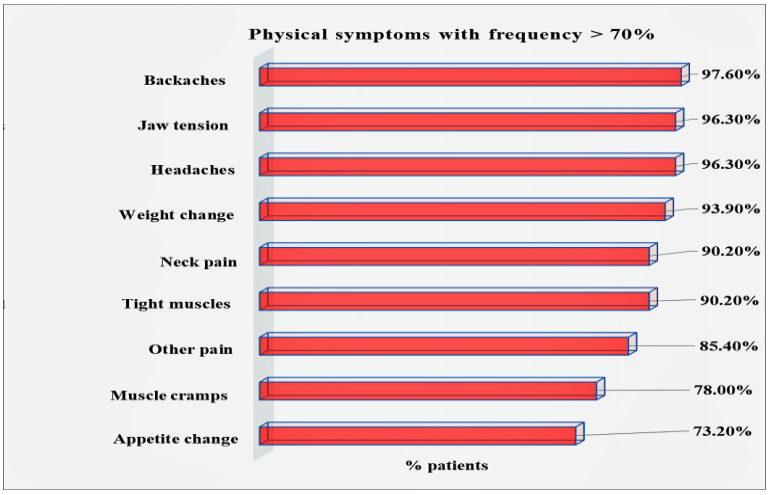

Figure 1. Physical symptoms with frequency over 70%.

Out of 23 psychological symptoms included in the *Stress Symptom Checklist,* only five showed frequencies over 60% (**Figure 2**). Anxiety was the most common psychological symptom shared by 92.70% of the patients (n = 76), followed by temper flare-ups 74.40% (n = 61), restlessness 69% (n = 56), frequent irritability 63.40% (n = 52), and depression 61% (n = 50). The remaining psychological symptoms were reported by less than 50% of the patients.

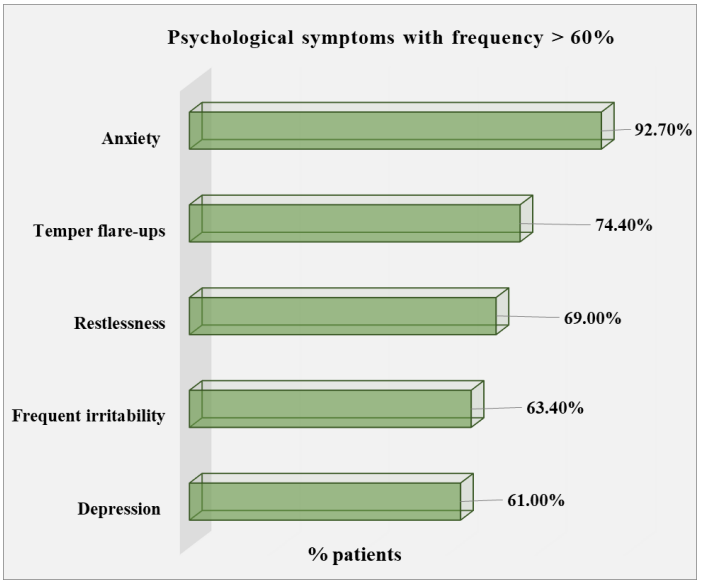

Figure 2. Psychological symptoms with frequency over 60%.

Discussion

Metastasis, which is resistant to conventional therapy, is the leading cause of cancer death (Tammela et al., 2020). Primary neoplasms are biologically diverse, and metastasis requires a series of sequential and selective steps that only a few cells can successfully complete. The outcome of cancer metastases is determined by a variety of interactions between metastatic cells and homeostatic mechanisms that are specific to a given organ microenvironment. (Fidler, 2002). Therefore, metastasis treatment should target not only cancer cells, but also contributing factors that enable the dynamic growth and survival of metastatic cancer cells.

Over the last 40 years, clinical and epidemiological studies have identified psychosocial factors, such as stress, chronic depression, and a lack of social support, as factors associated with cancer progression. (Chida et al., 2008). While evidence for the role of psychosocial factors in cancer onset is limited and somewhat contradictory (Michael et al.2009), there is strong evidence for links between psychological factors such as stress, depression, and social isolation and disease progression. (Hu C et al., 2021).

Therefore, we set out to study the validity of SSCL by analyzing the effects of stress on the body. We did this by setting a significance level for the most common symptoms to determine if a symptom was specific to the study group. In this study, the level of significance was 70%

Our results show that the majority of patients with MRONJ have experienced high to very high levels of stress, regardless of their gender, age, primary diagnosis, and phases of MRONJ. Exceptions are patients with phase 4of MRONJ, who have the highest average level of stress and without exception are in the category of "very high" level of stress.

A reason for the high levels of stress in cancer patients is the fear of disease progression. This is mainly due to lack of information.

Patients often prioritize the need for information about their disease and treatment. (Boberg et al, 2003) Research shows that increasing the level of knowledge helps patients make decisions. This in turn reduces stress and improves their quality of life. (Shea-Budgell et al., 2014)

Stress levels can also be reduced through psychotherapeutic interventions. (Herschbach et al., 2010)

Fatigue, tension headaches and muscle aches are symptoms that occur in Burnout syndrome, which is characterized by physical and emotional breakdown as a result of chronic stress. This triggers other adverse symptoms experienced by the study population: feeling discouraged in the morning, difficulty sleeping and interrupting sleep, stomach discomfort and stomach pain, tachycardia, muscle tremor, decreased appetite, shortness of breath and shortness of breath, reduced sexual interests, a feeling of sweating and redness of the face, in addition to stings, the interviewees felt on their bodies. (Datti, 1987, de Carvalho Farias et al., 2011).

In analyzing the results, we identified symptoms that recur in all patients. Our goal was to determine whether their manifestation alone is sufficient to adequately measure the degree of stress. We have achieved this successfully. Of the two categories of symptoms, the physiological ones are more common. Among them, the most common are different types of body pain, tension in the jaw and muscles, changes in appetite and weight.

The main psychological problem is anxiety, which is experienced by 92.70% of patients.

We also wanted to see if these symptoms were related in any way to the MRONJ phase or to the primary cancer. This proved very difficult due to the very small number of patients in phase 1 (only 1) and in phase 4 (only 4). There are no statistically significant differences in the results for phases 2 and 3. The results from Phases 1 and 4 cannot be included in the statistical analysis at all due to the very small number of patients. The problem with the primary disease is similar, in which, with the exception of breast and prostate cancer, the rest have a very small number of patients.

Again, due to the insufficient number of respondents, we were unable to obtain statistically significant results to say whether there was any relationship between the number of physical and primary cancers or the degree of MRONJ. The same applies to the number of mental symptoms

In the future, in cases like this, we need to consider whether some other type of analysis can provide the necessary information. Last but not least, we wanted to check whether there is a connection between stress levels and socio-demographic factors - gender, age, place of residence, education. This was possible only with the factors of gender, place of residence and education. With age, the two younger groups have very few patients.

Analysis of the primary disease shows that those responsible for MRONJ in women are due to a higher incidence of diseases such as breast cancer (Ruggiero et al., 2014). In men, it is prostate cancer

The phased classification facilitates the diagnosis and treatment of MRONJ (Ruggiero et al., 2014). This aims to reduce painful symptoms, control infection and restore social contact with family and friends, thus improving the physical and mental condition and therefore improving the quality of life of these individuals (Farias et al 2013, Oteri et al. al 2018).

Limitation of the study and future perspective

A limiting factor for summarizing the results in the present study is the insufficiently large sample. This is due to the fact that the study was conducted in only one site and patients are not outpatients, but only do follow-up examinations.

To prove the effectiveness of the questionnaire, the future perspective is to study patients not only with MRONJ, which is a limiting factor, but patients diagnosed with cancer.

Chronic stress today is associated with the pathogenesis of many diseases of society, including cancer. It provokes the active development of cancer cells and tumor microenvironment. Identifying the detrimental effects of stress, as well as developing approaches to prevent its harmful effects, is essential. Of equal importance is the discovery of additional pathways that alter therapeutic efficacy due to the fact that the influence of stress is not only on the development of tumor cells, but also on related physiological processes.

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