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REVIEW PAPER

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Gastro-esophageal reflux and obstructive sleep apnea – is there a link?

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ABSTRACT

Introduction. The epidemic of obesity has led to an increase in the occurrence of obstructive sleep apnea and gastro-esophageal reflux disease. The mechanism of development of gastro-esophageal reflux disease is multifactorial, and studies conducted in the last decade have shed new light on the causes of its development in patients with sleep apnea and obesity.

Aim. The aim of the study was to discuss the mechanism of development of gastro-esophageal reflux disease is multifactorial, and studies conducted in the last decade have shed new light on the causes of its development in patients with sleep apnea and obesity and the dysfunction of the lower esophageal sphincter.

Material and methods. An analysis of literature regarding gastro-esophageal reflux and obstructive sleep apnea.

Results. In obstructive sleep apnea and obesity, high levels of cytokines and insulin resistance are observed, resulting in disorders in the levels of ghrelin – a hormone responsible for normal gastrointestinal motility.

Conclusion. The effect of deviations in the ghrelin profile on the development of gastro-esophageal reflux disease remains a matter for further research.

Keywords. gastro-esophageal reflux, ghrelin, obesity, obstructive sleep apnea

Introduction

For several decades, an epidemic of obesity has been one of the major health problems in many countries. This results, among other things, in an increase in the occurrence of gastro-esophageal reflux disease (GERD) and obstructive sleep apnea (OSA).[1-3] GERD affects from 8-33% of the population and is defined as a disorder in which the stomach contents flow back up into the esophagus, causing complaints and/or leading to the development of complications.[4] Due to an increasing frequency of the occurrence of GERD-related esophageal adenocarcinoma, an effective prevention of GERD is an increasingly important health problem.[5] GERD most frequently occurs in males and persons with an excessive body weight, whereas inadequate diet, an intensive physical effort, some medicines, and the presence of the esophageal hiatal hernia favour its development.[6] Complaints associated with gastro-esophageal reflux (GER) include a burning sensation in the chest, regurgitation, epigastric pain, empty burping, and discomfort during swallowing.

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In addition, the stomach contents which flow backwards causing extra-esophageal symptoms, such as hoarseness and chronic cough. GER leads to the development of esophagitis and changes of the type of metaplasia, dysplasia and ultimately esophageal cancer.[4] In order to prevent GER, it is recommended to reduce body weight, discontinue smoking, modify diet, and resign from eating before bedtime. In therapy, prokinetic drugs are used, and drugs that suppress gastric acid secretion, while in the case of the therapy being ineffective, or the presence of complications, surgical treatment is considered.[7]

OSA is the most frequent breathing disorder during sleep, and concerns up to 7-20% of adults.[3] In OSA, there occurs a closure or significant narrowing of the airways while sleeping, resulting in an intensified breathing and waking-up effort. Multiple episodes of apnea cause drops in blood oxygen saturation levels and an increase in sympathetic tone, whereas episodes of waking-up result in sleep fragmentation and decrease in the effectiveness of sleep.[8] It was confirmed that an increase in heart rate and arterial blood pressure, an effect of oxidative stress, and elevation of parameters of the inflammatory state, lead to the development of complications within the cardiovascular system.[9] Clinical symptoms of OSA may be divided into those related with the occurrence of episodes of breathing cessation, pauses in breathing during sleep, snoring and waking-up with the sensation of gasping and, resulting from the lack of effectiveness of sleep, excessive sleepiness in the daytime, chronic fatigue, deterioration of cognitive functions, low mood and morning headaches. The main risk factors of OSA include excessive body weight, male gender, age over 40, large neck circumference and anatomical facial malformations.[10] The diagnosis is made based on the result of polysomnography (PSG), and the degree of severity depends on the value of apnea and hypopnea events (AHI). The strategy of sleep apnea therapy depends on the degree of its severity and concomitant diseases. Apart from the normalization of weight and improvement of sleep hygiene, the use of CPAP therapy is considered as the basic method of treatment which, by maintaining positive airway pressure, prevents collapse of the walls of the throat and maintains patency of the upper airway. In selected cases, preventive treatment brings about good outcomes, consisting mainly in the plasty of the soft palate.[8]

Gastro-esophageal reflux in the course of OSA and in obesity

In OSA, especially in its severe forms, GERD is a serious health problem.[11,12] It remains a matter of debate to what extent GERD is related with OSA, and to what degree it results from common with obesity risk factors.[13-15] The relationship between the two disorders is indicated by a study in which a beneficial effect of the CPAP therapy was confirmed on the course of both nocturnal and daytime GERD by improvement of the function of the lower esophageal sphincter (LES).[16,17] In the past, the occurrence of GER in OSA was explained by drops of pressure in the chest during futile respiratory efforts accompanying apnea. Due to the development of diagnostic techniques and possibilities to perform simultaneously esophageal pH-metry and impedance during PSG, the mechanism of GER has been described among patients with OSA. In their study, Penzel et al. observed the symptoms of GERD in all patients with OSA; however, during simultaneous performance of PSG and esophageal pH-metry, no time relationship was found between the occurrence of the episodes of apnea and esophageal pH drops.[18] Kuribayashi et al. also observed a more frequent occurrence of GER in the group of patients with OSA. Due to simultaneous performance of PSG with manometry and pH-metry, it was indicated that in the pathogenesis of nocturnal GER in OSA, the transistent lower espohageal sphincter relaxation (TLESR) plays the major role, and not the accompanying changes in the pressure gradient between the esophagus and the stomach. The researchers found that TLESR occurred more frequently in patients with OSA, and their number correlated with the number of reflux episodes.[19] In their subsequent study, Kuribayashi et al. observed that during the period of apnea episodes, the reflux of the gastric contents into the esophagus was prevented by compensatory tone increase on the level of gastro-esophageal junction and upper esophageal sphincter.[20] In turn, Xiao et al., in the group of patients with OSA, apart from the observation of a more frequent occurrence of acidic GER, observed an impaired cleaning of the esophagus from refluxed gastric contents.[21]

Obesity, especially of the visceral type, is an important risk factor for GERD. It has been confirmed that an excessive amount of visceral fat (VF) better correlated with the occurrence of GERD that the BMI value or body weight.[14,22-24] The mechanism of GER in obesity is complex and results mainly from a decreased tone and increased number of LES relaxations. An elevated intra-abdominal pressure, a high pressure gradient between the stomach and esophagus, and bad eating habits, were considered as less important factors.[25,26] The role of inflammatory parameters remains unclear, the value of which in obesity is elevated and correlates with the intensity of inflammatory changes in the esophagus. In their study, Nam et al. evaluated the relationships between the occurrence of GERD, and values of inflammatory cytokines and adipokines associated with VF. A significant relationship was observed between the amount of VF, leptin level, and occurrence of inflammatory changes in the esophagus. A similar relationship was found for the level of inflammatory cytokines IL-6 and IL-1; however, the consideration of the amount of

VF and leptin level resulted in cytokines no longer being significant as independent factors related with GERD.[27] Tseng et al., in their study, confirmed morning levels of peptide YY (PYY), ghrelin, leptin and adiponectin between patients with GERD and a control group. In the group of patients with GERD, the morning PYY levels were lower, while the levels of ghrelin slightly higher; however, the observed differences were statistically insignificant.[28]

Obesity is the most important factor for the development of GERD, whereas OSA increases its severity and frequency of occurrence.[15] In both disorders, GERD is the result of LES dysfunction; however, the cause of this dysfunction remains unknown.[19,25] The disorder common for OSA and obesity is an increase in the level of proinflammatory cytokines.[29,30] The concentrations of leptin, motilin, obestatin, adiponectin and resistin are related with the amount of adipose tissue in the body; nevertheless, no significant effect of OSA on their values has been observed.[31-33] Both OSA and obesity exert an effect on the levels of ghrelin.[34] Ghrelin stimulates intestinal motility and accelerates gastric emptying; therefore, its deficiency may result in a prolonged retention of the gastric contents favouring the development of GER.

Ghrelin is a hormone produced mainly within the gastrointestinal tract which, together with obestatin, is produced from preproghrelin- a precursor encoded by the GHRL gene. After disconnection from the precursor, ghrelin- by means of ghrelin O- acetylotransferase- is subject to modification to an acylated form, considered as biologically active. Apart from the acylated form of ghrelin, a des-acylated form of ghrelin is distinguished, the role of which in the body is unknown.[35-37] In addition, the results of determinations of the forms of ghrelin using mass spectrophotometry suggest that all the ghrelin in the body is acylated, while the des-acylated form is an artefact formed in the course of the preparation of samples.[38] Ghrelin participates in the regulation of body energy, and through central effects causes an increased appetite, initiates the intake of meals, exerts an effect on the sensation of taste and the reward center.[39-41] It also participates in the regulation of the metabolism of carbohydrates (by exerting an effect on the levels of insulin and increase in insulin sensitivity), regulation of the sleep-wake rhythm.[42-44] It is credited with a beneficial effect on the cardiovascular system and anti-inflammatory effect.[45,46] The peripheral effects of ghrelin include the stimulation of motility of the gastrointestinal system, acceleration of emptying of the stomach and increase in the secretion of hydrochloric acid.[47] The concentrations of ghrelin show daily variability, its secretion into the blood is of a pulse character and is related with the consumption of meals and the sleep-wake rhythm. The highest levels of ghrelin in blood occur approximately 30 minutes before meals, and their values are proportional to the intensity of the feeling of hunger. After the meal, together with an increase in insulin level, the concentration of ghrelin decreases. At night, the level of ghrelin initially increases and remains on a relatively high level, whereas during the second part of the night it gradually decreases, to increase again before the consumption of breakfast.[39,42,43]

Ghrelin profile in the course of sleep disorders and eating disorders

With obesity, decreased ghrelin values in a daily rhythm are observed, also its amplitude and mean levels are lower, except for morning levels which, according to the majority of reports, are higher in individuals with a normal body weight.[39] One of the potential causes is hyperinsulinemia accompanying obesity. This is suggested by the results of a study in which a mealtime increase in the level of insulin, similar to administration of exogenous insulin, resulted in a decrease in the ghrelin level.[44] In turn, while losing weight, the reduction of calories in the diet is associated with an increase in the ghrelin levels, up to very high values observed in the course of anorexia nervosa.[39,48] The subsequent disorder potentially decreasing ghrelin values is an increase in the levels of inflammatory parameters observed in obesity. Ghrelin is considered as a factor inhibiting inflammatory state, in addition, decreased ghrelin levels accompany an elevation of inflammatory parameters in the course of rheumatoid arthritis and in the case of Takayasu's arteritis.[49,50] The lack of effective sleep is the subsequent factor related with disorders in the ghrelin level. The result of studies assessing the effect of sleep deprivation and OSA on the level of ghrelin vary; in the majority of observations an elevated fasting level of ghrelin is noteworthy, as well as its lower values during the first hours of sleep.[33,43,45,51] In their study, Spiegel et al. evaluated the effect of short-term sleep deprivation on diurnal levels of ghrelin and leptin in a group of healthy individuals. During the period when the study participants experienced sleep deprivation, higher diurnal ghrelin levels and lower leptin levels were observed, and these changes were accompanied by a greater feeling of hunger and an increased appetite.[52] In turn, Dzaja et al., in their study of persons subjected to sleep deprivation, did not observe any increase in ghrelin levels during the first hours of the night, while no differences in ghrelin values were observed during the day.[42] Motivala et al. in a conducted study found that nocturnal ghrelin values were lower in a group of patients with chronic insomnia, compared to the control group.[53] In their study, Takahashi et al. evaluated morning levels of acylated and des-acylated ghrelin in patients with OSA, and the effect of treatment using the CPAP therapy. In the group of patients with OSA, ghrelin values were higher, while a repeated assessment after one-month CPAP therapy showed a de-

crease in the level of acylated form of ghrelin, compared to the values observed in the control group.[54] Nevertheless, in a study by Weiying et al., in a group of patients with OSA, morning ghrelin levels were lower than those observed in the control group.[34] In turn, Papaioannou et al. examined patients with OSA and did not observe any deviations in the determinations of fasting ghrelin, and those performed at 22.30.[55] Similarly, in the study by Sanchez-de-la-Torre et al. conducted among patients with OSA, no differences were found in the daily ghrelin profile, compared to the control group.[32] Fluctuation in ghrelin levels, similar to obesity, may be secondary with respect to elevated levels of inflammatory parameters and insulin resistance, accompanying sleep deprivation and OSA.[30,51] Higher fasting ghrelin levels are associated with a stronger feeling of hunger; therefore, they may be responsible for the tendency towards consumption of a higher amount of calories observed among persons with sleep disorders.[52] Unfortunately, in patients with OSA, this mechanism, by increasing the calorific value of diet, may lead to an increase in body weight and further intensification of breathing problems during sleep.

Occurrence of GERD and ghrelin

The mechanism of the development of GERD is multifactorial. Observations carried out by Nataha et al. conducted on rats indicate the role of ghrelin in the occurrence of gastrointestinal motility disorders accompanying GERD.[56] Ghrelin stimulates intestinal peristalsis and accelerates the emptying of the stomach; therefore, its low values, through prolonged gastric emptying may play a role in the development of GERD.[57] This hypothesis has been supported by Agrawal et al., who after administration to three groups of patients subsequently ghrelin, capromorelin/ghrelin receptor agonist, and placebo, observed in the first two groups a significant reduction in the number of reflux episodes.[58] Similarly, in a study by Rubenstein et al, lower fasting ghrelin levels correlated with the occurrence of GERD.[59] In turn, in the previously mentioned study by Tseng et al. conducted in patients with GERD, morning ghrelin levels were higher than in the control group; however, this difference was statistically insignificant.[28] In a study by Eren et al. no relationship was found between fasting ghrelin values and the intensity of GERD.[60] The available studies do not consider the pulsating character of ghrelin secretion; therefore, an assessment in a daily profile would allow full determination of its importance for the development of GERD.

Conclusion

GERD is an important health problem among patients with OSA and obesity. In both disorders, LES dysfunction plays the major role in the pathogenesis of GERD. Ghrelin is responsible for gastric emptying; therefore, its low values may favour the development of GER. A decrease in nocturnal ghrelin levels observed in sleep deprivation and OSA, and in the case of obesity in the whole daily profile, may be responsible for a different course of GERD. For this reason, further studies and evaluation the role of ghrelin in the pathogenesis of GERD are recommended, especially in the context of LES function and esophageal motility.

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