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REVIEW ARTICLE

The Association of Sleep Disorders, Obesity and Sleep-Related Hypoxia with Cancer

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Abstract: ***Background*:** Sleep disorders have emerged as potential cancer risk factors.

***Objective*:** This review discusses the relationships between sleep, obesity, and breathing disorders with concomitant risks of developing cancer.

***Results*:** Sleep disorders result in abnormal expression of clock genes, decreased immunity, and melatonin release disruption. Therefore, these disorders may contribute to cancer development. Moreover, in sleep breathing disorder, which is frequently experienced by obese persons, the sufferer experiences intermittent hypoxia that may stimulate cancer cell proliferation.

***Discussion*:** During short- or long- duration sleep, sleep-wake rhythm disruption may occur. Insomnia and obstructive sleep apnea increase cancer risks. In short sleepers, an increased risk of stomach cancer, esophageal squamous cell cancer, and breast cancer was observed. Among long sleepers (>9 hours), the risk of some hematologic malignancies is elevated.

***Conclusion*:** Several factors including insomnia, circadian disruption, obesity, and intermittent hypoxia in obstructive sleep apnea are contributing risk factors for increased risk of several types of cancers. However, further studies are needed to determine the more significant of these risk factors and their interactions.

Keywords: Cancer, risk factors, obesity, sleep, sleep apnea, intermittent hypoxia.

1. INTRODUCTION

1.1. Obesity as a Cancer Risk Factor

Among the various exogenous and endogenous risk factors for carcinogenesis, obesity plays a major contributing role [1-3]. Meta-analyses reveal that adiposity is correlated with various cancers including colorectal, breast, ovary, endometrium, kidney, gastric cardia, pancreas, biliary tract, esophageal adenocarcinoma, and multiple myeloma [4]. Moreover, the International Agency for Research on Cancer listed thyroid gland cancer, liver cancer, and meningioma, among pathologies associated with excess body fat [5]. Additionally, it has been noted that breast cancer along with colon cancer and endometrium cancer in women of postmenopausal age is associated with high body mass index (BMI) [6]. Therefore, various possible mechanisms have been proposed to correlate obesity and cancer.

Previous studies indicate that obesity causes oxidative stress, lowering antioxidant defense [7, 8]. Furthermore, obesity-related oxidative stress and obesity-related chronic low-grade inflammation may induce DNA damage and inhibit DNA reparative processes that may contribute to cancer cell growth [8]. There is evidence linking cancer develop-

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ment with the inappropriate secretion of adipokines, *i.e.* hormone-like substances produced by adipocytes, in obese individuals [9]. For example, adiponectin secretion is reduced in obesity; and low levels of this molecule have been associated with cancerogenesis [10, 11]. A recent meta-analysis revealed that the concentration of adiponectin in the serum was associated with diminished cancer risk for breast, colorectal, and endometrial cancers (odds ratio (OR) 0.7; 95% confidence interval (CI), 0.6-0.80) [12, 13]. On the other hand, the increased concentration of leptin has been shown to promote the proliferation of cancer cells [14-16]. In this regard, the same meta-analysis confirmed a positive association between leptin serum concentration and cancer risk (OR 1.26; 95% CI 1.05-1.51) of endometrium and kidney cancers [12]. Finally, the term "adiponcosis" was introduced to indicate the potential pathogenic association between obesity and cancerogenesis [17].

Obesity is correlated with sleep problems; however, there appears to be a bidirectional influence: obesity may lead to poor sleep and vice versa [18-21]. As but one example, obstructive sleep apnea (OSA) is the most common breathing disorder during sleep, and in the vast majority of cases, it is correlated with obesity [22]. OSA causes numerous pathophysiological consequences, including sleep fragmentation, sleep deprivation, disturbances of sleep architecture, intermittent hypoxia, autonomic system dysfunction, chronic inflammation, oxidative stress, and cardiovascular disturbances [23-26]. Combined results suggest that there is a relation between obesity, sleep problems, and cancer. These 3 conditions have become global epidemics [27-32]. In the present review, we analyze some recent studies focusing on the associations between sleep disorders, obesity, and cancer risk.

2. SLEEP DISORDERS IN CANCER PATIENTS

Sleep disturbances are among the common symptoms experienced by patients with different kinds of cancer [33]. Sleep quality is poor in cancer patients according to the Pittsburgh Sleep Quality Index [34], Questionnaire Core-30 developed by the European Organization for Research and Treatment of Cancer [35], or by polysomnography [36]. The study performed with the use of actimeters and sleep diaries in women with advanced breast cancer obtained a negative correlation with sleep quality [37]. However, the association of cancer and the quality of sleep needs further study [38].

It has been hypothesized that cancer disrupts homeostatic mechanisms in the brain leading to associated sleep problems. The molecules that are associated with cancer may influence sleep through somnogenic or anti-somnogenic actions. These molecules are interleukin-ß, interleukin-6, interleukin-4, interleukin-10, tumor necrosis factor (TNF), transforming growth factor ß, ghrelin and leptin [39]. Importantly, sleep problems in cancer patients may be regarded not only as a consequence of cancer or its treatment but also as one of the main risk factors for its development (Fig. **1**).

3. SLEEP DURATION AND CANCER RISK

Previous studies revealed a correlation between short sleep duration and decreased immunity [40]. Insufficient sleep correlates with increased levels of circulating TNF-α [41]. The up-regulation of TNF-α mRNA [42], as well as the activation of the transcription factors NF-κB in peripheral blood mononuclear cells, indicate a genomic response to inadequate sleep [43]. In humans, sleep deprivation leads to a decrease in the number of natural killers cells (NK) that play an important role in controlling cancer development [44]. It has been reported that sleep-deprived mice develop pulmonary metastasis earlier than normal mice with the same disease [45]. In addition, there is a decrease in NK cells, CD8+T cells, and cytotoxicity during sleep deprivation in the cancer microenvironment [45]. However, either abnormally short or long sleep durations were found to be associated with increased cancer risk.

In short sleepers, *i.e.* in patients sleeping 5-6 hours as compared with sleeping 7-8 hours, increased risk of stomach cancer was detected in the study encompassing 173,327 men (HR 1.29; 95% CI 1.05-1.59) [46]. The study involving 527 patients revealed significantly increased risk for esophageal squamous cell cancer associated with short sleep duration, *i.e.* <7 hours (OR 3.18; 95% CI 1.55-6.53) [47]. The risk of breast cancer was more than doubled (HR 2.1; 95% CI 1.12-3.59) in women younger than 60 years and reporting short sleep duration [48]. In a prospective study, the risk of estrogen-negative/progesterone-negative breast cancer was increased in black women sleeping <8 hours and more than doubled in those sleeping 6 hours (OR 2.22; 95% CI 1.19-4.12).

However, in assessing the entire population, the association between sleep duration and breast cancer was not confirmed [49]. Short sleep duration (<6 hours) associated with increased risk of breast cancer was confirmed (OR 1.53; 95% CI 1.10-2.12) [50].

But long sleep duration (>9 hours) was also found to be significantly associated with an increased risk of breast cancer (OR 1.59; 95% CI 1.17-2.17) [50]. Lower risk of hormone-related cancers, including breast cancer (HR 0.79; 95% CI 0.65, 0.97) was previously reported among long sleepers [51]. However, a recent large population-based study involving 5790 breast cancer patients did not provide evidence of a relation between sleep duration and breast cancer. This same study found a clear association with obesity [52]. Another study encompassing 4869 patients with colorectal cancer showed increased cancer mortality associated with short sleep duration (<5 hours) in the pre-diagnosis period [53]. However, a meta-analysis of different studies encompassing 723337 persons revealed that long sleepers were at greater risk of colorectal cancer (HR 1.29; 95% CI 1.09-1.52) [51]. Furthermore, a study encompassing 123858 women in the United States showed an increased risk of non-Hodgkin lymphoma in long sleepers (>9 hours) compared to those sleeping 7-8 hours (HR 1.45; 95% CI 1.00-2.11) [46]. Long sleep duration (>9h) was confirmed to be associated with non-Hodgkin lymphoma (hazard ratio, HR, 2.14; 95% CI 1.14-4.01) and other hematologic neoplasms (HR 1.70; 95% CI 1.03-2.82), in the study of 45984 adult Canadians [54].

In the general population, all-cancer mortality is weakly but significantly associated with abnormal sleep duration, both short sleep (five hours or less) and long sleep (>8 hours). This was reported in a meta-analysis of 14 cohort

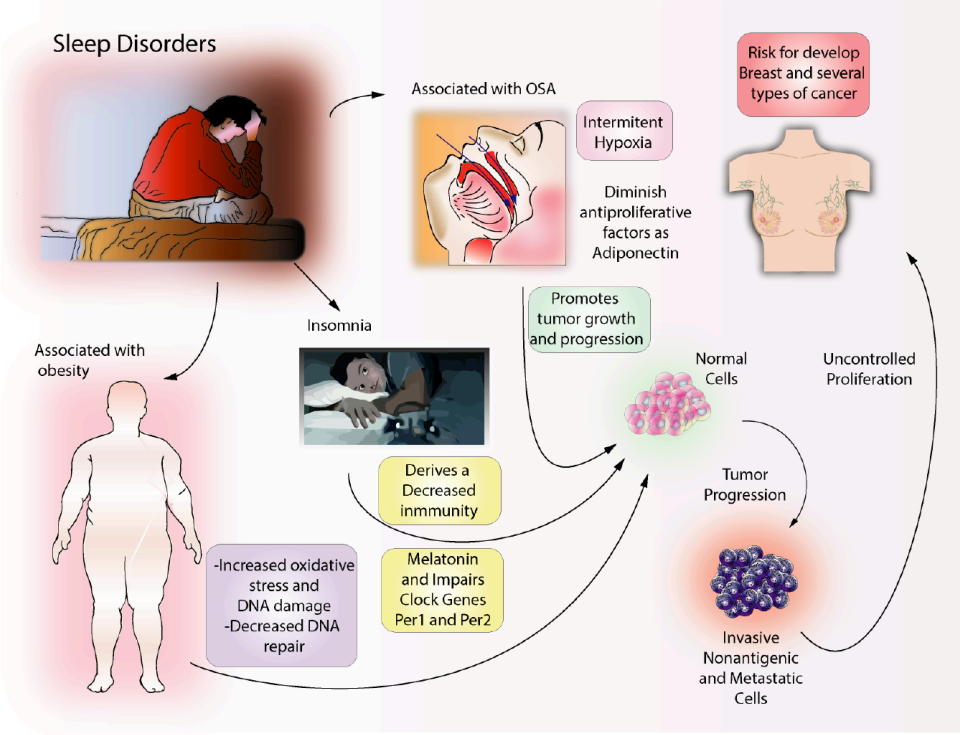

Fig. (1). Sleep disorders and associated diseases linked to cancer risk. Obesity is a well-known condition associated with cancer. Obesity increases oxidative stress in the body and induces DNA damage. In turn, DNA damage may promote oncogenic processes. Insomnia is a complex condition that may result in depression of the immune system and is associated with impaired melatonin secretion and regulation of clock genes. Obstructive Sleep Apnea may cause intermittent hypoxia with the resulting alteration of adiponectin, a key antiproliferative factor. It is possible obesity, insomnia, and OSA increase the risk for the development of several types of cancer including, breast, prostate, thyroid, gastric, and lung cancer. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

studies [55]. However, after taking into account 24-hour sleep-wake pattern, the prevalence of cancer in elderly persons (on average 74 years old) in Chinese general population appeared to be lower (OR 0.48; 95% CI 0.26-0.85) in those sleeping long at night with additional daytime naps as compared with persons sleeping shortly at night with additional daytime naps [56].

4. SLEEP-WAKE RHYTHM ABNORMALITIES AND CANCER RISK

There is evidence of an association between circadian rhythm abnormalities and cancer development. Clock genes control the process of daily physiological changes associated with circadian rhythm. Abnormal expression of clock genes like per 1, per 2, and different cyclins that regulate cell proliferation as well as cell apoptosis may contribute to the development of cancer [57, 58]. Disturbances in the expression of clock genes are linked to cancer cells' uncontrolled proliferation [57]. Both over- and under-expression of different clock genes were found in prostate cancer [59], non-small-cell lung cancer, kidney, liver, colon, and pancreatic cancers [60, 61].

The association between sleep-wake disruption and cancer development may be a result of melatonin release disruption. Melatonin, a hormone of the pineal gland, is produced in a cyclic rhythm depending on exposure to darkness and light and in normal conditions achieves its highest levels during nocturnal hours [62]. Melatonin has recently emerged as a strong suppressor in cancer development [63]. Excess light at night may affect the normal physiological nocturnal increase in melatonin concentrations, causing circadian disruption that may be one of the factors associated with carcinogenesis [64].

Melatonin acts through numerous pathways including actions against tumor cells proliferation and metastatic formation as well as against concomitant inflammation [65]. The anti-tumorigenic action of melatonin is related to its antioxidant properties [66]. In this aspect, the antioxidant activity of melatonin leads to destabilization of HIF-1α protein and to angiogenesis inhibition induced by hypoxia, as shown by *in vitro* studies of colon cancer cell line [67]. Adequate levels of melatonin may have protective effects against the development of cancer through its action as an inducer of apoptosis in cancer cells [68].

Another meta-analysis revealed low concentrations of melatonin in breast cancer patients (n=963) as compared with healthy controls. This finding suggests decreased levels of melatonin may be a risk factor for breast cancer [69]. Additionally, possible synergistic effects of melatonin combined with chemotherapy have been postulated in non-small-cell-lung cancer [65], pancreatic cancer [68], skin cancer [70], ovarian cancer [71], colorectal cancer [72], and other cancers, including breast, hepatic, and prostate cancer [73].

The circadian disruption caused by shift work or transoceanic flights has been classified by the International Agency for Research on Cancer as a probable carcinogenic factor [74]. However, a direct relationship between shift work, chronodisruption, and carcinogenesis in humans remains to be fully elucidated [75, 76]. A meta-analysis of 24 articles revealed that nurses' night shift work constituted a risk factor for various metabolic and cardiovascular disorders, as well as risk of breast cancer [77]. However, a study performed in the United Kingdom involving 2059 women with breast cancer revealed no risk of this neoplasm associated with night shift work, except a slight, albeit significant ($p<0.05$) trend associated with the average duration of night work per week [78].

Similarly, the results of a study conducted in Canada encompassing 406 patients with epithelial ovarian cancer did not confirm an increased risk of neoplastic disease associated with night shift work. However, an increased risk of epithelial ovarian cancer was found in the patients with the longest period during which night shift work was performed and women who self-identified themselves as "morning" chronotype (OR 1.64; 95% CI 1.01-2.65) [79]. These studies suggest additional research is needed to better understand the relationship between sleep disorders and cancer incidence.

5. INSOMNIA AND CANCER RISK

The risk of breast cancer was found to be increased in patients with insomnia (HR 1.73; 95% CI 1.57-1.90) [80]. Patients with breast cancer suffered from sleep disturbances including 8 percent insomnia syndrome prior to diagnosis [81]. Another study with 33332 women, who were followed for a mean 14.7 years, indicated that insomnia was a risk factor of breast cancer in patients suffering from all three symptoms of insomnia: difficulty initiating sleep, difficulty maintaining sleep, and having non-restorative sleep (HR 2.38; 95% CI 1.11-5.09) [82]. A retrospective study encompassing 11021 patients with insomnia detected an increased risk of breast cancer as compared with the population of age-matched women who did not complain of insomnia, adjusted HR 1.43; 95% CI 1.10-1.84. This study also found no relationship to hypnotic use [83].

On the contrary, the association of insomnia and increased risk of cancer was found in patients using sleeping pills in Korea. A study showed significantly increased risk for thyroid cancer, breast cancer, ovarian cancer, and lung cancer in women using any sedative-hypnotic drug as compared to non-users. There also was a significantly increased risk for prostate cancer, brain cancer, and lung cancer in men using any sedative-hypnotic drug as compared with non-users [84].

Finally, in a recent retrospective case-control study encompassing 7355 patients, the authors revealed that insomnia diagnosed prior to the diagnosis of oncologic disease was associated significantly with colorectal cancer (adjusted OR 1.54; 95% CI 1.35-1.75) [85].

6. SLEEP BREATHING DISORDERS, NOCTURNAL HYPOXIA, AND CANCER RISK

Typical features of OSA include repetitive episodes of complete (apnea) or partial (hypopnea) collapse of the upper airway. The apnea-hypopnea index (AHI) is used to gauge severity based on the mean number of events per hour of sleep: AHI >30/h indicates severe, >15/h indicates moderate, and AHI>5/h indicates mild form of OSA [86]. Although the main symptom of OSA is excessive daytime somnolence, about one-third of patients complain of disturbed sleep and about one-fourth of patients neglect any important symptoms despite the presence of OSA. Most sufferers of OSA remain undiagnosed and untreated [87].

Increasing attention has been paid to the possible link between OSA and cancer risk [88-92], although the first information linking intermittent hypoxia with cancer onset was reported earlier [93].

Experimental studies with mice showed that intermittent hypoxia (mimicking OSA) led to increased tumor growth compared with mice breathing room air. This effect was mediated by vascular endothelial growth factor [94, 95]. The study revealed that OSA with concomitant intermittent hypoxia and sleep fragmentation promoted tumor growth [96]. In mice bearing human subcutaneous melanoma xenografts, intermittent hypoxia exposure accelerated tumor progression and was associated positively with both metastases formation and resistance to treatment [97]. This effect is considered to be through the activation of the hypoxia-inducible factor (HIF) 1-alpha pathway [98]. In a group of 443 patients with melanoma who subsequently underwent polysomnography, the more invasive form of melanoma was associated with higher AHI and oxygen desaturation index, especially in patients younger than 56 years [99].

Diminished immune function and increased sympathetic tone may be responsible for increased oncogenesis in subjects submitted to intermittent hypoxia [89]. The injection of lung cancer cells in mice exposed to intermittent hypoxia led to the increased expression of programmed death-ligand 1 (PD-L1) as compared with the lung cancer cells injected in mice living in normal conditions [100]. Intermittent hypoxia mimicking OSA resulted in increased PD-L1 expression on splenocytes in young mice, but not in older mice [101]. In OSA patients, programmed cell death-1 (PD-1) receptor and its ligand (PD-L1) are overexpressed on the cells taking part in immune reactions, leading to a reduction in CD8+ T cells and thereby facilitating cancer growth [102]. Intermittent hypoxia in patients with OSA is shown by an increase in PD-L1 expression on monocytes and an increase in PD-L1 concentration in plasma. Again an age-related factor was revealed only in relatively young subjects (*i.e.* <55 years of age) [101].

Intermittent hypoxia also reduces serum concentrations of adiponectin as shown in experimental animal studies [103, 104]. Adiponectin is considered an anti-proliferative adipokine, preventing cancer growth [105, 106]. Thus, lowered concentrations of adiponectin in the serum of OSA patients partially may explain the increased susceptibility to cancer development. Concentrations of adiponectin are lower in OSA patients than in the controls [107]. These are associated with the severity of OSA [108] and independent from obesity presence [109].

The proteome of circulating extracellular vesicles (EV) was detected on sleep apnea models [110, 111] and in pa-

tients with sleep-disordered breathing [112, 113]. The biological function of EV may be associated with altered immune response in the course of cancer development and progression [114]. Heterogeneous EV composition encompasses proteins, RNA and DNA material that can be transported to remote body cells [115]. EV may be submitted to the changes in their proteome compositions in response to multiple stimuli, including oxidative stress and hypoxic stress, as well as heat shock and nutrient stress [116]. Chronic intermittent hypoxia, as seen in OSA patients, mainly contributes to the increase of inflammatory proteins in circulating microvesicles [117]. Experimental data from studies using human adenocarcinoma cells as well as exosomes from mice submitted to intermittent hypoxia and from OSA patients revealed that intermittent hypoxia led to the release of exosomes into the bloodstream thus enhancing carcinogenic potential through cell proliferation and migration. These results strongly suggest that circulating exosomes in OSA patients may influence the progression of cancer [110].

The association of OSA and cancer has been explored in epidemiological and clinical studies over the past few years. The results are equivocal. In a pioneering study, the observation of 1522 patients from the Wisconsin Sleep Cohort observed for 22 years revealed a significantly increased risk of cancer mortality associated with OSA, especially in patients with severe OSA and high ODI (HR 4.8; 95% CI 1.7-13.2) [118]. In a 20-years retrospective study of 386 persons without a history of cancer or stroke, cancer mortality was significantly increased in moderate to severe OSA (HR 3.4; 95% CI 1.1, 10.2) [119]. Another study encompassing 5427 patients diagnosed with suspected OSA at the time of observation (median of 4.5 years), showed that cancer mortality was associated with OSA severity (both with AHI and hypoxemia), especially in patients younger than 65 years of age. For the logarithmically transformed percent of the time during sleep spent with SaO_2 below 90% (TSat90) HR was 1.73 (95% CI 1.23-2.4) and for upper *versus* lower TSat90 tertile HR was as high as 14.4 (95% CI 1.85-116.6) [120]. Some studies, however, did not show increased mortality associated with the occurrence of OSA in cancer patients [121]. Most of the studies focused on an increased incidence of cancer in OSA patients than controls [122-124]. The main symptom of OSA (*i.e*. daytime sleepiness) was associated with an increased risk of cancer study in the persons <50 years of age (HR 4.09; 95% CI 1.58-10.55) [125]. Moreover, there is a high incidence of OSA among newly diagnosed lung cancer patients [126] and positive results of lung cancer screening are significantly associated with nocturnal hypoxemia resulting from OSA [127].

Recently, a group of 66 patients with lung cancer with sleep apnea revealed moderate-to-severe OSA (AHI>15/h) in 50 percent of patients [128]. In a case-control study based on the results of colonoscopy, the risk of colorectal cancer was significantly increased in OSA patients (OR 3.03; 95% CI 1.44-6.340 [129]. Furthermore, a study encompassing 7355 patients revealed that sleep apnea present before the diagnosis of oncologic disease was significantly associated with colorectal cancer (adjusted OR 1.76; 95% CI 1.54-2.00). In addition, any sleep disorder with concomitant depression was the strongest factor associated with colorectal cancer (adjusted OR 5.69; 95% CI 4.01-6.98) [85].

Intermittent hypoxia in OSA may increase cancer risk, as shown by meta-analysis [130]. A study of around 5.6 million persons revealed an increased risk of selected neoplasms (*e.g*., pancreatic, kidney, and melanoma), but a decreased risk of other cancers (*e.g*., colorectal, breast, and prostate cancers) in OSA patients [121]. A Canadian study with 9629 patients, followed-up for a median of 7.8 years, showed that there was no increase in the risk of cancer in association with OSA; neither with AHI or with desaturation [131]. Finally, a recent case-cohort study in a group of 1162 patients did not find an increased risk of cancer in moderate to severe OSA patients [132]. These combined results strongly suggest a relationship between severe OSA and sleep apnea with the incidence of several types of cancer.

HYPOTHESES, FUTURE DIRECTIONS, AND CONCLUSION

Research studies and meta-analyses reveal a possible link between obesity, sleep disorders, and increased risk of cancer. These factors, along with other pathologies, warrant additional studies, especially in high-risk groups. The aim is to formulate diagnostic and therapeutic procedures that are informed by these correlated factors.

In addition, some recent studies reported an inverse association between neuro-degenerative disorders like Alzheimer's disease with cancer incidence or mortality [133, 134]. Thus, additional studies regarding possible markers of early stages of neurodegenerative or proliferative disorders in persons with chronic sleep disturbances or obesity are needed in order to establish a clear correlation between neuro-degeneration and cancer development.

Another question is related to the possible accumulation of co-occurrence risk factors of cancer with other diseases. For example, patients with chronic obstructive pulmonary diseases (COPD), often smokers or ex-smokers, are at risk of developing lung cancer independently from the degree of bronchial obstruction [135-137]. COPD patients are especially at risk of developing lung cancer if they are obese, as recently observed in a study with a group of 433 patients followed up for 9 years (HR 3.3; 95% CI 1.3-8.5) [138]. Obesity in COPD patients, in turn, may be associated with non-diagnosed sleep disorders [139, 140]. The potential additive risk factors such as a combination of smoking, COPD, and obesity remain unaddressed in current literature.

AUTHORS' CONTRIBUTIONS

Anna Brzecka (AB), Karolina Sarul (KS), Tomasz Dyła (TD), Marco Avila-Rodriguez (MAR), Ricardo Cabezas-Perez (RCP), Vladimir N. Chubarev (VNC), Nina N. Minyaeva (NNM), Sergey G. Klochkov (SGK), Margarita E.Neganova (MEN), Liudmila M. Mikhaleva (LMM), Siva G. Somasundaram (SGS), Cecil E. Kirkland (CEK), Vadim V. Tarasov (VVT), Gjumrakch Aliev (GA) conceptualized and designed the study. AB, KS, TD, MAR, RCP, and GA collected and analyzed the data. AB, KS, TD, MAR, RCP, VNC, SGK, MEN, LMM, SGS, CEK, VVT, and GA discussed the analyses, the results, and their interpretation, and wrote the original manuscript draft. All authors reviewed and approved the manuscript before submission.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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