

# The Role of Oxidative Stress and Changes in the Composition of the Gut Microbiota in the Genesis of Adolescent Obesity

Marina A. Darenskaya\*, Lyubov V. Rychkova, Natalya V. Semenova,  
Natalya L. Belkova, Lyubov I. Kolesnikova

*Scientific Centre for Family Health and Human Reproduction Problems  
Irkutsk, Russian Federation*

## Abstract

Studying the pathogenetic mechanisms in the formation and development of obesity in adolescence is essential due to its high prevalence. Obesity was found to be associated with chronic inflammation in adipose tissue, dyslipidemia, the development of oxidative stress (OS), microbiota composition disorder, and other factors. A consequence of the OS progression is the accumulation in the body of cytotoxic compounds, including endogenous aldehydes, acting as mediators of damage and provoking characteristic shifts in metabolism. Gut microbiota contributes significantly to the development of metabolic disorders and obesity by modeling the cascade of enzymatic reactions of the macroorganism, interacting with receptors directly and/or with its metabolites and signaling molecules. In this context, it may be relevant to investigate the significance of the interaction of these systems to substantiate personalized approaches to the prevention and treatment of adolescent obesity. (**International Journal of Biomedicine. 2022;12(3):344-348.**)

**Keywords:** obesity • adolescents • oxidative stress • antioxidants • microbiota • gut

**For citation:** Darenskaya MA, Rychkova LV, Semenova NV, Belkova NL, Kolesnikova LI. The Role of Oxidative Stress and Changes in the Composition of the Gut Microbiota in the Genesis of Adolescent Obesity. *International Journal of Biomedicine.* 2022;12(3):344-348. doi:10.21103/Article12(3)\_RA3

## Abbreviations

**AOD**, antioxidant defense; **AT**, adipose tissue; **BFT**, biofeedback therapy; **GM**, gut microbiota; **LPO**, lipid peroxidation; **NADH**, nicotinamide adenine dinucleotide; **OS**, oxidative stress; **ROS**, reactive oxygen species; **SOD**, superoxide dismutase; **TAA**, total antioxidant activity.

## Relevance of studying the problem of childhood obesity

The problem of obesity is relevant to the health care system of many countries of the world.<sup>(1)</sup> Childhood and adolescent obesity require special attention because they are very often progressive and lead to the development of various kinds of complications in adulthood. It has been established that in the developed countries of the world, up to 25% of adolescents are

overweight and 15% are obese.<sup>(2)</sup> WHO experts attribute the high prevalence of childhood obesity to the changed economic and social conditions of life in modern society, the consequence of which is an unhealthy diet and low levels of physical activity.<sup>(3,4)</sup> The exogenous-constitutional form is the most common in the structure of obesity, characterized by a pronounced imbalance between caloric intake and expenditure.<sup>(3)</sup> As a polyethyological disease, this form of obesity requires both a comprehensive and individualized treatment approach. The main predictors of adolescent obesity, in addition to hereditary factors, are such factors as hypodynamy, imbalanced energy metabolism, a poor family history, and psychoemotional stress.<sup>(1)</sup>

\*Corresponding author: Prof. Marina A. Darenskaya, PhD. Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk, the Russian Federation. E-mail: [marina.darenskaya@inbox.ru](mailto:marina.darenskaya@inbox.ru)

Studying the pathogenetic mechanisms of obesity formation and development is becoming increasingly important now.<sup>(5)</sup> Obesity was found to be associated with chronic inflammation in adipose tissue, dyslipidemia, the development of oxidative stress (OS), microbiota composition disorder, and other factors.<sup>(6-8)</sup>

### Oxidative stress and obesity

OS is an important component of the pathogenesis of obesity and its possible complications.<sup>(9-11)</sup> Preclinical in vitro and in vivo studies have shown that OS has a stimulating effect on preadipocyte proliferation and differentiation, as well as an increase in adipocyte size.<sup>(12)</sup> In a healthy body, reactive oxygen species (ROS) are also involved in the activation of hypothalamic neurons involved in the regulation of eating behavior. In obesity, due to an increase in oxidative processes, the production of ROS increases, and the center of hunger is activated.<sup>(9)</sup> Obesity is characterized as an increase in white adipose tissue (AT) secreting several putative appetite-related adipokines. In addition, the following factors associated with obesity that are stimulated by OS can be identified: hyperglycemia, dyslipidemia, micronutrient deficiency, chronic inflammation, hyperleptinemia, and increased activity of muscle tissue to maintain excess body weight in obesity, endothelial dysfunction, disruption of mitochondrial respiratory function, and others.<sup>(5,13)</sup> Obesity is accompanied by increased levels of free fatty acids in the blood, which stimulates superoxide-anion radical production.<sup>(14)</sup> The progression of OS results in the accumulation of cytotoxic compounds in the body, including endogenous aldehydes that act as mediators of damage and provoke characteristic metabolic shifts.<sup>(9,13,15)</sup> The antioxidant defense (AOD) system plays an important role in protecting against the damaging effects of OS. AOD components act as stabilizers of biological membranes, inactivate free radicals, and prevent the development of chain processes of free radical oxidation of organic compounds, primarily unsaturated tissue lipids.<sup>(16)</sup> Primarily, special antioxidant enzymes provide this function: superoxide dismutase (SOD), catalase, enzymes of a glutathione redox system, and water- and fat-soluble vitamins.<sup>(16-18)</sup> The ratio of the activity of oxidative processes and AOD, as a rule, determines the intensity of the metabolism and its adaptation capabilities. Disruption of AOD is characterized by the development of LPO syndrome and can lead to a number of negative consequences for the cell: membrane damage, inactivation or transformation of enzymes, suppression of the fission process, and accumulation of inert polymerization products.<sup>(19)</sup> Available data allow us to consider obesity also as a chronic inflammatory process, which is accompanied by the activation of proinflammatory cytokines, such as IL-6, IL-1, and TNF- $\alpha$ , known mediators of the early stage of inflammation, as well as IL-8,  $\gamma$ -interferon, and IL-18.<sup>(6,7)</sup>

### Microbiota and Obesity

The microbiota is a key factor in maintaining the homeostasis of the human organism.<sup>(20)</sup> It performs a number of important functions, such as regulating energy metabolism, maturation, and maintenance of immune system function; vitamin synthesis; and regulating bile acid reabsorption in

the gut.<sup>(21)</sup> In addition, bacteria produce analogs of human hormones: serotonin, histamine, dopamine, norepinephrine, and testosterone. Influencing the intestinal wall, these substances entering the bloodstream affect our brain, shaping habits, taste preferences, and even behavior.<sup>(22)</sup> The concept of the “gut-brain-gut” axis has become a paradigm.<sup>(23)</sup> Some authors extend this axis by adding the interaction between gut microbiota (GM) and the immune system: “gut-brain-immune-system microbiota.” The gut microbiome is a kind of indicator of the macroorganism, reacting to physiological, dietary, climatic, and geographical factors by changing its qualitative and quantitative composition. According to many researchers, without belittling the role of heredity and environmental factors, it is GM that contributes significantly to the development of metabolic disorders and obesity by modeling the cascade of macroorganism enzymatic responses, interacting with receptors directly and/or with its own metabolites and signaling molecules.<sup>(21)</sup> In addition, GM can mediate the activation of inflammatory reactions and fibrogenesis.<sup>(24)</sup> Recent evidence suggests quantitative and qualitative differences in the GM composition among subjects at high and low risk of developing obesity and obesity-related complications.<sup>(21,25)</sup> Putative mechanisms include increased energy absorption from food, altered gut permeability, gut hormone release, induction of OS, and inflammation.<sup>(26)</sup> According to a study by Qiao et al.,<sup>(27)</sup> GM dysbiosis in obese mice was also caused, at least in part, by an increase in OS.<sup>(28)</sup>

Bacterial overgrowth syndrome and translocation of intestinal flora also lead to the development of OS and activation of the systemic inflammatory response.<sup>(29)</sup> Microbiota transplantation studies conducted in both animals and humans suggest that gut “dysbiosis” itself may lead to weight gain and insulin resistance.<sup>(30)</sup> The microbial composition of GM is influenced by both body weight and dietary components (such as fiber, polyphenols, and lipids). In obese individuals, weight loss decreases the ratio of *Firmicutes* to *Bacteroidetes*,<sup>(31)</sup> whereas a caloric high-fat diet increases it.<sup>(32)</sup> A high-fat diet in mice caused an increase in aerobic bacteria in Peyer’s Plaques, including *Streptococcus*, *Pseudomonas*, *Comamonas*, and *Flavobacterium*,<sup>(28)</sup> as well as the reduction of anaerobic and facultative anaerobic bacteria of the genus *Allobaculum* and *Lactobacillus*.<sup>(27,28)</sup> Bacteria also deploy specialized mechanisms to combat OS, which include enzymes such as SOD, thioredoxin reductase system, glutathione glutaredoxin, and NADH oxidase - NADH peroxidase systems.<sup>(33)</sup> It has previously been shown that a high-fat diet contributes to gut mucosal inflammation mediated by a decrease in the number of lactobacilli. The fact is that fat-rich foods ensure the selection of bacterial strains resistant to OS. And these turned out to be lactobacilli that secrete proinflammatory cytokines. Conversely, “good” *L. reuteri* strains, producers of anti-inflammatory substances, were displaced from the population.<sup>(34)</sup> The largest case-control study reported higher levels of *L. reuteri* in the fecal microbiota of obese individuals,<sup>(35,36)</sup> and fecal *L. reuteri* of humans correlated positively with body mass index. A higher oxidation-resistant phenotype was found in mice on a high-fat diet, especially those prone

to obesity. A high-fat diet induces the formation of more ROS in the gut<sup>(37)</sup> and markers of OS.<sup>(38)</sup> This causes a shift in the microbial composition toward the growth of bacteria resistant to oxidative conditions, such as *Escherichia coli* and *Enterococcus*.<sup>(27)</sup> Susceptibility to obesity is characterized by an unfavorable gut microbiome, predisposing to peripheral and central inflammation and weight gain. The results show that a high-fat diet led to an imbalance of *L. reuteri*, with anti-inflammatory function. This may be due to increased OS in the gut environment.<sup>(39)</sup>

Researchers at the Scientific Centre for Family Health and Human Reproduction Problems conducted comprehensive studies of OS reactions and the microbiota composition in adolescents with obesity. It has been found that obesity in adolescents is associated with an imbalance in the LPO-AOD system and depends on the patient's ethnicity.<sup>(18,40-42)</sup> In assessing the degree of oxidative cell damage in obese adolescents, the high sensitivity of the oxidative stress index (OSI) has been shown.<sup>(10,43)</sup> Analysis of the data in the LPO-AOD system showed a pronounced imbalance in adolescents with obesity in the form of increased values of primary and secondary LPO products, reduced values of TAA and SOD activity, as well as low values of  $\alpha$ -tocopherol in adolescent girls with obesity.<sup>(44)</sup> Conducting non-drug therapy and biofeedback therapy (BFT) did not lead to normalization of the indicated parameters, both in the group of teenage boys and girls with obesity, while an increase in the oxidized glutathione level was noted in girls after non-drug therapy and a decrease in  $\alpha$ -tocopherol level after BFT.<sup>(45)</sup> Due to the lack of efficacy of the above types of therapy with respect to the parameters of redox status in adolescents with obesity, additional pharmacological correction by prescribing antioxidant drugs becomes relevant.

The researchers at our Centre also conducted studies on GM in obese children and adolescents.<sup>(46)</sup> The gut microbiome of adolescents with normal body weight and obesity was analyzed by two mutually complementary methods (bacteriological analysis according to the industry standard and metasequencing of the V3-V4 region of the *16S rRNA* gene).<sup>(47,48)</sup> It was shown that obese adolescents have an imbalance of the colonic microbiota characterized by a low content of bifido- and lactoflora representatives, a spectrum of *Escherichia coli* associations, and a high frequency of registration of opportunistic microorganisms and their associations.<sup>(47)</sup> Additionally, the frequency of occurrence of bifidobacteria in the gut microbiome of adolescents by PCR diagnostics was determined. A disturbance in the species composition of bifidoflora in adolescents with obesity was shown, which was associated with a decrease in the frequency of occurrence of the most physiologically important species: *B. longum*, *B. adolescentis*, *B. bifidum* and an increase in the level of *B. catenulatum* detection.<sup>(48)</sup> The important role of the duration of breastfeeding in the formation of a stable community in the gut microbiome of adolescents was confirmed.<sup>(49)</sup> A decrease in the representation of phylotypes in the structure of the gut microbiome and their diversity was observed only in adolescents with obesity, but the dysbiotic state of the biocenosis, which has features characteristic of early transition to complementary feeding, persisted when breastfeeding less

than 3 months, both in obesity and normal body weight.<sup>(50,51)</sup> On the other hand, significant differences in the composition of the gut microbiome were observed in adolescents born by cesarean section: first of all, a decrease in the proportion of *Bacteroidetes* and *Actinobacteria* in the total microbiome and an increase in the representation of proteobacteria, mainly of the Enterobacteriaceae family. A significant difference was revealed between the composition of GM in the obese and control groups: *Dorea* (phyla *Firmicutes*), *Bacteroides*, *Parabacteroides* (phyla *Bacteroidetes*), *Slackia*, and *Collinsella* (phyla *Actinobacteria*) prevailed in obese patients.<sup>(52)</sup> Prediction of the functional content of the gut microbiome showed the dominance of biosynthetic pathways over the pathways of destruction, assimilation, and utilization. Based on the abundant distribution of the potential activity of the predicted metabolic pathways, different degrees of metabolic activity of GM are predicted in obese adolescents, which suggests that even with differences in taxonomic composition, the gut microbial community can compensate for the absence of certain taxonomic groups by implementing the necessary metabolic functions due to other phylogenetically close taxa.<sup>(53)</sup>

In adolescents with obesity and functional bowel disorders, the GM composition differs from that in adolescents without functional bowel disorders. Disturbances in the GM composition are associated with an increase in the level of potential pathobionts, which can lead to the development of microinflammation in the intestinal wall and exacerbate the symptoms of functional bowel disorders.<sup>(54)</sup> Functional bowel disorders in obese adolescents was associated with an imbalance in the minor components of GM and a disturbance in its metabolic and regulatory functions.<sup>(55)</sup>

## Conclusion

Studying the pathogenetic mechanisms in the formation and development of obesity in adolescence is essential due to its high prevalence. Obesity was found to be associated with chronic inflammation in adipose tissue, dyslipidemia, the development of OS, microbiota composition disorder, and other factors. A consequence of the OS progression is the accumulation in the body of cytotoxic compounds, including endogenous aldehydes, acting as mediators of damage and provoking characteristic shifts in metabolism. Gut microbiota contributes significantly to the development of metabolic disorders and obesity by modeling the cascade of enzymatic reactions of the macroorganism, interacting with receptors directly and/or with its metabolites and signaling molecules. In this context, it may be relevant to investigate the significance of the interaction of these systems to substantiate personalized approaches to the prevention and treatment of adolescent obesity.

## Sources of Funding

This work was supported by the Russian Federation Grant (NSh- 3382.2022.1.4).

## Competing Interests

The authors declare that they have no competing interests.

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