

RESEARCH PAPER

IMPACT OF CHRONIC SODIUM CYCLAMATE ADMINISTRATION AT A DAILY ACCEPTABLE DOSE ON CARBOHYDRATE METABOLISM AND INSULIN RESISTANCE

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ABSTRACT

Sodium cyclamate, a widely used non-caloric artificial sweetener, has been associated with potential metabolic disturbances. This study evaluated the effects of chronic sodium cyclamate administration (10 mg/kg/day, peroral) on carbohydrate, protein, lipid, and mineral metabolism, as well as insulin resistance and body weight, in experimental rats over 60 days. Chronic cyclamate consumption significantly increased blood glucose, glycated hemoglobin, and insulin levels, with glucose rising by 68.4% and insulin by 66.4% relative to baseline by day 60. Glucose tolerance tests revealed marked impairment, with the area under the glucose curve increasing by 73.3%. Liver glycogen content decreased by 41.83%, accompanied by elevated ALT and AST activities, indicating hepatic involvement. Biochemical analysis showed increases in total protein and albumin levels, while urea and creatinine concentrations were elevated, reflecting altered nitrogen metabolism. Lipid profile assessment revealed progressive increases in total cholesterol, triglycerides, LDL-C, HDL-C, and VLDL-C, with corresponding changes in atherogenic coefficients, suggesting negative effects on lipid metabolism. Chronic administration also disrupted mineral homeostasis, decreasing potassium and calcium levels while moderately altering sodium levels. Insulin resistance indices, including HOMA-IR, FIRI, QUICKI, and Caro index, demonstrated significant reductions in insulin sensitivity over time. Notably, body weight was slightly reduced during the experiment, indicating that sodium cyclamate did not promote weight gain under these conditions. Collectively, these findings demonstrate that prolonged sodium cyclamate intake adversely affects glucose tolerance, insulin sensitivity, and multiple metabolic parameters in rats, highlighting potential health risks associated with chronic exposure.

Keywords: Sodium cyclamate; artificial sweeteners; carbohydrate metabolism; glucose tolerance; insulin resistance, HOMA-IR, QUICKI, FIRI.

INTRODUCTION

Sugar substitutes are chemical compounds or products that are perceived as sweet by human taste receptors and are used as alternatives to sugar and other naturally sweet products (such as honey or molasses). They are commonly applied to impart sweetness to various foods and beverages. Unlike sugar, compounds such as xylitol, sorbitol, and fructose undergo metabolism in the body with a reduced need for insulin, and their moderate consumption does not usually lead to severe hyperglycemia (Chattopadhyay et al., 2014). Substances that have no caloric value, undergo metabolism without the involvement of insulin, and do not affect blood glucose levels are referred to as non-nutritive sweeteners (Chattopadhyay et al., 2014). Currently available sugar substitutes and sweeteners possess both advantages and limitations; therefore, it is essential to evaluate and analyze their specific characteristics and safety profiles. The selection of sugar substitutes should be based on the intended purpose of their use. If the goal is to control blood glucose levels (as in diabetes, impaired glucose tolerance, or insulin resistance) and the consumption is long-term, the use of steviol glycosides or erythritol, as well as their combinations, is appropriate. These substances minimally affect insulin secretion and do not produce any adverse effects with prolonged use. If the aim of using sugar substitutes is weight loss, products with zero caloric content and a taste profile closest to traditional sugar—such as sodium cyclamate, aspartame, sucralose, and potassium acesulfame—are recommended. For frequent consumption, choosing natural sweeteners such as steviol glycosides and polyols is preferable to prevent potential adverse effects. However, no modern sugar substitute can fully satisfy the body's craving for sweetness. Experiencing a sweet taste without glucose intake induces a temporary sensation of hunger, which may lead to increased appetite.

An ongoing critical question among researchers is the effect of authorized sugar substitutes and sweeteners on human health. While acceptable daily intake (ADI) levels have been established, there is a need for more comprehensive long-term studies to assess potential adverse effects. Gallus et al. identified that the potential risk of cancer development in individuals consuming artificial sweeteners is present at an early stage (Gallus et al., 2007). Research by Mattes and colleagues demonstrated that consumption of artificial sweeteners may contribute to weight gain rather than weight loss (Mattes & Popkin, 2009), and in patients with diabetes, it was associated with deterioration of glycemic control, blood pressure, and lipid profiles. Artificial sweeteners influence glucose regulation by reducing glucose reabsorption. Their consumption can lead to impaired glucose absorption and transport in the intestine, development of insulin resistance, and a decrease in insulin secretion, ultimately disrupting glucose homeostasis. Systematic reviews and meta-analyses have confirmed an association between artificial sweetener intake, altered blood glucose levels, and the risk of type 2 diabetes. The intestine plays a central role in this process, as artificial sweeteners affect gut microbiota composition and function, altering glucose absorption and systemic glucose concentrations. Glucose is primarily absorbed in enterocytes of the small intestine via apical GLUT-1 transporters and basolateral GLUT-2 transporters. The binding of glucose to sweet taste receptors in the gut stimulates the secretion of incretin hormones, including GLP-1 and GLP-2, which in turn enhances GLUT-2 translocation and glucose transport. Animal studies have shown that sweeteners such as sucralose, saccharin, and acesulfame-K activate GLUT-1 transporters in enterocytes. However, these compounds do not affect T1R3 receptors or α -gustducin signaling pathways (Maillet et al., 2015; Margolskee et al., 2007). Furthermore, sucralose, saccharin, and acesulfame-K also stimulate GLUT-2 activity, leading to increased intestinal glucose reabsorption (Maillet et al., 2015). In contrast, aspartame consumption

does not appear to influence insulin production in experimental models.

Natural sugars and sugar substitutes initially enhance incretin synthesis, which promotes insulin secretion from pancreatic β -cells. However, artificial sweeteners do not stimulate incretin production. Additionally, glucose and artificial sweeteners can modulate insulin secretion via β -cell calcium (Ca^{2+}) channels and cAMP signaling, enhancing the interaction of sweet taste receptors with pancreatic β -cells. Although the above-mentioned scientific data describe the mechanisms of action of sugar substitutes, conflicting opinions still exist among researchers.

Among sugar substitutes, sodium cyclamate is widely utilized and considered cost-effective. Currently, this compound is extensively employed in the food industry and is readily available in most grocery stores. Sodium cyclamate is approximately 30–50 times sweeter than sucrose and is often used in combination with other sweeteners like saccharin to enhance sweetness and mask bitter aftertastes. It is water-soluble, stable under heat, and has no caloric value, making it appealing for use in diabetic and weight-management products.

Sodium cyclamate is utilized in various food and beverage products, including sugar-free soft drinks, desserts, jams, canned fruits, and as a tabletop sweetener. Its stability at high temperatures and water solubility makes it suitable for use in a wide range of food products, including carbonated beverages, desserts, and salad dressings. It is often combined with other sweeteners like saccharin to produce a synergistic sweetening effect. The compound is also employed in the pharmaceutical industry to mask the unpleasant taste of certain medications.

Cyclamate is minimally toxic; however, it is metabolized by intestinal bacteria into cyclohexylamine, a compound with higher toxicity (Hasan et al., 2023). In rats, approximately 18.9% of ingested cyclamate is converted to cyclohexylamine. The concentration of cyclohexylamine in plasma depends on the extent of cyclamate breakdown by intestinal flora and its subsequent excretion from the bloodstream. The recommended acceptable daily intake (ADI) of cyclamate is 10 mg per kilogram of body weight (Spencer et al., 2016). Recent studies have raised concerns about the long-term use of cyclamate. A study published in 2023 found that mixtures of cyclamate and saccharin significantly increased levels of HbA1c and malondialdehyde (MDA), markers associated with oxidative stress, in healthy individuals (Hasan et al., 2023).

Regarding carcinogenicity, early animal studies suggested a potential link between cyclamate and bladder cancer (Weihrauch & Diehl, 2004). However, subsequent evaluations concluded that cyclamate does not cause cancer in humans. Despite this, it remains banned in the United States due to historical concerns. Although sodium cyclamate has been extensively studied by many researchers, there is still insufficient information regarding its chronic consumption at the acceptable daily intake levels. Therefore, in our study, we administered sodium cyclamate at the permitted daily dose to experimental animals for a period of two months and investigated its effects on metabolism, body weight, and insulin resistance.

MATERIAL AND METHODS

At present, to investigate the effects of sodium cyclamate on carbohydrate metabolism, 25 male Wistar albino rats weighing 140–200 g were selected. The experiments were carried out at the Toxicology Laboratory vivarium of the National Reference Laboratory of the Committee for Sanitary and Epidemiological Welfare and Public Health under the Ministry of Health of the Republic of Uzbekistan (based on the contract between the Committee and Tashkent Pediatric Medical Institute, dated March 10, 2022).

Prior to the start of the experiments, the purchased rats were kept under quarantine for 14 days and subsequently acclimatized for an additional week. Experimental animals were maintained under controlled laboratory conditions at a room temperature of 22 ± 3 °C, relative humidity of 30–70%, with a 12-hour light/dark cycle. Housing and feeding of the rats were conducted in accordance with the requirements of ICSMC 33215-2014.

The study protocol was approved by the Ethics Committee under the Ministry of Health of the Republic of Uzbekistan (No. 4 of May 19, 2022, reference No. 4/19-1667, dated 20.05.2024). All experimental procedures were conducted in accordance with the *Guide for the Care and Use of Laboratory Animals* (NRC, 2011).

For the experimental group, sodium cyclamate was administered orally at a dose of 10 mg/kg body weight once daily for 2 months, dissolved in distilled water (Azeez et al., 2019; Mandeville et al., 2023; Pang et al., 2021; Singh et al., 2023). Prior to the start of the experiment, blood samples were collected from the animals under light ether anesthesia for the determination of baseline glucose,

insulin, glycated hemoglobin (HbA1c), oral glucose tolerance test (OGTT), and biochemical parameters, which served as control values. After 30 and 60 days of treatment, the same parameters were re-assessed, and differences between time points were evaluated.

In addition, before initiation of the experiment, 5 rats were randomly selected and sacrificed by decapitation under light diethyl ether anesthesia. Their liver tissues were collected for the determination of baseline glucose and glycogen levels, which were used as control reference values. For the study, sodium cyclamate manufactured by LLC “NovaProdukt AG” (Moscow, Russian Federation) was purchased from the “Korzinka” retail chain belonging to Anglesey Food LLC, located in Tashkent, Uzbekistan. For biochemical and immunoassay analyses, blood samples were collected from the tail vein of the experimental animals. For this purpose, the rats were placed in specially designed metal restrainers adjusted to their body length, leaving the tail exposed. To induce hyperemia, the tail was immersed in warm water at 40–50 °C for several minutes. After drying, the tail vein was punctured using a G-24 injection needle (Vasilyeva et al., 2023), and the collected blood was transferred into gel-containing yellow-top tubes to obtain serum of sufficient quality. Blood sampling was performed at baseline (prior to the start of the experiment), and on days 30 and 60 of the study. The samples were centrifuged using a TDZ4-WS centrifuge (Hunan Xiangyi Laboratory Instrument Development Co., Ltd., China) at 3000 rpm for 5 minutes to separate plasma from cellular components. Hemolyzed blood samples were excluded from further analysis.

Biochemical Laboratory Examination Methods

For the determination of biochemical parameters including glucose, glycated hemoglobin, albumin, total protein, urea, creatinine, cholesterol, triglycerides, high-density lipoproteins (HDL), low-density lipoproteins (LDL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), sodium, calcium, and potassium, reagents manufactured by Human (Germany) were used, purchased from *Osiamedika LLC*. The measurements were performed using the Humastar 100 automated biochemical analyzer (Human, Germany) at the Department of *Medical and Biological Chemistry, Medical Biology and General Genetics*, Tashkent Pediatric Medical Institute. Serum insulin levels were quantified using the Rat Insulin ELISA Kit (ELK Biotechnology Co., Ltd., USA), with assays performed on the Mindray MR-96A semi-automated immunoassay analyzer (manufactured in the People’s Republic of China).

Prior to the start of the experiment, as well as on days 30 and 60, an oral glucose tolerance test (OGTT) was conducted in the rats. For this, animals were fasted overnight. Following baseline blood sampling in the morning, a glucose solution was administered once directly into the stomach using an atraumatic gavage needle at a dose of 2 g/kg body weight. Subsequent blood samples were collected at 30, 60, 90, and 120 minutes post-administration (Ghezzi et al., 2011; King Editor, n.d.; Tang et al., 2018). Glucose concentrations were determined using the method described above, and a “glucose concentration–time” curve was plotted. The area under the curve (AUC) was then calculated to assess glucose tolerance.

Determination of Hepatic Glycogen Content

To determine glycogen and glucose levels in liver tissue, five experimental animals were decapitated under diethyl ether anesthesia both before and at the end of the study. Liver tissue samples were collected immediately after decapitation.

Currently, several methods are available for glycogen quantification. Liver tissues were extracted either by boiling in a 30% potassium hydroxide (KOH) solution or by homogenization in trichloroacetic acid (TCA) solution. Glycogen was then precipitated from the extract using ethanol. Following centrifugation, the precipitate was subjected to acid hydrolysis and neutralization. Quantification was performed either by measuring copper reduction or by direct processing of the precipitated glycogen with the anthrone reagent. An alternative procedure was applied according to the protocol described in “*Practicum on Biochemistry*” (Severin S.E., Solovyova G.A., eds., 2nd revised and supplemented edition, Moscow State University Press, 1989, 509 p.) (Carroll et al., n.d.). For calculation of glycogen content, the determined glucose concentration was multiplied by a correction factor of 0.9, since the molecular weight of the glucose residue in glycogen is 162, while that of free glucose is 180 (162:180 = 0.9) (Carroll et al., n.d.).

Assessment of Insulin Resistance. In this study, the following formulas were used to assess insulin resistance (Table 1.).

Table 1. Methods of calculating insulin resistance.

Index	Formula	Units	Reference
HOMA-IR	$(\text{Glucose (mmol/L)} \times \text{Insulin } (\mu\text{U/mL})) \div 22.5$	mmol/L, $\mu\text{U/mL}$	(Matthews et al., 1985)
FIRI	$(\text{Glucose (mmol/L)} \times \text{Insulin } (\mu\text{U/mL})) \div 25$	mmol/L, $\mu\text{U/mL}$	(Duncan et al., 1995)
Caro Index	$\text{Glucose (mmol/L)} \div \text{Insulin } (\mu\text{U/mL})$	mmol/L, $\mu\text{U/mL}$	(Caro et al., 1991)
QUICKI	$1 \div (\log \text{ Insulin } (\mu\text{U/mL}) + \log \text{ Glucose (mg/dL)})$	mg/dL, $\mu\text{U/mL}$	(Otten et al., 2014)
TG/HDL-C Index	$\text{Triglycerides (mmol/L)} \div \text{HDL-C (mmol/L)}$	mmol/L	(McLaughlin et al., 2003)
TrG Index	$\text{Ln} [(\text{Triglycerides (mg/dL)} \times \text{Glucose (mg/dL)}) \div 2]$	mg/dL	(Simental-Mendía et al., 2008)
Metabolic Index (MI)	$[\text{Triglycerides (mmol/L)} \times \text{Glucose (mmol/L)}] \div [\text{HDL-C (mmol/L)}]^2$	mmol/L	(Roitberg et al., 2014)

Statistical Analysis

Statistical processing of the experimental data was performed using the JMP statistical software package. The significance of differences was evaluated using one-way ANOVA and nonparametric pairwise comparisons via the Wilcoxon method.

RESULTS AND DISCUSSION**Effect of Sodium Cyclamate on Carbohydrate Metabolism**

Chronic and long-term administration of cyclamate was associated with an increase in blood glucose levels. Prior to cyclamate administration, the mean blood glucose concentration in the experimental animals was 4.4 mmol/L. After 30 days of treatment, it increased to 7.14 mmol/L, and by day 60 it reached 7.46 mmol/L (Table 2). These results indicate that chronic consumption of cyclamate over 2 months led to a 69.6% increase in blood glucose levels.

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Table 2. Effects of Sodium Cyclamate on Blood Carbohydrate Metabolism Parameters, $M \pm m$

	Glucose, mmol/L	HbA1C, %	Insulin, mU/l
Baseline ($n = 20$)	4,40±0,09	3,37±0,08	9,50±0,21
Day 30 of the Experiment ($n = 20$)	7,14±0,19	5,74±0,10	18,67±0,10
p	0,001	0,001	0,001
Change Relative to Baseline, %	+ 61,2 %	+ 70,2 %	+ 95,6 %
Change Relative to Baseline ($n = 18$)	7,46±0,13	5,93±0,07	15,88±1,06
p	0,001	0,001	0,001
Change Relative to Baseline, %	+ 68,4 %	+ 76,0 %	+ 66,4 %

Furthermore, the level of glycated hemoglobin increased by 70.2% on day 30 and 76.0% on day 60 of the experiment. These increases indicate that sodium cyclamate has a negative effect on blood glucose levels.

In our experiment, insulin levels under cyclamate administration increased by 95.6% on day 30 and 66.4% on day 60 relative to baseline.

These elevations in insulin demonstrate the role of cyclamate in inducing hyperinsulinemia. Similar to other artificial sweeteners, cyclamate may contribute to the development of insulin resistance, as reported in several studies (El Amrousy et al., 2022; Kakleas et al., 2020; Балаева-Тихомирова et al., n.d.).

Effect of Sodium Cyclamate on General Metabolism

Chronic administration of sodium cyclamate also had a significant impact on blood biochemical parameters (Table 3). Analysis of protein and nitrogen-retaining compound metabolism showed that 30 days of cyclamate administration increased total protein levels by 14.5% ($p < 0.05$). By day 60, total protein levels were only 5.1% higher than baseline.

Table 3. Effect of Sodium Cyclamate on General Metabolism

Indicators	Baseline	Sodium cyclamate, 10 mg/kg-day	
		Day 30	Day 60
Indicators of Protein and Nitrogen-Retaining Compound Metabolism			
Total protein, g/L	66,20±0,89	75,8±0,57*	69,6±0,71*
Albumin, g/L	37,32±0,68	44,3±0,90*	43,6±0,78*
Urea, mmol/L	4,99±0,13	6,06±0,21*	7,19±0,18**
Creatinine, $\mu\text{mol/L}$	36,66±0,82	68,58±1,10*	78,54±2,18*
Liver enzymes			
ALT, U/L	55,45±2,06	85,56±1,47*	96,74±2,36*
AST, U/L	113,4±1,9	122,5±1,7*	121,0±6,4
Indicators of Lipid Metabolism			
Cholesterol, mmol/L	1,04±0,02	1,51±0,09*	1,33±0,07*
Triglycerides, mmol/L	0,67±0,03	0,76±0,04	0,93±0,06*
HDL-C, mmol/L	0,13±0,01	0,15±0,01	0,19±0,01*
LDL-C, mmol/L	0,22±0,05	0,24±0,01	0,34±0,03*
VLDL-C, mmol/L	0,53±0,02	0,56±0,02	0,99±0,07*
(AC)	1,02±0,09	1,86±0,32*	0,69±0,08*
Indicators of Mineral Metabolism			
Na⁺, mmol/L	143,7±1,0	151,3±1,36 *	133,9±1,9*
K⁺, mmol/L	5,08±0,13	2,93±0,21*	2,81±0,15*
Ca²⁺, mmol/L	2,09±0,01	0,86±0,02*	0,79±0,02*

Note: * – Values marked with an asterisk are statistically significant ($p < 0.05$).

Sodium cyclamate administration also led to an increase in albumin levels: on day 30, albumin was 18.7% higher than the control,

and on day 60, it was 16.8% higher. Prior to the experiment, the mean urea concentration in the animals' blood was 4.99 ± 0.13 mmol/L. After 30 days, it increased by 21.4%, and by 60 days, it had risen by 44.1%. Blood creatinine levels at baseline were 36.66 ± 0.82 μ mol/L, increasing by 77.7% on day 30 and 103.5% on day 60.

In studies conducted by Usman et al., cyclamate administration in rats resulted in a 51.5% increase in creatinine and a 30.5% increase in urea after 7 weeks (Usman et al., 2022). According to literature data, chronic administration of sodium cyclamate may potentially induce bladder carcinogenesis in experimental animals (BOPP et al., 1986).

The effect of cyclamate on liver tissues was significant. ALT activity increased by 59.7% on day 30 and 74.5% on day 60 compared to the control, and these increases were statistically significant. AST activity showed an 8.0% increase on day 30, which was statistically significant ($p < 0.01$), whereas the 6.7% increase on day 60 was not statistically significant ($p > 0.05$). In studies conducted by other researchers, 7-week administration of cyclamate in rats resulted in 79.7% increase in ALT activity and 61.7% increase in AST activity (Usman et al., 2022).

According to the results, at the start of the experiment, total cholesterol and triglyceride levels were 1.04 ± 0.02 mmol/L and 0.67 ± 0.03 mmol/L, respectively. By day 30, these levels increased by 45.1% and 13.9% ($P > 0.05$), and by day 60, they rose by 27.8% and 38.2%, respectively. Literature data report that cyclamate administration increased total cholesterol and triglyceride levels by 55.4% and 49.4% (Usman et al., 2022). These findings indicate that sodium cyclamate negatively affects lipid metabolism.

Administration of sodium cyclamate did not affect HDL-C and LDL-C levels on day 30, but by day 60, HDL-C and LDL-C levels increased by 54.5% and 86.8%, respectively. Meanwhile, VLDL-C levels on day 60 were 86.8% higher than baseline. In contrast, results from Usman et al. showed a 66.7% increase in LDL-C and a 12.7% decrease in VLDL-C under cyclamate administration (Usman et al., 2022).

Furthermore, chronic administration of sodium cyclamate affected microelement metabolism. By day 30, sodium (Na^+) levels increased by 5.3%, while potassium (K^+) and calcium (Ca^{2+}) levels decreased by 43.4% and 59%, respectively. By the end of the experiment, Na^+ , K^+ , and Ca^{2+} levels had changed by 6.8%, 45.7%, and 63.4%, respectively.

Cyclamate is commonly used in the form of its sodium salt, which may lead to additional sodium intake through dietary products. This could indirectly affect sodium-potassium balance, blood pressure, and the metabolism of other minerals. Some animal studies have reported renal damage following administration of cyclamate or cyclamate-saccharin mixtures, which may influence the urinary excretion or reabsorption of minerals such as calcium, magnesium, potassium, and phosphate (Cristina Guimarães et al., n.d.). Cyclamate also stimulates insulin secretion, which can alter the cellular uptake of minerals including potassium, magnesium, and phosphate. Additionally, cyclamate can be metabolized by gut microbiota into cyclohexylamine, a compound that may affect liver and kidney function and consequently modify mineral metabolism indirectly (Ferraz de Arruda et al., 2004).

Effect of sodium cyclamate to glycogen metabolism in the liver.

Chronic administration of the sweetener sodium cyclamate resulted in changes in glycogen synthesis in the liver. According to the experimental results, glucose and glycogen levels in liver tissue decreased by 41.99% and 41.83%, respectively, after 60 days of sodium cyclamate administration (Figure 1).

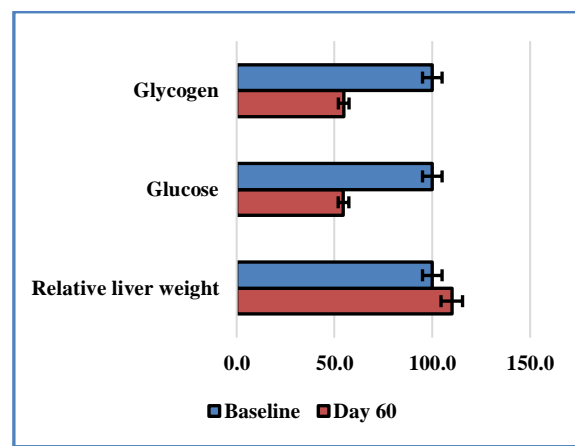


Figure 1. Effect of Sodium Cyclamate on Carbohydrate Metabolism Parameters in Liver Tissue (Results Presented as % Change). Light color – baseline; dark color – day 60 of the experiment.

Glycogen content in the liver of healthy control animals was nearly twice as high compared to animals that received the sugar substitute. The slight increase in relative liver weight (RLW) caused by sodium cyclamate administration was not statistically significant. These results indicate that chronic administration of synthetic sodium cyclamate negatively affects carbohydrate metabolism in the body, impairing glycogen formation in the liver.

There are currently conflicting views regarding the effects of sodium cyclamate on human health. Sodium cyclamate is widely used in the production of carbonated beverages, fruit juices, syrups, chewing gums, and jams. Following studies in rats that demonstrated the development of bladder cancer under chronic cyclamate exposure, this compound was removed from the “Generally Recognized as Safe” (GRAS) list in the United States, and its use in the food industry was prohibited (K.D. Aparnathi, 2017). However, cyclamate continues to be extensively utilized in many Asian and European countries, including Uzbekistan.

Cyclamate is metabolized in the small intestine by gut microbiota into cyclohexylamine, a compound with carcinogenic potential, which has been shown to induce bladder and kidney tumors in rats (Ižaković et al., 2021.; Renwick et al., 2004; Singapurwa et al., 2021). Observational studies in humans have suggested that cyclamate consumption may be associated with infertility, tachycardia, and hypertension (Singapurwa et al., 2021). Investigations into the effects of cyclamate on bone tissue using osteoblast cell cultures revealed that exposure to 0.06 μ M cyclamate can negatively affect microfilament and microtubule structures, potentially impairing mineralization and reducing Ca^{2+} ion levels. In vitro studies also indicate that cyclamate may inhibit osteoblast differentiation and proliferation (Singapurwa et al., 2021) (Diniz et al., 2022).

Moreover, chronic cyclamate consumption has been associated with pathological changes in the cardiovascular and nervous systems, thyroid adenomas, erythrocytes, leukocytes, bone cells, and reproductive cells (Saad et al., 2014). Rat studies demonstrated that consumption of beverages containing 0.5–2.0% cyclamate significantly increased mortality rates (Patil et al., 2023). Intake of beverages containing 2% cyclamate also elevated the activity of glutamate transaminase and lactate dehydrogenase (BOPP et al., 1986). Nevertheless, cyclamate remains approved for use in 55 countries worldwide (Singapurwa et al., 2021).

Experimental studies indicate that administering sodium cyclamate at a dose of 10 mg/kg/day for two weeks in rats resulted in a 49% increase in blood glucose levels (Emanuella et al., 2022, n.d.). This effect is associated with a reduction in *Akkermansia muciniphila*

populations, bacteria that normally reduce lipopolysaccharide (LPS) levels and coat cell surfaces with Gram-negative bacteria, thickening the mucosal layer. LPS binds to Toll-like receptor 4 (TLR-4) on macrophages, triggering the production of inflammatory mediators that promote pancreatic β -cell inflammation and insulin resistance (Emanuella et al., 2022, n.d.; Setiady et al., n.d.). Similarly, Setiady et al. reported that 5 weeks of cyclamate administration at 13.5 mg/kg/day in rats led to a 24.8% increase in blood glucose levels (Setiady et al., n.d.). Collectively, these studies suggest that cyclamate may induce dysbiosis in the gastrointestinal tract, contributing to the development of insulin resistance.

Effect of Sodium Cyclamate to Glucose Tolerance Test

When sodium cyclamate was chronically administered to experimental animals at the permitted dose, significant changes were observed in the oral glucose tolerance test (OGTT), indicating an alteration in glucose metabolism (Figure 2.).

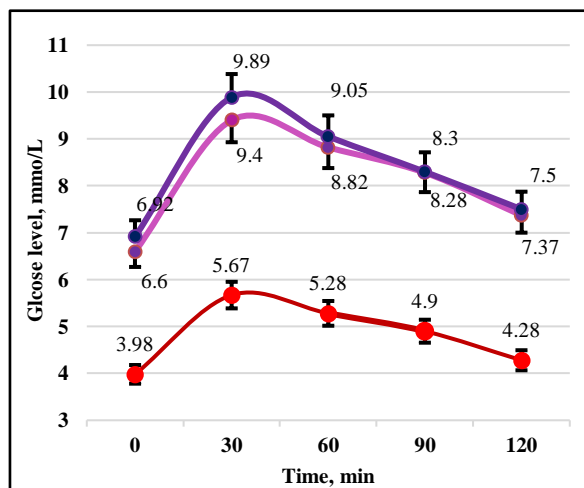


Figure 2. Glucose Tolerance Test in Rats Administered Sodium Cyclamate. Red curve – control (intact) animals, Pink curve – day 30 of cyclamate administration, Blue curve – day 60 of cyclamate administration. Y-axis – glucose concentration (mmol/L), X-axis – time (minutes)

Chronic administration of sodium cyclamate at a dose of 10 mg/kg body weight per day to rats markedly reduced insulin sensitivity, particularly by day 30 and more pronouncedly by day 60 of the experiment.

To quantify these effects objectively, the area under the glucose curve (AUC) was calculated, allowing a numerical comparison rather than relying solely on visual inspection of the glucose response curves (Fig. 3).

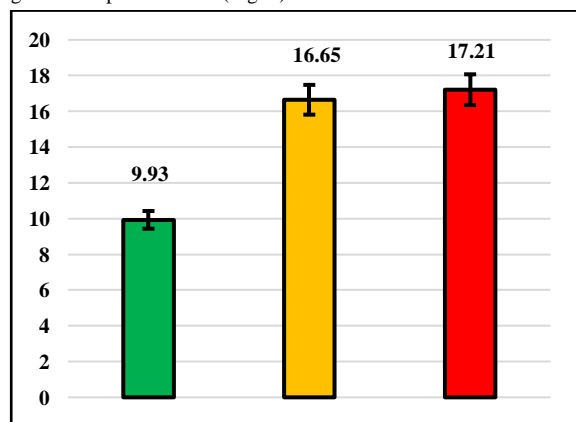


Figure 3. Area under the "glucose concentration-time" curve in animals administered sodium cyclamate Green bar – baseline value, yellow bar – day 30 of the experiment, red bar – day 60 of the experiment; ordinate axis – mmol-h/L.

The results indicate that in animals administered sodium cyclamate, the area under the "glucose concentration-time" curve increased by 67.7% on day 30 and by 73.3% on day 60 compared to baseline values.

In the study conducted by Hasan et al. (2023), consumption of sodium cyclamate was observed to increase fasting blood glucose levels by up to 23% (Hasan et al., 2023). Artificial sweeteners may influence glycemic control, as replacing available carbohydrates can reduce glucose absorption. However, this does not necessarily improve glucose homeostasis, since alterations in intestinal glucose transport, insulin resistance, and reduced insulin secretory capacity induced by artificial sweeteners can impair glucose regulation. In our study, prolonged consumption of sodium cyclamate led to elevated blood glucose levels. This effect may result from cyclamate-induced alterations in the gut microbiota or from activation of Glut2 in the small intestine. Persistent hyperglycemia associated with long-term intake of artificial sweeteners may contribute to the development of insulin resistance and type 2 diabetes mellitus (T2DM). Evidence from systematic reviews and meta-analyses remains conflicting. While some analyses of RCTs and prospective cohort studies in healthy individuals found no conclusive evidence that artificial sweeteners increase the risk of T2DM, other cohort studies reported a positive association between sweetener intake and T2DM incidence, independent of adiposity, though attenuated after BMI adjustment. Importantly, most cohort studies rely on baseline exposure and may be affected by reverse causation. Overall, current systematic and meta-analytic data do not consistently support a protective effect of artificial sweeteners against T2DM in humans.

Effect of Sodium Cyclamate on Body Weight.

Although sodium cyclamate is a non-caloric artificial sweetener, several studies indicate that its chronic consumption may indirectly contribute to body weight gain. Experimental studies in rodents have demonstrated that long-term intake of sodium cyclamate can impair glucose tolerance, reduce insulin sensitivity, and alter the secretion of key metabolic hormones, promoting fat deposition despite the absence of caloric intake (Emanuella et al., 2022, n.d.; Setiady et al., n.d.). Additionally, sodium cyclamate has been shown to modify gut microbiota composition, particularly reducing populations of *Akkermansia muciniphila*, which are critical for maintaining metabolic homeostasis and regulating lipid absorption (Emanuella et al., 2022, n.d.). These alterations may increase energy storage and contribute to weight gain. Although human data are less conclusive, these findings highlight that even non-caloric sweeteners can influence metabolic pathways and potentially affect body weight through mechanisms beyond direct caloric contribution.

Animal studies have demonstrated that artificial sweeteners contribute to body weight gain. The perception of sweetness stimulates insulin secretion, which facilitates the uptake of glucose into tissues. However, since artificial sweeteners do not elevate blood glucose levels, this response can lead to hypoglycemia and increased food intake. Consequently, in experimental settings, rats receiving artificial sweeteners gradually consumed more calories over time, resulting in increased body weight and adiposity (Tandel, 2011).

In our study, the administration of sodium cyclamate alone did not significantly affect body weight. On the contrary, by the end of the experiment, the absolute body weight of the rats decreased by 6.6% compared to the baseline ($p > 0.05$) (Table 4). In contrast, when saccharin was administered, the body weight of the experimental animals increased by 26.4% and 52.8% on days 30 and 60, respectively, relative to baseline values.

This corresponded to an average daily weight gain of approximately 1 g per animal. These results suggest that, unlike some other artificial sweeteners, sodium cyclamate alone does not promote weight gain and may even slightly reduce body mass under the conditions of this study.

Table 4. Effect of Sodium Cyclamate on Body Weight.

Indicators	Sodium cyclamate		
	Baseline (n=20)	Experimental days	
		30 (n=20)	60 (n=18)
Body weight, g	175,8±4,0 (144,0÷201,0)	171,4±4,0	164,3±5,8
Change Relative to Baseline (n = 18), %		2,5	6,5
Daily body weight, g		- 0,15	- 0,19

The average daily body weight change was 0.15 g/day during the first 30 days of sodium cyclamate administration, indicating a slight reduction in body mass. By the end of the 60-day experimental period, the daily weight change increased in magnitude to 0.19 g/day, reflecting a progressive, though modest, decline in body weight over time.

Effect of Sodium Cyclamate on Insulin Resistance Indices

The administration of sodium cyclamate significantly affected insulin resistance markers in experimental rats. Specifically, HOMA-IR values increased by 214.9% on day 30 and 179.8% on day 60 compared to baseline, indicating a substantial reduction in insulin sensitivity over time (Table 5). Similarly, the Fasting Insulin Resistance Index (FIRI) rose by 215.4% on day 30 and 179.9% on day 60, corroborating the HOMA-IR findings. In the study conducted by Lee et al., HOMA-IR values were found to be associated with the onset of new diabetes and vascular diseases. Individuals with higher HOMA-IR exhibited an increased risk of developing diabetes and cardiovascular complications (Kim et al., 2020). In a study conducted in Bangladesh, the FIRI index was shown to be effective in identifying insulin resistance. Individuals with higher FIRI values were found to have an increased risk of metabolic syndrome (Bhowmik et al., 2016). In our study, long-term consumption of sodium cyclamate resulted in a significant increase in HOMA-IR and FIRI indices.

The Caro index, which inversely correlates with insulin resistance, decreased by 19.2% on day 30, but returned to baseline levels by day 60. Additionally, the QUICKI index, another indicator of insulin sensitivity, decreased by 14.3% on both day 30 and day 60 relative to baseline. A study by Aliyu et al. confirmed that the QUICKI index is a reliable tool for evaluating insulin sensitivity (Aliyu et al., 2025). Scientific studies have shown that the Caro index and HOMA-IR index are consistent in assessing insulin resistance. The Caro, HOMA-IR, and QUICKI indices have been applied to evaluate insulin resistance in patients with chronic pancreatitis (Pakhomova et al., 2020). Kseneva et al. compared the effectiveness of the Caro index with other insulin resistance indices and recommended its use for assessing insulin resistance (Kseneva et al., 2022). In our study, QUICKI reached elevated values under the influence of cyclamate, reflecting increased insulin resistance. However, the Caro index did not show significant changes.

The administration of sodium cyclamate did not produce statistically significant changes in the TG/HDL-C ratio compared to baseline values. However, the Triglyceride-Glucose Index (TGI)

showed a gradual, progressive increase: by approximately 8% on day 30 and 11% on day 60, indicating a trend toward impaired metabolic function. In their studies, researchers found that patients with elevated TGI index exhibited increased insulin resistance, as well as higher risk of diabetes, metabolic syndrome, and cardiovascular disease (Kurniawan & Info, n.d.). Sun et al. (2025) reported that the TGI index demonstrated high sensitivity and accuracy in assessing insulin resistance (Sun et al., 2025). Another study confirmed that the TGI index is an effective marker for evaluating insulin resistance across different populations (Lopez-Jaramillo et al., 2023). In 2024, Park et al. reported that the TGI index showed higher sensitivity and accuracy than HOMA-IR in assessing the risk of metabolic syndrome (Park, 2024). Wen et al. emphasized that the TGI index could predict the risk of diabetes even in individuals with normal glucose and triglyceride levels (Wen et al., 2025).

The Metabolic Index (MI) increased by 71.8% on day 30 relative to baseline, demonstrating a marked early effect of cyclamate on metabolic parameters. By day 60, MI values were not substantially different from baseline, suggesting a possible adaptation or plateau effect over prolonged exposure.

Table 5. Effect of Sodium Cyclamate on Insulin Resistance Indices

Indexes	Sodium Cyclamate		
	Baseline (n=20)	Experimental days	
		Day 30 (n=20)	Day 60 (n=18)
HOMA-IR	1,88±0,05 (1,47÷2,27)	5,92±0,16*	5,26±0,35*
FIRI	1,69±0,04 (1,33÷2,4)	5,33±0,14*	4,73±0,32*
Caro	0,47±0,02 (0,34÷0,58)	0,38±0,01*	0,50±0,04
QUICKI	0,35±0,001 (0,34÷0,36)	0,30±0,001 *	0,30±0,003*
TG/HDL-C	1,30±0,07 (0,96÷2,25)	1,42±0,09	1,21±0,11
TGI	7,75±0,05 (7,47÷8,20)	8,35±0,05*	8,59±0,06*
MI	11,67±1,25 (6,10÷28,47)	20,05±2,73 *	11,92±1,50

Note: * – Values marked with an asterisk are statistically significant (p < 0.05).

Overall, these results suggest that while sodium cyclamate did not significantly alter classic lipid ratios, it may contribute to subtle, progressive changes in lipid-glucose-related indices, reflecting early disturbances in insulin sensitivity and metabolic regulation.

In our study, it was found that even the administration of sodium cyclamate at the permitted dose, when given long-term, led to a significant increase in the indices of HOMA-IR, FIRI, Caro, QUICKI, TGI, and MI in experimental animals as early as day 30 compared to baseline values. By the end of the study, the indices HOMA-IR, FIRI, QUICKI, and TGI showed a significant increase relative to baseline. The simultaneous elevation of several indices reflecting insulin resistance, along with the rise in blood glucose and insulin concentrations and the increase in glycated hemoglobin levels, indicates that long-term exposure to sodium cyclamate, even at the permitted dose, may induce insulin resistance.

Research by Malaisse et al. demonstrated that sodium cyclamate, when administered at a 10.0 mM concentration, augmented insulin release from isolated rat pancreatic islets in the presence of glucose. This suggests that sodium cyclamate may stimulate insulin secretion, which could contribute to altered insulin dynamics and resistance over prolonged exposure (Malaisse et al.,

1998). Artificial sweeteners like sodium cyclamate may affect glucose homeostasis by altering gut microbiota composition, leading to increased intestinal glucose absorption. Specifically, they may upregulate glucose transporters such as SGLT1 and GLUT2, which can enhance glucose uptake and potentially contribute to insulin resistance (Pang et al., 2021). Studies by Pepino et al. demonstrated that consumption of artificial sweeteners may contribute to weight gain by promoting elevated peak insulin levels and modifying metabolic responses (Pepino et al., 2013).

CONCLUSION

The present study demonstrates that chronic administration of sodium cyclamate, even at a dose considered permissible for daily intake, induces significant disturbances in glucose homeostasis, insulin sensitivity, and multiple metabolic pathways in experimental rats. Prolonged exposure resulted in hyperglycemia, hyperinsulinemia, impaired glucose tolerance, and marked reductions in insulin sensitivity indices, indicating the development of insulin resistance. In parallel, alterations in hepatic glycogen storage, nitrogen metabolism, lipid profile, and mineral balance further underscore the systemic metabolic burden imposed by cyclamate consumption. Although no body weight gain was observed, the adverse biochemical and metabolic changes suggest that sodium cyclamate may pose health risks when used chronically. These findings warrant careful reevaluation of the long-term safety of sodium cyclamate as a non-caloric sweetener and emphasize the need for further mechanistic and clinical studies to clarify its potential role in the pathogenesis of metabolic disorders.

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