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Saliva of obese patients – is it different?

Czy ślina osób otyłych jest inna?

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Summary

Obesity is a major public health concern that increases the risk of cardiovascular disease, type 2 diabetes and cancer. The incidence of obesity has increased significantly in recent years, not only in adults, but also in adolescents and children. This is evidenced by rapidly developing bariatric surgery, the most effective method of treating morbid obesity. Obesity is a multifactorial disease, and its pathogenesis is not completely understood. Numerous studies have been performed to clarify pathogenetic mechanisms, based mostly on blood and sometimes urine samples. Saliva is easily accessible and can be obtained non-invasively. Our aim was to review studies performed on saliva obtained from obese subjects in order to answer the title question.

Obese people have different composition of salivary bacteria. Changes in the concentration of sialic acid, phosphorus and peroxidase activity as well as a lower flow rate of stimulated whole saliva promote dental caries and periodontal disease. Concentrations of salivary uric acid, endocannabinoids and CRP are increased in obesity and may provide a useful index of cardiometabolic risk. Assessment of fasting salivary ghrelin might facilitate choosing the best type of bariatric surgery for a specific patient. A significant decrease in salivary cortisol in women with morbid obesity also seems interesting.

There is sufficient evidence to state that the saliva of obese and lean subjects is different. Saliva as an easily accessible research material seems promising, as shown by the few studies performed so far.

Keywords: **obesity • saliva • cortisol • ghrelin • uric acid • endocannabinoids • dental caries**

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Introduction

Obesity is a major public health problem worldwide. It is a complex metabolic disorder defined as a body mass index (BMI) ≥30 kg/m^2, often associated with cardiovascular diseases, insulin resistance, type 2 diabetes, dyslipidemia and cancer [9]. The incidence of obesity has increased significantly in recent years, making obesity a worldwide epidemic. According to the World Health Organization, by 2015 approximately 2.3 billion adults worldwide will be overweight and more than 700 million obese [22]. Increasing numbers of bariatric operations, the only effective treatment for morbid obesity, show the scale of the problem [20]. Overweight and obesity depend on: exogenous factors (including bad eating habits and insufficient or no physical activity) and genetic factors, possibly affecting regulation of hormones such as adiponectin, leptin and ghrelin [13,20,45].

Saliva is a secretion of minor and major salivary glands. The composition of saliva varies between individuals. On average, approximately 99.5% of the saliva is water, the remainder consisting of inorganic (0.2%) and organic (0.3%) compounds, as well as dead and living cells. Among the enzymes found in saliva, some are important for defense functions, such as lysozyme, the salivary peroxidase enzyme system or lactoperoxidase, while others are digestive enzymes such as salivary amylase, α-D-glucosidase, maltase, lipase and ribonuclease. Non-protein organic substances are: urea, creatinine, uric acid, amino acids, carbohydrates (such as glucose), lipids (including cholesterol), and corticosteroids (from parotid secretions).

Obesity increases the risk of systemic diseases, many of which are known to influence salivary glands and oral health. However, information on the impact of obesity on salivary gland function and oral health is limited.

The aim of this study was to review the current literature on saliva of morbidly obese people and assess its potential participation in the development of obesity and its associated diseases or a reflection of disturbances caused by obesity.

Obesity and cortisol

Cortisol, also called hydrocortisone, is the main representative of the steroids produced by the fasciculata layer of adrenal glands. The secretion of cortisol, known as the 'stress hormone', normally proceeds in pulses and is associated with the rhythm of sleep and wakefulness. Production of cortisol in the adrenal glands is regulated by adrenocorticotropic hormone (ACTH), produced by the pituitary gland [15]. The determination of cortisol in saliva is usually performed after a night dexamethasone inhibition test [10]. The assessment of cortisol in saliva is a common, non-invasive alternative or complement of determinations in blood and urine. However, it is important to avoid contamination, which can substantially distort the results. Only 0.25% contamination of saliva with blood causes excessive cortisol results [4]. Cortisol, as one of the non-esterified steroid hormones, readily enters the saliva in a mechanism of passive diffusion according to the gradient of concentration [4,33]. Available studies have shown a significant decrease in salivary cortisol concentration in women with morbid obesity (BMI> 40) compared to the control group. Furthermore, a correlation has been demonstrated between cortisol concentration in the plasma, in the saliva and BMI of patients [36]. A lower concentration of cortisol in saliva was also observed in children with overweight and obesity compared to lean children [23]. It should also be noted that obesity can result from continuous exposure to stress. Psychologically difficult situations cause uncontrollable binge eating disorder (BED) in which cortisol plays an important role. Continuous stimulation of the hypothalamic-pituitary-adrenal axis may result in serious neurobiological changes [25]. Interesting results were obtained by performing multiple measurements of cortisol in the saliva of obese subjects after bariatric surgery. The relation between binge episodes and concentration of cortisol in saliva was observed. In obese women with known BED, a decreased cortisol concentration in saliva was observed after bariatric surgery compared with obese women without binge attacks [25]. These results suggest differences in neuroendocrine regulation in obese patients.

Potential markers of obesity

Several studies have shown that an elevated concentration of uric acid in serum is associated with obesity, hypertension, and metabolic syndrome [26,32]. Soukop et al. [40] suggested that salivary uric acid may be a useful biomarker for noninvasive assessment of cardiometabolic risk. The study showed that the concentration of uric acid was significantly higher in patients with metabolic syndrome, regardless of the salivary flow rate compared to people with overweight or obesity, but without metabolic syndrome. The link between concentration of salivary uric acid and metabolic syndrome was stronger in women than in men. A correlation was also observed between serum and salivary uric acid, systolic and diastolic blood pressure, waist circumference, BMI, blood glucose, triglycerides, high-density lipoprotein (HDL) and the number of cardiometabolic risk factors [40].

The endocannabinoid system and its role in the regulation of energy balance seems an important mechanism leading to obesity and type 2 diabetes [7,12,24,29,37]. Matias et al. [29] measured endocannabinoids and N-acylethanolamines in fasting serum and saliva of patients with normal weight in comparison to obese subjects with insulin resistance. They found that obese people had higher concentrations of endocannabinoids and related N-acylethanolamines in saliva than plasma. Moreover, endocannabinoid 2-arachidonoylglycerol, N-arachidonoylethanolamide (anandamide) and N-acylethanolamine (oleoylethanolamide and palmitoyletha-

nolamide) had significantly higher concentrations in obese than in normal subjects. Lifestyle and weight loss significantly reduce the salivary concentration of N-arachidonoylethanolamide, which seems a possible marker of obesity [29].

Obesity is related to a higher risk of inflammatory diseases. C-reactive protein (CRP) is a sensitive marker of systemic inflammation [31]. Some reports indicate an increase in the concentration of CRP in the serum of obese children as compared to lean children [35]. It was also found that the concentrations of CRP in saliva of obese children are significantly higher than in children of normal weight [17,31].

One factor involved in the development of obesity is low concentrations of antioxidants. In obese individuals, a decreased concentration of antioxidants was observed not only in serum but also in saliva [8]. The opposite results were obtained in obese children, in whom the concentration of antioxidants in saliva was higher compared to children of normal weight. The authors explain the obtained results by the fact that the saliva was collected from obese children who came from families of high social status, who commonly followed a diet rich in plant nutrients and antioxidants [19].

Studies in recent years indicate that phosphate metabolism may be associated with the rotation of fat in adipocytes. The concentration of phosphate in the saliva may be an early marker of metabolic disorders associated with the development of obesity. A significant increase has been observed in salivary phosphate content in obese children compared with children of normal weight. Interestingly, no significant difference in concentrations of phosphate was observed in the plasma between the two groups of children. The reason for the increase of salivary phosphate concentration is not fully understood. It is known that the type II sodium-phosphate cotransporters (Na/Pi-2b) and type III sodium phosphate cotransporters, PiT1 and PiT2, which are involved in phosphate resorption in the kidney, are also present in the salivary glands. This may be connected with independent phosphate metabolism in the salivary glands with local regulation [21].

Also ghrelin, a hunger hormone, may be associated with development of obesity. Recent studies indicate that it is also produced and released by the salivary glands [5,6,18]. Benedix et al. [6] observed higher concentrations of ghrelin in saliva than in serum of both lean and obese individuals. Moreover, significantly lower fasting serum ghrelin levels were observed in lean, as compared to obese subjects, while there was no difference in the ghrelin concentrations in saliva between the groups. Salivary ghrelin concentrations decreased significantly after a standardized meal [6]. The same authors [5] in another report described the changes in both fasting and postprandial salivary ghrelin concentrations in patients undergoing surgical treatment of obesity. They also observed differences in salivary ghrelin concentrations depending on the type of bariatric surgery: laparoscopic sleeve gastrectomy, Roux-en-Y gastric bypass or laparoscopic adjustable gastric banding. They did not observe a significant difference of fasting salivary ghrelin concentration between study groups before bariatric surgery At 6 months, the concentration of fasting salivary ghrelin decreased in patients undergoing laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass, whereas in patients after laparoscopic adjustable gastric banding it was similar to the levels before surgery. Interestingly, it seems that 12 months after bariatric surgery only in patients undergoing Roux-en-Y gastric bypass did the concentration of fasting salivary ghrelin decrease continuously as opposed to patients after laparoscopic sleeve gastrectomy. The concentrations of ghrelin increased to values higher than before the operation, while in those after laparoscopic adjustable gastric banding there was no significant change [5].

The development of obesity is also influenced by peptide YY. Peptide YY is a satiety hormone released into the bloodstream from endocrine L-cells of the intestinal epithelium after a meal. Its presence has also been demonstrated in human saliva. The concentration of peptide YY increases in saliva after a meal. The acute increase in PYY in the saliva causes a stronger feeling of fullness which is caused by activation of the Y2 receptor expressed in the tongue epithelial cells. In a study of obese mice, a chronic increase of PYY concentration in the saliva leads to a significant reduction in food intake and body weight [1].

Recently in the diagnosis of various diseases, saliva is useful as a material that is easily accessible and can be obtained non-invasively. An evaluation of salivary adiponectin concentrations may be useful in the diagnosis of obesity and its metabolic complications. There was a positive correlation between the resistive and adiponectin concentrations in saliva with its concentration in the serum of healthy individuals. Visfatin was also present in the saliva, but its concentration did not correlate with the concentration in serum. The authors suggest that the introduction of salivary determinations of adipokines may help to contribute to the elucidation of the physiology and role of adipokines not only in the development of obesity and insulin resistance, but also in inflammation, lack of energy balance or the stress response [27].

The measurement of saliva pH also seems to be useful in the diagnosis of obesity and its metabolic complications. There was a positive correlation in women between saliva pH and clinical parameters (triacylglycerol, glucose and apolipoprotein B, concentrations of which increased in plasma in the metabolic syndrome). In addition, the correlation between salivary pH and clinical parameters associated with metabolic syndrome tended to be stronger in women during menopause than in premenopausal women [42].

Is obesity an oral bacterial disease?

It is believed that oral bacteria can take part in the development of obesity in three different ways. First, they promote insulin resistance by reducing the concentration of adiponectin and increasing tumor necrosis factor (TNF) and concentrations of circulating lipopolysaccharide [11,16]. Second, bacteria increase metabolic efficiency, which means that consumption of even small amounts of calories leads to a significant increase in body weight, in the absence of changes in diet and exercise. Third, oral bacteria might increase host appetite, although there is no research supporting this theory [16].

Obesity is generally deemed to be an inflammatory disease. In view of this, one might ask whether it is an epidemic involving an infectious agent. One of the direct factors taking part in the development of obesity may be oral bacteria. Goodson et al. [16] conducted a study on the salivary bacterial populations of overweight women (BMI between 27 and 32) by DNA probe analysis. The results were compared with data from the bacterial flora of healthy individuals from periodontal disease studies. It was observed that out of 40 species of bacteria, many of them differed in women with overweight, compared to healthy individuals. Furthermore, in 98.4% of overweight women a single bacterial species (*Selenomonas noxia*) is present in saliva at levels greater than 1.05% of the total salivary bacteria. On the basis of these data, it is suggested that salivary bacterial composition changes in overweight women. It is possible that bacterial species may be an indicator of developing overweight, but more research is needed [16].

Bacterial flora in oral biofilm is associated with obesity in adolescents. Obesity was found to be significantly associated with the amounts of bacterial cells in the subgingival biofilm. In adolescents with obesity, a three times higher amount of a total of 23 species of bacteria was observed in comparison to young people of normal weight. Moreover, obese people have in the saliva six more bacterial species, including *Proteobacteria phylum*, *Campylobacter rectus* and *Neisseria mucosa*. The link between obesity and the number of bacterial cells in the oral subgingival biofilm was not affected by any of the studied variables: chronic disease, flow rate of whole saliva, medication, visible plaque index (VPI%), bleeding on probing (BOP%) or meal frequency [46].

Relationship between obesity and dental caries

Obesity is associated with increased risk of inflammatory diseases, including the link of obesity with chronic periodontitis in adults [3,38,39]. Obesity and dental caries are diseases of multifactorial etiology. Their development is affected by nutritional factors and sociodemographic background [30]. However, the current research on the occurrence of dental caries in people with obesity is conclusive.

Pannunzio et al. [34] evaluated the whole stimulated salivary parameters pH, flow rate, buffer capacity, concentrations of protein, phosphate, calcium, sialic acid and peroxidase activity change in children with overweight and obesity compared to children with normal weight. They observed increased concentrations of free sialic acid and total protein in stimulated saliva of obese children compared to the control group. Both concentration of phosphate and peroxidase activity in saliva decreased in obese and overweight children compared to lean ones. There was no difference in the saliva flow rate between all groups. The authors suggest that overweight and obesity lead to changes in concentrations of sialic acid, protein, and phosphorus as well as peroxidase activity in stimulated saliva, which may promote dental caries [34]. It was also observed that obese children have a higher risk of tooth erosion than children of normal weight. What is more, the erosion is focused on anterior teeth. However, despite frequent dental erosion in obese children, the researchers did not find a higher risk of caries in this group of children compared to lean children [41].

Another study on saliva of obese adolescents (BMI> 30) assessed the flow rate of stimulated whole saliva and dental caries. A higher number of decayed surfaces and a lower flow rate of stimulated whole saliva were observed in obese adolescents. What is more, obese subjects had more gingival inflammation [30]. Similar results were obtained by other authors [2,14,28,30,43,44]. Willerhausen et al. [43] found that 44.7% of primary school children with underweight and 40.7% of those with normal weight had naturally healthy teeth, whereas only 30.5% and 31.7% of children with overweight and obesity, respectively, had naturally healthy teeth. Alm et al. [2] found that obese adolescents had more proximal caries than those with normal weight, and more frequent consumption of snack products in early childhood may be the cause of caries at the age of 15 years. The prevalence of obesity and dental caries in children is associated with economic status and education of parents. Children with caries were overweight and had less educated parents and lower income in the families [14]. Thus the development of both dental caries and obesity in children and adolescents is affected by the frequency, method and type of nutrition. It should be remembered that children often snack between main meals and care for oral hygiene to a lesser extent, which contributes to dental caries and leads to weight gain.

Conclusion

In conclusion, obesity is a major health problem, associated with increased mortality. Thus it is important to understand its pathogenesis. There is a limited number of reports on saliva of obese people. Obese individuals have different composition of salivary bacteria than lean individuals. In addition, they often have periodontal disease, as it changes the concentration of sialic acid, phosphorus and peroxidase activity as well as the

lower flow rate of stimulated whole saliva, which promote dental caries [16,29,46]. Women with morbid obesity have significantly decreased salivary cortisol [33,36]. Increased concentrations of salivary endocannabinoids, uric acid and CRP may be a useful marker of obesity and monitoring of cardiometabolic risk [29,31,38]. Assessing concentrations of fasting salivary ghrelin may be helpful in choosing the type of bariatric surgery. Available papers encourage further studies on the pathomechanism of obesity using saliva as a material that is easily accessible and can be obtained non-invasively.

Based on a review of the literature, the question arises whether the saliva and changes in its composition contribute to the emergence of obesity or obesity causes changes in the composition of saliva. The answer is not easy, because so far there has been too little research on the pathogenesis of obesity using saliva as a study material. It is clear that the development of obesity is affected by an increased concentration in the saliva of both ghrelin and cortisol. Probably in the pathogenesis of obesity salivary endocannabinoids also take part, by their role in the regulation of energy balance. Also, it seems that the bacterial flora of the mouth has a significant impact on obesity; however, to confirm this theory it is necessary to perform a study on a larger group of obese people. Regarding the second part of the question, it is clear that obesity leads to a change in the concentration of free sialic acid, total protein and phosphate as well as activity of peroxidase, which contributes to the formation of dental caries. However, it should be remembered that both the development of dental caries and obesity are caused by excessive eating.

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