

COMORBIDITY OF CHRONIC TINNITUS AND PSYCHOLOGICAL STRESS - WHICH CAME FIRST, THE CHICKEN OR THE EGG?

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received: 1.10.2019;

revised: 24.4.2020;

accepted: 30.6.2020

SUMMARY

Subjective tinnitus is a frequent, debilitating hearing disorder causing severe emotional stress and psychological suffering. Likewise, many reports show that the onset of tinnitus occurs at the time of high stress or after a period of stress. It is also common for existing tinnitus to become worse during exposure to stress. However, in clinical practice the association between tinnitus and stress is often neglected. Extensive search of the Web of Science database has shown a low ratio of scientific articles about coexistence of stress and tinnitus compared to other stress-related conditions. Specifically, there are about sixteen times more articles investigating comorbid stress in chronic pain, about six times more in chronic fatigue, and about four times more in fibromyalgia. Previous studies of biological markers of stress in tinnitus patients showed normal diurnal levels of stress hormone cortisol. However, experimental studies of tinnitus subjects showed a blunted reactive cortisol response after a psychosocial stress test, exposure to noise in the laboratory and a dexamethasone suppression test. In addition, tinnitus subjects showed increased sympathetic tone, and weakened sympathetic response after exposure to mental arithmetic task. In tinnitus subjects oxidative metabolism shows imbalance with shift from antioxidant enzyme preponderance towards oxidative stress predominance. Relaxation therapeutic programs reduce stress-sensitive immunological parameter tumor necrosis factor alpha. Although existing data indisputably proves existence of comprehensive connections between tinnitus and psychological stress, there is still no empirical evidence to show whether stress as a etiological, or just contributing factor. Further research should give the ultimate answer on this subject.

Key words: tinnitus - stress - psychological - comorbidity - holistic health - mental health

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INTRODUCTION

Subjective tinnitus is the phantom sensation of the hearing apparatus, the perception of sound without external acoustic stimulation (Kompis et al. 2004). Patients usually refer to it as to buzzing, ringing, grinding, whistling, humming, roaring, chirping, howling or clicking in the ears (Atik 2014). It is conservatively estimated that the prevalence is about 10-15% in the adult population, and the number of patients increases after the age of 50 (Axelsson & Ringdahl 1989, Holmes & Padgham 2011). Historically, a lot of famous personalities reported to suffer from tinnitus, such as Joan of Arc, Ludwig van Beethoven, Bedrich Smetana, Michelangelo, Leonardo da Vinci and Charles Darwin to name the few. Last mentioned even made daily records of tinnitus frequency and amplitude (Morgenstern 2005). Tinnitus prevalence is expected to increase in all age groups in the future (Hebert & Lupien 2009). The most important predictor of tinnitus presence is hearing loss, especially sensorineural loss associated with age and noise exposure (Nondahl et al. 2002, Waye et al. 2002). The "US Veterans Administration Benefits Report" ranked tinnitus as the second most prevalent service-related disability (Langguth et al. 2009, Swan et al. 2017). Lately, prevalence of sensorineural occupational noise hearing loss and tinnitus is increasingly found in young population, and The World Health Organization is currently compiling statistical data on tinnitus loads caused by

environmental and recreational noise (Vio & Holme 2005). Based on the duration, tinnitus is divided into acute (<3 months), subacute (3-12 months) and chronic (>12 months), and based on severity into slight, mild, moderate, severe and serious or catastrophic (Zeman et al. 2014, Wallhausser-Franke et al. 2017). Several studies have demonstrated the close association between tinnitus and comorbid psychological disorders showing that tinnitus causes distress leading to deterioration in psychological well being and hampering the daily life enjoyment of affected individuals (Harter et al. 2004, Reynolds et al. 2004, Londero et al. 2006, Adoga et al. 2008, Durai et al. 2017). It impinges on the quality of life of affected individuals to varying degrees occurring as a minor irritation to some and in extreme cases result in the intentional or ambivalent self destructive act of suicide (Simpson & Davies 1999, Szibor et al. 2019). Some of the psychological disorders associated with tinnitus are anxiety, depressive disorders, hysteria, insomnia, anger, fear, and despair (Reynolds et al. 2004, Adoga et al. 2008, Crocetti et al. 2009, Jacques et al. 2013, Cronlein et al. 2016). However, there could also be a reversal in this relationship with an increase in tinnitus severity during periods of poor psychological well being (Rauschecker et al. 2010). It is well known that a significant number of patients with tinnitus reported that occurrence, exacerbation or progression of tinnitus was preceded by stress episodes. Therefore, this association could be said to be dual (Alpini & Cesarani 2006).

Table 1. Results of advanced search in Web of science database for topic #1 (tinnitus and stress), topic #2 (chronic pain and stress), topic #3 (chronic fatigue and stress) and topic #4 (fibromyalgia and stress)

Statistical parameter	T + S (N)	CP + S (N)	CF + S (N)	F + S (N)
Total articles	477	7812	2724	1725
Highest annual rate of articles	50	751	191	112
Average citation per item	18.10	28.65	35.09	33.04
Citation sum	8 633	223 837	95 577	56 996
Citation sum (without self-citations)	7558	202 819	86 218	49 343
Most cited article citations	197	1 921	1 910	1 654
Highest annual rate of citations	1 305	26 312	9 756	5 352
Citing articles	5 966	144 565	65 158	33 697
Citing articles (without self-citations)	5 693	139 612	63 416	32 321

T – tinnitus; CP – chronic pain; CF – chronic fatigue; F – fibromyalgia; S – stress; N – number

METHODS

The studies and their analysis examined in the present work are the result of extensive text mining and database searching through five databases (Medline/PubMed, Embase, PsychInfo, CINAHL, Web Of Science (WoS)) as well as individual journal search for all results retrieved by searches of any of the general terms: “tinnitus”, “subjective tinnitus”, “hearing loss”, “stress”, “distress”, “emotional stress”, “psychological stress”, “stress hormones”, “oxidative stress”, “hypothalamus-pituitary-adrenal axis”, “autonomic nervous system”, “immunologic system”, “anxiety”, “depression”, “insomnia”, “suicide”; and their combinations. We selected only studies written in English. References to published reviews were used to obtain additional articles. Additionally, we performed WoS advanced search using “Tinnitus” and “Stress” as keywords for TS=(Tinnitus AND stress), from 1955 to 2019. Search was conducted on July 10, 2019. Topic retrieved a total of 477 articles published in the Clinical Medicine and Life Sciences section. The h-index of these publications was 47, average citations per item were 18.10, the sum of times cited was 8633. There were 5966 citing articles. The greatest number of articles was published in the field of otorhinolaryngology (N=170). Out of 477 articles, 388 were original scientific articles, 63 were reviews of literature, 16 were proceedings papers, 14 were meeting abstracts, 5 were book chapters. First article was written in 1991 and the number of articles significantly increased after 2008 (greatest annual rate in 2017 (N=50)). The article with the greatest number of citations had a total of 197 citations. Afterward, we performed WoS advanced search using “Chronic pain”, “Chronic fatigue” and “Fibromyalgia” as keywords for TS=(Chronic pain AND stress), TS=(Chronic fatigue AND stress) and TS=(Fibromyalgia AND stress). All listed disorders are permanent sensations that fluctuate over time and are considered chronic stressors. Due to many common features, and possible common mechanisms of development, they have often been compared with tinnitus in literature. Table 1 summarises the comparison of advanced search results between four

topics, conducted in WoS. As seen, results showed large discrepancy between scientific interest for emotional stress in patients with tinnitus and “other” stress-related conditions, in favor of “other” stress-related conditions. It is interesting because in clinical practice all groups generally express a significant amount of subjective discomfort. Low tinnitus/“other” stressors ratio of scientific records addressing the coexistence with emotional stress suggests that otorhinolaryngologists/ audiologists less often recognize mental disorders of tinnitus sufferers, and make appropriate referrals for psychiatric evaluation and care.

DISCUSSION

Tinnitus is an aural disorder that primarily produces psychological distress, mood disorders and high levels of anxiety. These alterations are a consequence of suffering from the chronic phantom sound in the ears, resulting in higher general physiological arousal (Heinecke et al. 2008). Patients complain of various difficulties including insomnia, lower quality of life, concentration problems, sensitivity to stress, irritability, and fear of serious illness (Vesterager 1994, Durai et al. 2017). However, it seems that there might also be a reversal interaction. More specifically, the severity of tinnitus is reported by sufferers to be exacerbated by stress and fatigue (Alpini & Cesarani 2006, Rauschecker et al. 2010). Cognitive maladjustment to stressful situations could favor tinnitus onset and maintenance (Hallam et al. 1988, Schmitt et al. 2000). Although this causal relationship has been incorporated in the classical knowledge on tinnitus, it derives from anecdotal and clinical observations. Unfortunately, empirical data are lacking. However, in literature there is indirect evidence of an association between stress or distress and the clinical course of tinnitus (Sahley & Nodar 2001, Canlon et al. 2013, Schaaf et al. 2014). One retrospective study that measured several stress-related parameters using questionnaires reported that patients with sudden hearing loss and tinnitus had a greater number of stressful events and daily hassles in their lives, along with fewer coping abilities, compared to another clinical

group, suggesting that tinnitus is a consequence of stress (Schmitt et al. 2000). In addition, German authors reported that subjective anxiety, perceived stress and tinnitus disturbance, as well as a stress-related immunological parameters decreased in patients with tinnitus after a relaxation therapy program (Weber et al. 2002). Predictive factors for tinnitus severity (not presence) are anxiety disorders and poor well-being at the onset (Holgers et al. 2000, Holgers et al. 2005). Neuroticism, a personality factor associated with increased experienced levels of anxiety, sadness, embarrassment, and guilt, has also been identified as a risk factor for tinnitus severity (Langguth et al. 2007). The significance of hearing loss in this case is moderate (Holgers et al. 2005).

Functional and electroencephalographic brain imaging studies in tinnitus patients have shown aberrant links between limbic (involved in emotions) and auditory system structures (Vanneste et al. 2010, Leaver et al. 2011). Structural brain differences (i.e., grey matter decrease) involving parts of the limbic system have also been reported. More specifically, less grey matter in the nucleus accumbens and the left hippocampus suggests a depletion that could be related to long-term exposure to stress, among other factors (Muhlau et al. 2006, Landgrebe et al. 2009, Leaver et al. 2011). In their tinnitus study, Rauschecker and colleagues suggested that a limbic system dysfunction would actually trigger tinnitus by blocking its inhibitory input to the thalamus. That is, a tinnitus signal would originate from the lesion-induced plasticity of the auditory pathways (i.e., some degree of peripheral damage is assumed to be always present, even when not measurable in the audiogram). Normally, this signal would be tuned out by feedback connections from limbic regions, which would prevent tinnitus from reaching the auditory cortex. In the presence of limbic damage, this "noise-cancellation" would collapse and chronic tinnitus would result. This could explain why some individuals with hearing loss do not experience tinnitus (Weisz et al. 2006, Rauschecker et al. 2010).

Another line of research has focused on the hypothalamus-pituitary-adrenal (HPA) axis functioning responsible for the stress response via the stress hormone cortisol. A study from Canadian authors showed that circadian levels of cortisol did not differ across tinnitus and control groups when cortisol was averaged across days of the week, so all groups displayed "normal" levels. However, a greater number of patients with tinnitus had chronically elevated cortisol levels over a 1-week period relative to controls, that is, had a greater number of samples above the median, suggesting chronically elevated basal cortisol levels over a 1-week period (Hebert et al. 2004). Another study investigated cortisol response after exposure to the Trier Social Stress Task. Results showed that tinnitus participants had blunted reactive cortisol compared to those in control group, suggesting the termination of HPA axis

function (Hebert & Lupien 2007). In addition, further research from the same authors demonstrated that tinnitus patients also had lower reactive cortisol levels following noise exposure in the laboratory. In contrast, subjective stress ratings were higher compared to control group, and tinnitus subjective intensity increased throughout testing (Hebert & Lupien 2009). This might explain why individuals with tinnitus tend to avoid noisy social situations, and this could contribute to their higher depression scores (Hebert et al. 2004, Hebert & Lupien 2009). Similarly to previous observations, a recent study by Simoens and Hebert demonstrated that tinnitus subjects had stronger and longer-lasting cortisol suppression after low dexamethasone administration (0.5 mg), compared to control group. Additionally, the discomfort threshold was lower after cortisol suppression in tinnitus ears (Simoens & Hebert 2012). Phenomena of normal diurnal cortisol and blunted reactive cortisol in tinnitus sufferers could be explained through dual negative feedback of HPA control – via mineralocorticoid (MR) receptors which are assessed in basal cortisol levels, and glucocorticoid (GR) receptors which are more critical for terminating the HPA axis stress response. GR receptors found in hypothalamus are also present in the inner ear, and there are some indications that through them cortisol exerts a direct influence on hearing detection thresholds. However, their function still remains unclear (Mazurek et al. 2012, Simoens & Hebert 2012).

Except for the neuroendocrine system, it is considered that the autonomic nervous system (ANS) plays a significant role in maintaining tinnitus, especially the sympathetic branch (Cohen & Khalaila 2014, Lupis et al. 2014, Carnuta et al. 2015, Het et al. 2015). This idea is corroborated by the old finding that sympathectomy can relieve tinnitus symptoms in patients with Ménière's disease (Garnett Passe 1951). Several studies have observed a positive association between tinnitus-related distress and sympathetic tone and a negative association between tinnitus-related distress and parasympathetic tone (Datzov et al. 1999, Choi et al. 2013). In accordance to these results, German authors reported that heart rate (HR) and heart rate variability (HRV), as indicators of ANS activity, showed blunted sympathetic activity in response to acute stress induced by mental arithmetic test. HRV measures did not differ between tinnitus and control group, and HR in the tinnitus group was overall decreased and blunted compared to the control group (Betz et al. 2017). A possible explanation is through long-term adaptation of the cardiac system to mild/moderate chronic psychological stress, similar to competitive athletes' adaptation to chronic physical stress (Rimmele et al. 2007). Conversely, research from Finish authors demonstrated that transcutaneous vagal nerve stimulation (tVNS) in tinnitus patients induces a shift in ANS function from sympathetic preponderance towards parasympathetic predominance – observed trough

increased variability of R-R intervals and HRV age decrease (Ylikoski et al. 2017). In addition, tVNS showed to be successful in modulating tinnitus-related beta- and gamma-band activity (measured by both cortical oscillatory power and synchronization), correlating strongly with tinnitus handicap inventory scores (Hyvarinen et al. 2015). Research on catecholamine and serotonin showed no significant differences in baseline serum levels of norepinephrine (NE), epinephrine (Epi) and 5-hydroxyindoleacetic acid (5-HIAA) between tinnitus and control group (Kim et al. 2014).

Reaction to psychological stress can also be observed in the immune system (Moynihan 2003, Szczepek et al. 2014). Particularly, stress is found to impact hormonal regulatory function, causing immune cells to become insensitive to hormones and consequently resulting in suppression of immune system responses, triggering increased susceptibility to diseases (van West & Maes 2001). Both animal and human research has demonstrated that an acute stressor changes neopterin levels (Breinekova et al. 2007, Lindsay et al. 2015). U.S. authors' research is the first one that simultaneously investigated response of the sympathetic nervous system, endocrine system and immune system in tinnitus respondents experimentally exposed to psychosocial stress. They performed a mental arithmetic task and collected salivary secretions at four different time intervals for analysis of specific autonomic (alpha-amylase (sAA)), endocrine (cortisol), and immune (neopterin) markers. SAA levels were lower in the tinnitus group in comparison to subjects without tinnitus, suggesting impaired sympathetic activity in the subjects with tinnitus, but no significant effects could be obtained for salivary cortisol or neopterin (although salivary neopterin levels were trending toward significance over all measurements) (Alsalmán et al. 2016). However, study from German authors showed reduction in tumor necrosis factor alpha (TNF- α), a stress-related immunological parameter, after participation in a standardised 10-week relaxation program. This data suggest that the training offered improved stress-managing capabilities in chronic tinnitus sufferers, and that TNF-alpha may be conceived as a potent stress marker. No alterations were noted for interleukin 6 (IL-6) or interleukin 10 (IL-10) (Weber et al. 2002). Turkish research on brain-derived neurotrophic factor (BDNF) showed its lower serum concentrations, but it appears that there is no correlation between BDNF gene polymorphism and tinnitus (Coskunoglu et al. 2017).

The latest studies focused on investigation of the oxidative metabolism, principally natural antioxidant barrier in a body of tinnitus subjects (Koc et al. 2016, Celik & Koyuncu 2018, Ekinci & Kamasak 2019, Ensari et al. 2019). It is suspected that oxidative stress disrupts the sensorineural epithelium of the labyrinthine, acoustic, and vestibular nerves (An et al. 2014). In addition, some experimental studies reported that reactive

oxygen species (ROS) can damage the cochlear sensory epithelium, causing acoustic trauma (Gilles et al. 2014, Park et al. 2014). Normally, the human cochlea contains antioxidant vitamins, glutathione and various enzymes against oxidative molecules (Ewert et al. 2012). Excessive noise exposure may cause ROS accumulation, which can lead to cell necrosis and apoptosis. Thus, sensorineural epithelium is at risk for ROS-induced lesions in cochlea (Lynch & Kil 2005). Recent research from Turkish authors reported an increase in total oxidant status (TOS) and oxidative stress index (OSI) in tinnitus patients, and normal total antioxidant status (TAS) (Ekinci & Kamasak 2019). Contrary to that, several other studies reported significantly lower TAS in tinnitus respondents compared to the control group, suggesting oxidative stress and antioxidant enzyme imbalance (Koc et al. 2016, Celik & Koyuncu 2018). Accordingly, numerous parameters of oxidative metabolism are reported to be disrupted in tinnitus sufferers, as well as some trace elements (Berkiten et al. 2015, Yasar et al. 2017, Celik & Koyuncu 2018, Pawlak-Osinska et al. 2018). Further investigation is needed in this area.

Table 2 summarizes some of the most relevant studies illustrating the relationship between tinnitus and biological markers of stress.

Cognitive behavior therapy is deemed to be the most promising psychiatric treatment for tinnitus individuals, possibly because it reduces stress and distress through the development of coping strategies (Andersson et al. 2002, McKenna et al. 2017, Li et al. 2019). The treatment program includes patient education and reassurance, psychological counseling, hearing aids and maskers as appropriate (Goebel 2000). In individual cases promising results were achieved using combined approach with transcranial magnetic stimulation, acupuncture or yoga practice (Arhin et al. 2016, Richter et al. 2017, Koksoy et al. 2018). According to Folmer, the aim of tinnitus management programs should be to reduce the severity of each patient's tinnitus. That is, clinicians should help patients to learn how to pay less attention to their tinnitus and be less bothered by it over time. A realistic goal of an effective tinnitus management program is to help patients understand and gain control over their tinnitus, rather than tinnitus having control over them (Folmer 2002). Some authors group tinnitus severity into the following; help-seekers, non-help-seekers; complainers and non-complainers (Hallberg & Erlandsson 1993, Attias et al. 1995). Others classify tinnitus severity into three subgroups based on the predictive factors for incapacitating tinnitus and these are audiological tinnitus, somatic tinnitus and depression and anxiety related tinnitus, with the latter group being the largest subgroup (Holgers et al. 2000). Only in about 2–6% of all tinnitus patients the symptoms cause a considerable amount of psychological distress interfering with their lives (Axelsson & Ringdahl 1989, Heller 2003, Betz et al. 2017).

Table 2. Chart review of relevant experimental and observational studies investigating relationship between tinnitus and biological markers of stress

Reference	Sample	System investigated	Level	Parameter	Instrument of assessment	Result
(Weber et al. 2002)	26	Immunologic	Immune response	TNF- α ; IL-6; IL-10	Relaxation program	Decreased; Normal; Normal
(Hebert et al. 2004)	18	Endocrine	HPA axis	Diurnal cortisol	Circadian assessment	Normal
(Hebert & Lupien 2007)	18	Endocrine	HPA axis	Reactive cortisol	Trier Social Stress Task	Decreased
(Hebert & Lupien 2009)	20	Endocrine	HPA axis	Reactive cortisol	Noise exposure	Decreased
(Simoens & Hebert 2012)	21	Endocrine	HPA axis	Reactive cortisol	Dexamethasone suppression test	Decreased
(Kim et al. 2014)	344	Endocrine; ANS	HPA axis; Sympathetic branch	Cortisol; NE; Epi; 5-HIAA	Baseline assessment	Normal; Normal; Normal; Normal
(Alsalmán et al. 2016)	10	ANS; Endocrine; Immunologic	Sympathetic branch; HPA axis; immune response	α -amylase; Reactive cortisol; Neopterin	Mental arithmetic task	Decreased; Normal; Normal
(Koc et al. 2016)	54	Metabolic	Oxidative metabolism	TOS; TAS; OSI; PON	Baseline assessment	Increased; Decreased; Increased; Decreased
(Betz et al. 2017)	19	ANS	Sympathetic branch	HR; HRV	Mental arithmetic task	Decreased; Normal
(Ylikoski et al. 2017)	97	ANS	Parasympathetic branch	HRV	Transcutaneous vagal nerve stimulation	Increased
(Coskunoglu et al. 2017)	52	Immunologic; Metabolic	Immune response; CNS metabolism	BDNF	Baseline assessment	Decreased
(Yasar et al. 2017)	80	Metabolic	Trace elements metabolism	Zn; Cu; Pb	Baseline assessment	Normal; Decreased; Normal
(Celik & Koyuncu 2018)	35	Metabolic	Oxidative metabolism	TOS; TAS; OSI; LOOH; NTL; DL	Baseline assessment	Increased; Decreased; Increased; Increased; Decreased; Increased
(Pawlak-Osinska et al. 2018)	51	Metabolic	Oxidative metabolism	GSH; GPx plasma; GPx RBC; GST; SOD; MDA; NO ₂ ⁻ /NO ₃ ⁻ ; CP	Baseline assessment	Increased; Decreased; Decreased; Increased; Decreased; Increased; Increased; Normal
(Ekinci & Kamasak 2019)	25	Metabolic	Oxidative metabolism	TOS; TAS; SPEA; OSI	Baseline assessment	Increased; Normal; Increased; Increased
(Ensari et al. 2019)	40	Metabolic	Oxidative metabolism	Apelin	Baseline assessment	Decreased

TNF – tumor necrosis factor; α – alpha; IL – interleukin; HPA – hypothalamic-pituitary-adrenal; ANS – autonomic nervous system; NE – norepinephrine; Epi – epinephrine; 5-HIAA – 5-hydroxyindoleacetic acid; TOS – total oxidant status, TAS – total antioxidant status; OSI – oxidative stress index; PON – paraoxonase-1; HR – heart rate; HRV – heart rate variability; BDNF – brain-derived neurotrophic factor; Zn – zinc; Cu – copper; Pb – lead; LOOH – lipid hydroperoxide; NTL – native thiol level; DL – disulphide level; GSH – glutathione; GPx plasma – glutathione peroxidase activity; GPx RBC – erythrocyte glutathione peroxidase activity; GST – glutathione S-transferase; SOD – superoxide dismutase; MDA – malondialdehyde; NO₂⁻/NO₃⁻ – concentration of nitrate/nitrite; CP – ceruloplasmin oxidase; SPEA – serum prolidase enzyme activity

The psychological understanding of why tinnitus becomes problematic in a small proportion of patients suggests that in those cases, it acquires a negative emotional significance through maladaptive cognitive appraisal and dysfunctional processes in the ANS. Thus, the negative, catastrophic interpretations of the tinnitus percept are sustained and habituation to the tinnitus fails (Hallam et al. 1988, McKenna et al. 2014).

CONCLUSION

Tinnitus has become a source of increasing health concern affecting all strata of the public, manifesting with comorbid psychological stresses. It has unknown pathophysiology and only a few available therapeutic measurements. The aim of clinical assessment of tinnitus sufferers is to determine the potential etiological factor that could lead to tinnitus. A large number of factors implicated in tinnitus are unpreventable. However, psychological stress is not one of them and could be successfully treated through otopsychiatric programs. Unfortunately, psychological comorbidities are often neglected with the specialist giving medications for tinnitus alone and when improvement is not noticeable by the patients eventual result is disappointment and frustration. Therefore, the close collaboration of the audiologist, psychiatrist, psychologist and psychotherapist is important for the effective treatment of these patients. Additionally, future tinnitus studies should focus on research of neuroendocrine, ANS, immunologic and metabolic disturbance, as it could give new insight into pathophysiology and potential pharmacological targets in the case of tinnitus.

Acknowledgements: None.

Conflict of interest: None to declare.

Contribution of individual authors:

Jure Pupić-Bakrač contributed to the design of the study, manuscript writing, literature searches, analyses and interpretation of data.

Ana Pupić-Bakrač contributed to the manuscript writing, literature searches and analyses, interlibrary requests, table design, stylistic and grammatical revisions to manuscript.

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