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RESEARCH ARTICLE

Effects of Monosodium Glutamate (MSG) intake during pregnancy and lactation on calcium levels in the teeth and alveolar bones of rat offspring

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ABSTRACT

Monosodium glutamate (MSG) is a widely used food additive that enhances flavor. However, excessive MSG intake during pregnancy and lactation may pose health risks to both the mother and the developing fetus, particularly in terms of tooth and bone development. This study aimed to investigate the effect of maternal oral administration of MSG during pregnancy and lactation on calcium levels in the teeth and alveolar bones of rat offspring. This research is a laboratory experiment with a post-test-only control group design. Thirty pregnant Sprague Dawley rats were randomly allocated into three groups: a control group receiving distilled water and two treatment groups receiving MSG at doses of 3 mg/g BW and 6 mg/g BW, respectively. MSG was administered orally from the 5th day of pregnancy until the end of the lactation period. The calcium levels in the teeth and alveolar bones of the offspring were measured using atomic absorption spectrophotometry (AAS). Data were analyzed using one-way ANOVA and post hoc LSD. The mean calcium levels in the teeth and alveolar bones of the offspring in the MSG treatment groups were significantly lower than those in the control group ($p < 0.05$). The reduction in calcium levels was dose-dependent, with the higher MSG dose (6 mg/g BW) resulting in a more pronounced decrease compared to the lower dose (3 mg/g BW). Maternal MSG intake during pregnancy and lactation leads to a dose-dependent decrease in calcium levels in rat offspring's teeth and alveolar bones, suggesting that excessive MSG intake during these critical periods potentially leads to impaired tooth and bone development.

Keywords: alveolar bone; calcium levels; lactation; monosodium glutamate; pregnancy; tooth

INTRODUCTION

The tooth is a complex structure composed of different highly organized hard and soft tissues, including highly calcified enamel, dentin, and cementum, in addition to the soft tissues, which include the dental pulp and periodontal ligament.[1] As the hardest tissue in the human body, the development of teeth is a delicate process that hinges on adequate mineral intake, particularly calcium, during the embryonic stage.[2] Pregnancy and lactation are the most important periods for the mother to supply her nutritional needs to support the proper growth and development of their children. The quantity and quality of proper maternal nutrition can also influence the growth and development of children's teeth and bones.[3,4] Adequate prenatal nutrition is a vital cornerstone not only for the newborn's overall health but also specific to the proper formation of teeth and alveolar bones, the very foundation of lifelong oral health.

During critical periods of pregnancy, consumption of food additives can pose health risks to both the mother and the developing fetus. Monosodium glutamate (MSG), a sodium salt derived from glutamic acid, is one such additive.[5,6] While some food safety regulatory agencies, such as the United States (US) Food and Drug Administration (FDA), classify MSG

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as generally recognized as safe (GRAS), clinical trials involving human and animal subjects have suggested potential health hazards.[7,8] Controversy surrounds the safety of MSG stems from studies indicating various adverse effects on human health, including obesity, metabolic syndrome, and damage to multiple organ systems such as the kidneys, immune system, reproductive system, nervous system, cardiovascular system, and cerebrovascular system.[9,10]

Studies conducted on pregnant rats have revealed that MSG exposure can induce teratogenic effects, increase oxidative stress, and cause damage to brain tissues, potentially impairing fetal development.[11,12,13] Additionally, investigations have demonstrated that MSG exposure in rats alters metabolic and neuroendocrine-immune functions, with a potential impact on the development of teeth and bones.[14,15,16] In a newborn baby's life, more free glutamate is ingested per kilogram of body weight during nursing than at any other stage. According to the American Academy of Pediatrics Committee, MSG has limited effect on lactation and risk to nursing infants.[16,17]

MSG consumed during pregnancy can cross the placenta, exposing the developing fetus to this substance. Recent studies have confirmed the placental transfer of MSG in animal models and highlighted its implications for fetal exposure. MSG was shown to penetrate the placental barrier and distribute almost evenly among embryonic tissues. Research indicates that the fetal brain can absorb significantly more glutamate than the mother, which may lead to detrimental effects on neuroendocrine functions.[11,12,13,14] Excessive glutamate can damage growth hormone-releasing hormone (GHRH) and thyrotropin-releasing hormone (TRH) neurons in the hypothalamus, leading to decreased secretion of growth hormone (GH) and thyroid-stimulating hormone (TSH) from the pituitary gland. Deficiencies in these hormones can adversely affect enamel mineralization and tooth eruption.[15,18,19] The disruption of parathyroid hormone and thyroid hormone balance caused by MSG may also interfere with bone and bone marrow development. Hypothyroidism impairs calcitonin's ability to counterbalance the continuous secretion of PTH, leading to decreased calcium levels in alveolar bone and teeth.[18,19,20]

Despite the growing evidence of the adverse effects of MSG on fetal development, there is a paucity of research specifically investigating the impact of maternal MSG intake on the mineralization of teeth and alveolar bones in offspring. Furthermore, most studies have focused on the prenatal effects of MSG, while the potential consequences of continued exposure during the lactation period remain largely unexplored. Given the critical role of calcium in the development and mineralization of hard tissues, it is essential to elucidate the dose-dependent effects of MSG on calcium levels in the teeth and alveolar bones of offspring exposed to the additive during both prenatal and postnatal periods. Considering the potential risks associated with MSG intake during pregnancy and lactation, as well as its possible impact on the development of teeth and bones in offspring, further research is needed. This study aimed to investigate the effect of maternal oral administration of MSG during pregnancy and lactation on calcium levels in the teeth and alveolar bones of rat offspring.

MATERIALS AND METHODS

This experimental study employed a posttest-only control group design to investigate the effects of maternal MSG intake on calcium levels in the teeth and alveolar bones of Sprague Dawley rat offspring. The research was conducted at the Nutrition Laboratory of the Inter-Study Center at Universitas Gadjah Mada, Yogyakarta, and the Soil Laboratory of the Faculty of Agriculture at Jenderal Soedirman University, Purwokerto. Ethics approval was obtained from the Health Research Ethics Committee of Dr. Moewardi General Hospital, Surakarta (No.619/VII/HREC/2017), ensuring adherence to ethical guidelines for in vivo animal studies.

In this study, 30 pregnant Sprague Dawley rats, aged 10-12 weeks and weighing 250-300g, were randomly divided into three groups

of 10 rats each. The control group received oral administration of 2 ml of distilled water, while the two treatment groups were orally administered 2 ml of distilled water containing MSG at doses of 3 mg/g BW and 6 mg/g BW, respectively. The oral administration was performed daily from the 5th day of pregnancy and continued throughout the lactation period.[21] The offspring (first-generation) were the units of analysis, with inclusion criteria being 21 days of postnatal age, male sex, and eruption of the lower incisors.

Vaginal smears were collected from all female rats using a 0.2 ml pipette, and the obtained vaginal fluid was placed on a glass slide and left to air-dry. The slides were then stained by immersion in a vessel containing crystal violet for 1 minute, followed by a second vessel containing sterile distilled water for another minute. After staining, a drop of glycerol (approximately 0.015 ml) was placed on the smear, and a coverslip was applied. The stained smears were examined under a light microscope to identify the cell types present. Rats in the estrous stage, characterized by the predominance of cornified squamous epithelial cells in clusters, were selected for mating and placed in cages with male rats. To confirm pregnancy, vaginal smears were re-examined within 24 hours after mating, with the presence of sperm indicating day 0 of pregnancy.[22]

To avoid potential embryotoxic effects on rat fetuses, MSG administration commenced on the 5th day of pregnancy. The MSG doses for each treatment group were prepared by diluting the appropriate amount of MSG in 2 ml of sterile distilled water. The control group received 2 ml of sterile distilled water without MSG. Oral administration of the prepared solutions was performed using a gastric tube, ensuring accurate dosing and minimizing the risk of aspiration. The treatment continued daily from the 5th day of pregnancy throughout the lactation period, allowing for the assessment of both prenatal and postnatal effects of MSG exposure on the developing offspring.[21]

One first-generation rat offspring from each mother, which matched the inclusion-exclusion criteria, was euthanized under inhalation anesthesia using ether to obtain teeth and alveolar bone samples. The upper and lower jaws were carefully dissected and cleaned of soft tissue using a scalpel. Incisions were made in the incisor regions to separate the teeth and alveolar bone. The extracted incisors and alveolar bone were then thoroughly cleaned using a toothbrush, 0.9% NaCl solution, and distilled water to remove any debris. The samples were air-dried until free of moisture and subsequently crushed into a fine powder. Using a digital scale, 0.05 g of each powdered sample (teeth and alveolar bone) was weighed

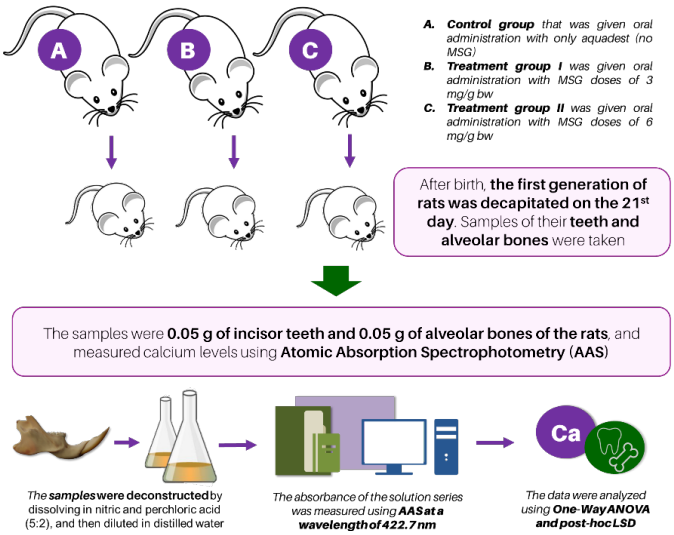

Figure 1. Experimental design and sample collection

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and recorded as the dry weight. The prepared samples were then further dried to ensure the complete removal of any remaining distilled water, guaranteeing the accuracy and reliability of the subsequent analyses (Figure 1).

To determine the calcium levels in teeth and alveolar bone samples, the tissues were subjected to acid digestion. The samples were dissolved in a mixture of nitric and perchloric acids (5 : 2 ratio) in a total volume of 5 ml. The solution was then heated on a hotplate for approximately 30 minutes until no further gas formation was observed. Following digestion, the solution was diluted with distilled water to a final volume of 50 ml. The diluted samples were allowed to stand for 24 hours to facilitate the complete removal of organic compounds and ensure the release of elemental bonds within the sample matrix. The calcium levels of the prepared samples were measured using atomic absorption spectrophotometry (AAS) at a wavelength of 422.7 nm.

The calcium levels obtained from the teeth and alveolar bone samples were analyzed using one-way ANOVA followed by a post hoc LSD test to determine significant differences among experimental groups ($p < 0.05$). All analyses were performed using appropriate statistical software to ensure the reliability and validity of the results.

RESULTS

The mean calcium levels in the teeth and alveolar bones of rat offspring for each group are presented in Table 1 and Table 2, respectively. As shown in Table 1 and Table 2, the mean calcium levels in the

Table 1. Mean calcium levels of teeth

NO	Treatment	Sample number (n)	Mean (%) ± SD
1	Distilled water	10	16.710 ± 1.114
2	MSG dose 3 mg/g BW	10	12.706 ± 0.877
3	MSG dose 6 mg/g BW	10	9.961 ± 0.501

Table 2. Mean calcium levels of alveolar bones

NO	Treatment	Sample number (n)	Mean (%) ± SD
1	Distilled water	10	7.204 ± 0.443
2	MSG dose 3 mg/g BW	10	5.175 ± 0.341
3	MSG dose 6 mg/g BW	10	3.720 ± 0.296

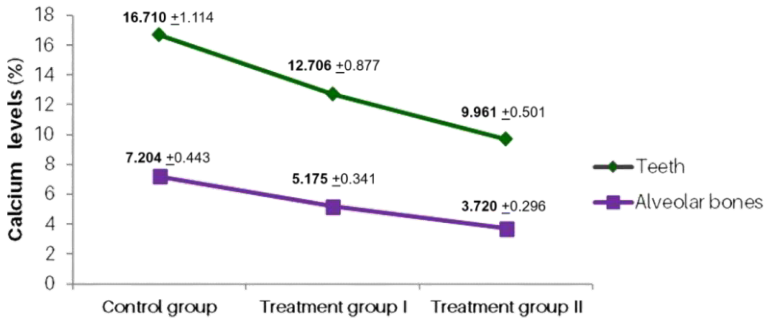

Figure 2. The mean calcium levels of teeth and alveolar bone in rat offspring. The calcium levels in each treatment group were lower than in the control group, with the control group receiving distilled water, treatment group I receiving MSG 3 mg/g BW, and treatment group II receiving MSG 6 mg/g BW.

Table 3. Statistical test results of calcium levels of teeth and alveolar bones

NO	Treatment	Calcium levels of teeth		Calcium levels of alveolar bones	
		One-way ANOVA	Post hoc LSD	One-way ANOVA	Post hoc LSD
1	Distilled water		$p^a = 0.003$*		$p^a = 0.001$*
2	MSG dose 3 mg/g BW	p = 0.000*	$p^b = 0.021$*	p = 0.000*	$p^b = 0.009$*
3	MSG dose 6 mg/g BW		$p^c = 0.000$*		$p^c = 0.000$*

Note: *: significant differences (p < 0.05)

teeth and alveolar bones of the treatment group were lower than those of the control group. A comparison of the mean calcium levels in the teeth and alveolar bones of the rats is illustrated in Figure 2.

The one-way ANOVA test (p = 0.000; p < 0.05) indicated statistically significant differences in the calcium levels of the teeth and alveolar bones among the groups. Further analysis using the post hoc LSD test confirmed statistically significant differences in calcium levels of the teeth and alveolar bones between the treatment and control groups, as detailed in Table 3.

DISCUSSION

The results of this study indicate that maternal oral administration of MSG during pregnancy and lactation leads to a decrease in calcium levels in the teeth and alveolar bones of rat offspring. This is evidenced by the significantly lower calcium levels in the teeth and alveolar bones of the treatment groups compared to the control group. The reduction in calcium levels might be attributed to the potentially disruptive effects of MSG on the developing fetal endocrine system and calcium metabolism. These results align with those of research by Dhindsa et al[20] which provided early evidence of the detrimental effects of MSG exposure on bone and bone marrow histogenesis in mice. MSG treatment leads to repression in bone ossification and accumulation of adipose tissue in bone marrow, potentially impacting bone deposition and resorption. However, the results of this study contradict the findings of Blais et al[23] which showed no detrimental effects of MSG intake on bone mineral density in mice. In contrast, MSG supplementation improved bone mineral density in mice under moderate protein restriction. The difference in results might be caused by several factors, such as the dose of MSG administered, the duration of exposure, and the developmental stage of the experimental animals. The current study focused on prenatal and early postnatal exposure to MSG, which may have a more significant impact on developing bones and teeth compared to previous studies.

In the current study, MSG was administered to pregnant rats from the 5th day of gestation until the end of the lactation period at doses of 3 mg/g BW and 6 mg/g BW, and the effects of exposure were examined in the offspring. In contrast, Blais et al[23] supplemented adult mice with MSG at doses of 5, 10, and 20 g/kg BW diet for 12 weeks. Prenatal and early postnatal exposure to MSG may significantly impact tooth and bone development, as evidenced by various studies. Research has shown that MSG administration during the critical period of odontogenesis (pregnancy and lactation) may disrupt the process of enamel formation and mineralization, which impacts the structure and hardness of tooth enamel in rat offspring.[24] Other studies have also reported that the administration of MSG during pregnancy leads to decreased fetal weight, crown-rump length, and placental weight, along with delayed chondrification and incomplete ossification of fetal skeletons.[13] Furthermore, MSG exposure has been linked to adverse effects on placental trophoblast cells, including impaired trophoblast invasion, differentiation, and increased oxidative stress levels.[25] These factors are crucial for proper placentation and embryonic development, and their disruption may contribute to the observed alterations in tooth and bone development.

The dose-dependent reduction in calcium levels observed in the current study may be attributed to the cumulative effects of MSG on the developing endocrine system and calcium metabolism throughout the prenatal and postnatal periods. The higher dose of 6 mg/g body weight/day resulted in lower calcium levels compared to the 3 mg/g body weight/day dose, suggesting a greater degree of disruption in calcium homeostasis and mineralization processes. This finding is consistent with those of previous research by Khalaf and Arafat,[19] which reported that low-toxicity doses of MSG (3 g/kg BW) caused a decrease in diameter and irregular shape of thyroid follicular cells, while high-toxicity doses (6 g/kg BW) led to a loss of shape and destruction of these cells. Deconstructed and damaged thyroid follicular cells, along with decreased TSH secretion, can lead to reduced production of triiodothyronine (T_3) and thyroxine (T_4) hormones. The disruption of the colloid endocytosis process, which is essential for the formation of these hormones, can result in a decrease in T3 and T4 levels, ultimately leading to prenatal hypothyroid conditions.[19] Impaired thyroid function can disrupt the delicate balance of hormones involved in calcium homeostasis and mineralization of teeth and bones, contributing to the dose-dependent effects observed in the present study.[26]

MSG acts on glutamate receptors, releasing neurotransmitters that play important roles in both normal physiological and pathological processes.[27] Glutamate receptors are divided into three groups of metabotropic receptors (mGluR) and four types of ionotropic receptors: N-methyl-D-aspartate (NMDA) receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid (AMPA) receptors, delta receptors, and kainate receptors. These receptors are widely distributed throughout the central nervous system, particularly in the hypothalamus, hippocampus, and amygdala, where they regulate autonomic and metabolic functions.[28] The hypothalamus is part of the brain responsible for the reproduction of several important hormones and chemicals that control cells and organs. Transcription factors and signaling molecules are the result of hypothalamic secretion that functions for the process of differentiation and proliferation in the early stages of gestation.[29] Research indicates that glutamate's excitotoxic effects can damage hypothalamic neurons, including those responsible for releasing GHRH and TRH, which are crucial for regulating GH and TSH secretion. Therefore, damage to hypothalamic neurons that produce GHRH and TRH can lead to decreased secretion of GH and TSH, disrupting normal physiological functions that depend on these hormones.[30,31] Excessive activation of glutamate receptors can lead to neurotoxicity, disrupting the function of these neurons and affecting hormone secretion. This has been observed in studies involving the hypothalamic-pituitary-adrenal (HPA) axis, where glutamate's excitatory effects impair hormone release regulatory mechanisms.[18,30]

These hormonal imbalances can persist postnatally, affecting the offspring's development and calcium metabolism, as deficiencies in these hormones can adversely affect enamel mineralization, tooth eruption, and development.[15,32] MSG-induced hypothyroidism during prenatal or postnatal periods can also disrupt parathyroid hormone and thyroid hormone balance, interfering with bone and bone marrow development. Hypothyroidism impairs calcitonin's ability to counterbalance the continuous secretion of parathyroid hormone, leading to decreased calcium levels in teeth and alveolar bone.[20] Furthermore, the continuation of MSG exposure during the lactation period may exacerbate these adverse effects, as breast milk is a crucial source of calcium for the developing infant, and any disruption in maternal calcium metabolism or hormonal balance can impact the quality and composition of the milk.[33] Thus, the combined prenatal and postnatal exposure to MSG may have a more pronounced effect on the mineralization of teeth and bones in the offspring compared to prenatal exposure alone.

It is important to note that the findings of this study are based on an animal model, and further research is needed to confirm the relevance of these results in humans. However, the potential risks associated with excessive MSG intake during pregnancy and lactation should not be overlooked.

Pregnant and lactating mothers should be cautious about their intake of MSG-containing foods and opt for a balanced, nutritious diet to support optimal fetal and infant development. This study provides evidence that maternal MSG intake during pregnancy and lactation can lead to decreased calcium levels in the teeth and alveolar bones of offspring in a rat model. The underlying mechanisms may involve disruption of the endocrine system and impaired calcium metabolism. These findings highlight the importance of carefully considering dietary factors, especially the consumption of food additives such as MSG, during critical periods of prenatal and early postnatal development. Pregnant and breastfeeding mothers should be cautious with their intake of MSG-containing foods and choose a balanced and nutritious diet to support optimal fetal and infant growth and development, ensuring proper mineralization and growth of teeth and bones.

CONCLUSION

Maternal MSG intake during pregnancy and lactation has shown to result in a dose-dependent decrease in calcium levels in rat offspring's teeth and alveolar bones, suggesting that excessive MSG intake during these critical periods potentially leads to impaired tooth and bone development.

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CONFLICT OF INTEREST

We have no conflicts of interest to disclose.

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