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Article

Subchronic intraperitoneal toxicity of Sio2NPs on body weight and thyroid gland hormones in female Rats

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Abstract: This study investigated the toxicity effect of Sio2NPs on body weight and thyroid gland in female rats; the experiment was included. The experimental animals were randomly divided into three groups, including two treatment groups (treated with a low dose (25mg/Kg) and high dose (100mg/Kg of body weight) of sio_2 NPs and one group as a control. Each group of them was divided into three subgroups according to the injection periods of exposure (10, 20, and 30) days daily, then measure the body weight and Thyroid function hormones (T3, T4, TSH), the results showed that there was a significant decrease ($p<0.05$) in the body weight of animals that exposed to SiO_2 NPs at two doses (25 and 100 mg/kg) during (10 days) while increased during (20, 30 days) but the highest value recorded in the animals that were treated for (30 days) at both doses. On the other side, the T3 findings recorded a significant decrease ($p< 0.05$) for the animals that exposed to SiO_2 NPs at low and high doses (25 and 100 mg/kg) (during (10 days) when compared with the control group As well as, there was a significant decrease ($p< 0.05$) in the level of T3 for all animals that treated with these doses during (20 and 3 days) in serum of animals that were treated with both doses of SiO_2 NPs when compared with the control group ($p< 0.05$), while T4 showed s decreasing in the treated group during (10 and 20, 30 days) compared to a control group with highly significant (($p< 0.05$), finally while TSH showed a highly increasing in treated group during (10 and 20, 30 days) compared to control group ($p< 0.05$). The study revealed that Exposure to Sio2NPs at different concentrations caused structural and functional and in the thyroid gland, characterized decrease in T3 and T4 hormone levels and an increase in the TSH hormone level and caused hypothyroidism This led to a decrease in the metabolism process and thus the body weight of animals gained a significant increase.

Keywords: nanoparticles, Sio2NPs, Thyroid gland, T3, T4, TSH, Body weight, female rats.

Introduction

Nanotechnology refers to developing, manufacturing, and applying materials at the atomic, molecular, and macromolecular levels to create new nanoparticles [1]. These particles are distinguished by their small size, which ranges from 1-100 nm [2]. The physiological and chemical features of nanoparticles are used to classify them, with silicon dioxide nanoparticles being one of them [3]. SiO2 NPs are widely employed as biomarkers, cancer treatments, drug delivery vehicles in the

biomedical area, and additives in chemical polishing, varnishes, cosmetics, and foodstuffs in the nonmedical field [4].

Nanoparticles can enter the body through different rout such as; inhalation, absorption through the skin or the digestive tract, voluntary injection, or implantation for drug delivery [5]. Following that, when these particles engage with biological systems, they can have both positive and negative effects on the exposed live beings, as cells can ingest NPs, which subsequently interact with cellular organelles [6].

SiO2 NPs (E551) are incorporated as anticaking agents in some powdered foods, such as salt, spices or dried milk, to enhance flow properties [7]. TiO2 NPs (E171), which contain up to 43% of NPs [8], are used as whitening agents in candies, chewing gums or bakery [9]. The consumption of these NPs, added directly to food or migrated from packaging, has long been considered toxicologically harmless [10]. However, some studies have suggested that food NPs can induce local and systemic toxicity, raising concerns about possible health risks [11]. Weight loss, epithelial cell damage in intestinal microvilli, severe inflammation of the colon, as well as oxidative hepatic toxicity, inflammation or lipid metabolism dysregulation have been observed in rats or mice orally exposed to high doses of Ag NPs (up to 2.5 mg/kg bw/d) [12].

Regarding SiO2 NPs, long-term studies in rats or mice have reported contrasting results. Liver and kidney toxicity has been recorded after chronic oral administration of SiO2 NPs [13], whereas other studies did not record toxicity [14]. The endocrine system is susceptible to environmental pollutants, and it has been reported that about 10% of the population suffer from thyroid gland disorders, which may be considered a significant public health problem suggested the possible time and dose-dependent disrupting potential of Certain nanoparticles on thyroid gland function and histology in female rats [15]. the current study aimed to investigate the intraperitoneal toxicity of Sio2NPs on the body weight and thyroid gland in female rats.

Material and methods

Preparation of Sio2 NPs Solutions

The Sio2 NPs (silicon dioxide NPs) which is used in this study obtained from sky spring nanomaterials company properties of this product are: The Sio2 NPs (silicon dioxide NPs) used in this study were obtained from sky spring nanomaterials company, the properties of this product are: White powder in Appearance, Purity is 99.5%, The Particle size is 20 nm in diameter, The specific surface area is 160 m^2 /g. , spherical and Bulk Density: 0.08_0.10 g\cm^3.

Preparation of SIO2 NPs Suspension

The preparation of an injected suspension of different concentrations from sio2NPs used in this study was prepared by dissolving the powder of sio2 nanoparticles in distilled water and mixing by vortex for 10 minutes. Wo concentrations of sio_2NPs solution were prepared (25 mg/kg of sio2NPs (Low dose) and 100 mg/kg of sio_2NPs (High dose).

Lab animals

Fifty-four adult female Sprague-Dawley rats having ages between 8-10 weeks and weighing 225-250 gm. They were obtained from Biotechnology Research Center (BRC) ⁄ AL Nahrain University, then these animals housing in the laboratory of the Biotechnology Research Center, AL Nahrain University and kept for adaptation for 15 days before starting the experimental under the controlled temperature conditions (25 °C), and proximately 12 h light/12 h dark

cycle. The animals were provided with pellets and tap water for feeding and drinking.

Study groups

The experimental animals were randomly divided into three groups, two as treatment and one as control. Each group of them was divided into three subgroups according to the injection periods of exposure (10, 20, and 30) days daily doses per week except on public holidays through the intraperitoneal route; each one consists of 6 rats as shown in the below details:

Group 1, 2, and 3 (Control animals): the animals received an intraperitoneal injection of distilled water

Group 4, 5, and 6: the animals received an intraperitoneal injection with a low dose (25mg/Kg) of body

Groups 7, 8, and 9: All the animals in these groups received an intraperitoneal injection with a high dose (100mg/Kg of body weight) of sio_2 NPs

The serum was separated by centrifugation of blood at (3000) rpm for (15) minutes for the hormonal and biochemical testing; then, the serum was split into multiple equal sections in Eppendorf tubes and maintained at -20oC.

Body Weights Measurements

All animals for each group were weighed before and after the exposure periods (10, 20, and 30) day.

Hormonal Analysis

The Cobase 6000 (c501) analyzer measured thyroid hormones (T3, T4, and TSH) in collected serum.

Principle of Triiodothyronine T3

With polyclonal antibodies mainly directed against T3, the Elecsys T3 assay uses a competitive test approach. Endogenous T3, which is produced by the action of 8 anilino 1 naphthalene sulfonic acid (ANS), competes with the biotinylated T3 derivative for binding sites on the ruthenium complex-labeled antibodies [16].

Principle test of Total thyroxine T4

With an antibody directed explicitly against T4, the Elecsys T4 assay uses a competitive test approach. Endogenous T4 competes with the additional biotinylated T4 derivative for the binding sites on the ruthenium complex) tagged antibodies [16]

Principle of Thyroid-Stimulating Hormone TSH.

The Elecsys TSH test is a 3rd generation sandwich principal assay. Monoclonal antibodies designed against human TSH are used in the test. The ruthenium complex-labeled antibodies are a chimeric construct of human and mouse-specific components. Consequently, HAMA (human anti-mouse antibodies) interfering effects are virtually abolished [17].

Statistical Analysis

The Statistical Analysis System- SAS; [18] application was used to determine the impact of various factors on all of the study's parameters. The least significant difference –the LSD test (Analysis of Variation-ANOVA), was also used to compare the means substantially.

Results

the data showed there was a significant decrease ($p<0.05$) in the body weight of animals that were exposed to SiO_2 NPs at two doses (25 and 100 mg/kg) (231.66±0.67) and (226.50±0.76) respectively during (10 days) when compared to the control set (240.30±0.56). In addition, there was a considerable increase ($p<0.05$) in the body weight for treating animals with the same doses (271±0.61) and (281±0.79), respectively, during (20 days) when compared with the control group (241.20±0.47). Finally, the results also revealed a considerable increase ($p< 0.05$) in the animals that were treated for (30 days) at both doses (300±0.67) and (324±0.99) separately, when compared to the control set (240.50±0.56) as in Figure 1.

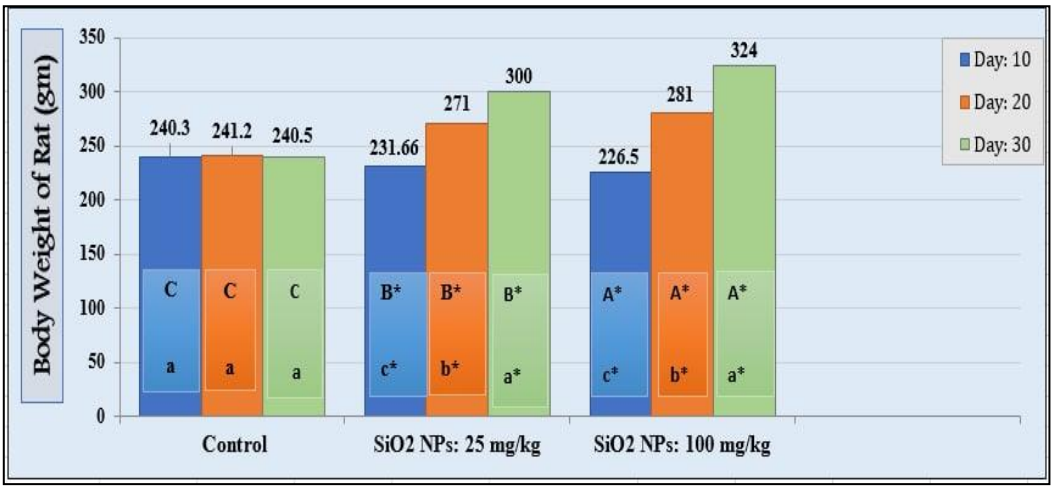

Figure 1. Effect of SiO_2 NPs at different concentrations (25 and 100 mg/kg) during different exposure periods on body weight of Rats.

- **(*) Mean significant difference($p\leq0.05$).**
- **(A, B, C) Represent the significant difference between groups when time is a variable factor and concentration is a fixed factor.**
- **(a, b, c) Represent the significant difference between groups when time is a fixed factor, and concentration is a variable factor.**

The results of the present study showed a decrease in the body weight (gm) of the treated animals at first (10 days) compared to the untreated animals (control); the current study agreed with the previous study that applied the SiO_2 NPs in Freshwater Fish at dose 12 mg\L during different period of exposure, the results revealed essential reduction ($P<0.05$) in the body weights of the animal only after 30 and 60 days in compared to the control group [19]. Another previous study demonstrated that the sio2NPs initiated a central reduction of the body weight in rats after intraperitoneal injection at a dose of 2mg/kg for (2,4,6,8,10,12 and 14) weeks [20]. Another previous study demonstrated that sio2NPs caused an essential reduction of the body weight in the rats after intratracheal contact at doses of (2,5 and 10 mg/kg) daily for 15 treatments [21]. Other previous studies also demonstrated that the TiO2 NPs initiated a noteworthy reduction of body weight in rats after oral contact at doses of 10 and 50 mg/ kg-1 from the 8th to 13th week [22]. It suggested that oral exposure to nanoparticles (Tio2) caused digestive disturbances, especially effective on the mucous membrane, which leads to appetite loss (anorexia), considering the reasons for the high toxicity that eventually decreases the body weight of animals [23], While in our study, we found

that sio2NPs produced a significant reduction in body weight in rats after intraperitoneal injection at doses of (25,100)mg/kg daily at (10days) due to the effect of nanoparticles on the digestive system, which caused disturbances in mucous membrane, leading to anorexia, and that there is no absorption of Sio2NPs, which leads to diarrhea.

In this study, we propose that this increase in body weight is due to thyroid hormones' role in regulating body and fat weight homeostasis by decreasing the fat content of the body; the absence of thyroid hormones is supposed to decrease vitality expenditure and affect flowing leptin levels indirectly during the regulation of adipose tissue mass, growth fat mass, and maybe decrease the weight of the body; thus, small thyroid hormone ranks growth fat mass and decrease power expenditure, resulting in weight increasing.

Moreover, the study was investigated the thyroid gland function by measuring their hormone levels T3, T4 and TSH and statistical analysis performed for all animals exposed to SiO_2 NPs and reported that the T3 hormone demonstrated a significant decrease ($p< 0.05$) for the animals that exposed to SiO_2 NPs at low and high doses (25 and 100 mg/kg) (1.22 ±0.011) and (1.16 ±0.008) respectively, during (10 days) when compared with the control group (1.40 ±0.003). As well as, there was a significant decrease ($p< 0.05$) in the level of T3 for all animals treated with these doses (1.18 ±0.008) and (1.12 ±0.007) respectively, during (20 days) when compared with the control group (1.43 ± 0.21). Also, the result for (30 days), demonstrated a significant increase ($p< 0.05$) in the serum of animals that were treated with both doses of SiO_2 NPs (0.920 ±0.04) and (0.810 ±0.02), respectively, when compared with the control group (0.810 ±0.02), as presented in Figure 2.

While the value of T4 hormone showed a significant decrease ($p< 0.05$) for the animals that were exposed to SiO2 NPs at both doses (25 and 100 mg/kg) (35.15 ±0.74) and (31.14 ±0.82) respectively, during (10 days) when compared with the control group (45.86 ±1.49), the result also demonstrated a significant decrease ($p<0.05$) in the level of T4 hormone of treatment animals with these two doses (23.32 ±0.72) and (21.63 ±0.60) respectively, during (20 days) when compared with the control group (47.34 ±0.73). Finally, the result showed a significant decrease ($p< 0.05$) in the level of T4 hormone in all animals that were treated with SiO2 NPs for (30 days) (16.31 ±0.37) and (13.83 ±0.56) respectively, when compared with the control group (48.3±2.01), as presented in Figure (3-4). Finally, concerning the outcomes of the TSH hormone, the results in Figure 4 presented a noteworthy rise ($p< 0.05$) for the animals that were exposed to SiO_2 NPs at two doses (25 and 100 mg/kg) (2.145±0.001) and (2.182±0.002), respectively, during (10 days) when compared with the control set (0.197±0.001). Also, there was an essential rise ($p< 0.05$) in the level of TSH of treatment animals with these two doses (2.25 ±0.17) and (2.42 ±0.30), respectively, for (20 days) when compared with the control group (0188 ±0.001). As well, the result recorded a significant increase ($p<0.05$) in the level of TSH hormone in all animals that were treated during (30 days) with both doses (3.152 ±0.17) and (3.621 ±0.27) separately when it is compared to the control set (0.195 ±0.02).

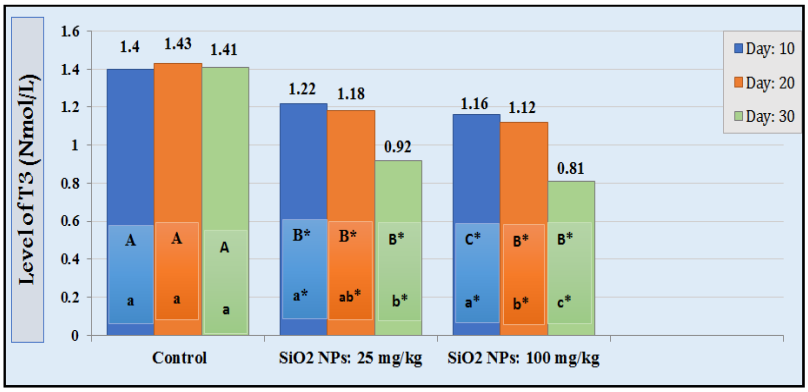

Figure 2. Effect of SiO_2 NPs at different concentrations (25 and 100 mg/kg) during different exposure periods on T3 hormone of Rats.

- **(*) Mean significant difference ($p \leq 0.05$).**
- **(A, B, C) Represent the significant difference between groups when time is a variable factor and concentration is a fixed factor.**
- **(a, b, c) Represent the significant difference between groups when time is a fixed factor, and concentration is a variable factor.**

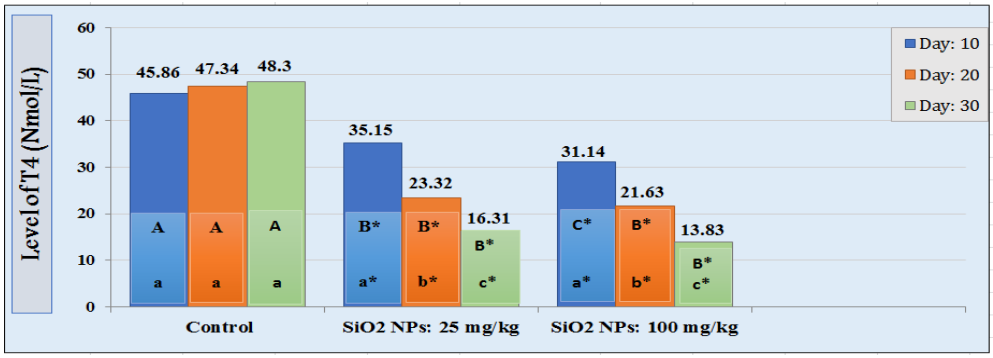

Figure 3. Effect of SiO_2 NPs at different concentrations (25 and 100 mg/kg) during different exposure periods on T4 hormone of Rats.

- **(*) Mean significant difference ($p \leq 0.05$).**
- **(A, B, C) Represent the significant difference between groups when time is a variable factor and concentration is a fixed factor.**
- **(a, b, c) Represent the significant difference between groups when time is a fixed factor, and concentration is a variable factor.**

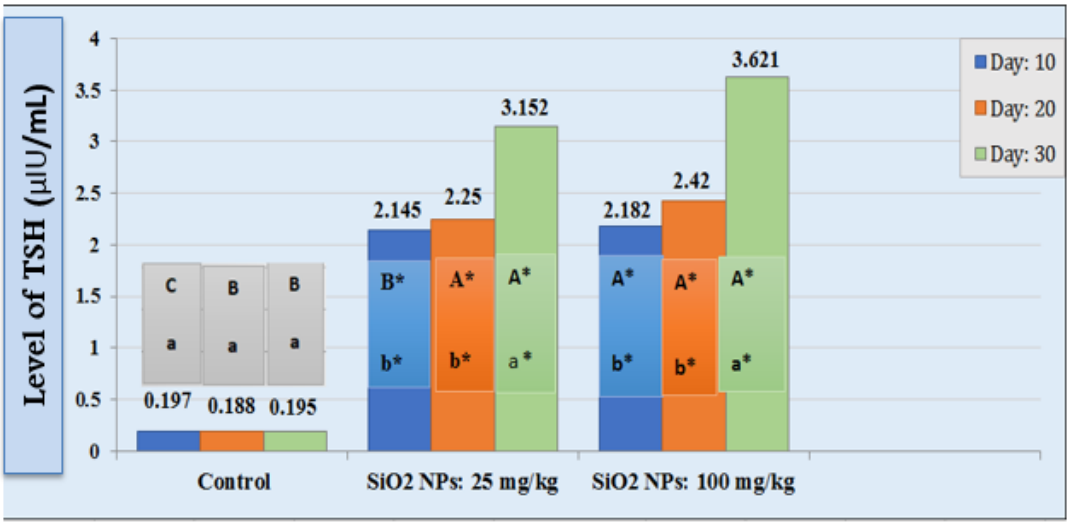

Figure 4. Effect of SiO_2 NPs at different concentrations (25 and 100 mg/kg) during different exposure periods on TSH hormone of Rats.

- **(*) Mean significant difference ($p \leq 0.05$).**
- **(A, B, C) Represent the significant difference between groups when time is a variable factor and concentration is a fixed factor.**
- **(a, b, c) Represent the significant difference between groups when time is a fixed factor, and concentration is a variable factor.**

The outcomes of the current study demonstrated a gradual significant decrease in the level of the thyroid hormones (T3 and T4) and a gradual increase in the level of the TSH hormone. The production and release of thyroid hormones by the thyroid gland are regulated by pituitary secretion of TSH and hypothalamic secretion of TRH, and this regulatory control of circulating thyroid hormone concentrations is commonly referred to as the hypothalamic-pituitary-thyroid axis [34]. These findings agreed with the results of a previous study that was reported by [35], who showed there is a significant decrease in the level of the T4 hormones in the serum of zebrafish larvae that were exposed to Tio2 (0.1 mg/kg) nanoparticles that combined with pentachlorophenol in compared with the control group. Another previous study that was reported by [36] showed there are essential reductions in the level of T3 and T4 and a rise in the level of the TSH hormone in the serum of rats after intraperitoneal injection at a dose of (30,60 mg/kg) for (7,14 and 28) days. Moreover, other previous studies demonstrated that the AgNPs caused an essential reduction in the level of T3, T4 and the serum of rats after intraperitoneal injection at a dose of (12,5,25 and 50mg/kg) for 4 weeks [37]. Another previous study demonstrated that ZnoNPs caused a significant decrease in levels of T3 and T4 in the serum of rats after intraperitoneal injection at doses of (30 and 60mg/kg) for (7,14, and 28) days [39]. Another previous study demonstrated that AgNPs caused a significant decrease in the level of T4 in the serum of rats after intraperitoneal injection at a dose of (12,5,25 and 50mg/kg) for 30 days [15]. Another previous study demonstrated that SeNPS caused a significant decrease in levels of T3 and T4 in the serum of rats after intraperitoneal injection at a dose of (0.5 mg/kg) daily for 5 consecutive days [39]. Another previous study demonstrated that PS NPs caused an essential rise in TSH levels in the serum of rats after oral administration at a dose of (1,3,6 and 10mg/kg) for five weeks [40].

On the other hand, this study disagreed with a previous study conducted by [41] that showed there is a decrease in the level of the TSH hormone and no significant change in the level of the T3 and an essential rise in the level of the T4 in the serum of rat after intraperitoneal injection at a dose of (0.5 ml) from Fe2Nio4 nanoparticle solution for (2,7, and 14) days. A study demonstrated that Fe2O3NPs (orally administration) at the dose of (5mg/kg) and AgNPs (by intraperitoneal injection) mixture together at the dose of (50mg/kg) daily for 79 days caused a noteworthy reduction in the level of the TSH and significant rise in the level of the T3, T4 in the serum of rat [42]. Another previous study demonstrated that Sio2NPs caused a significant increase in the level of T4 with a non-significant change in the level of TSH and T3 in the serum of rats after oral administration at doses (1.500mg/kg) daily for 90 days [43]. Another previous study demonstrated that Al2O3NPs at a dose (of 70mg/kg) and ZnONPS at a dose (of 100mg\kg) alone or their combination after orally administered caused a noteworthy reduction in the level of the TSH and an essential rise in the level of the T4, and T3 in the serum of rat daily for 75 days [44].

Discussion

The current study disagreed with the previous study that caused a significant increase in body weight in the rats after intratracheal instillation to Sio2NPs at doses of (5mg/kg) daily for week [24]; other previous studies disagreed with the current study, which demonstrated that the ZnoNPs caused a significant increase of the body weight in the rat after intraperitoneal injection at doses (30,60 mg/kg) for a certain period (7,14,28) days [25] And according to above-obtained results, there was an increment in the body weight at the (20,30days) this is raised of body weight increases depending on the concentration of the injected substance and periods of exposure, where the increase in the concentration of SiO_2 NPs through prolonged periods leads to more increment in total body weight. The current study agreed with the previous study that caused a significant increase in body weight in the rats after intratracheal contact at doses of (5mg/kg) daily for week [24]. Another previous study demonstrated that sio2NPs caused a significant increase in body weight in the rats after feeding by gavage with feed at doses of (0.1,1.0,10 and 100mg/kg) for 3 months [26].

The current study disagrees with the previous study demonstrated that the TiO2 NPs initiated a substantial reduction of body weight in rats after oral contact at doses of 10 and 50 mg/ kg from the 8th to 13th week [22]; in another study conducted by [27], they observed a significant decrease ($P< 0.05$) in the body weight of mice that treated orally with different doses of Al2O3 NPs (1.5, 3, and 6 mg/kg) for 13 weeks in comparison with a control group. On the other hand, [28] used three different doses of Al2O3 NP (15, 30, and 60 mg/ kg) by gavage oral dosing albino male mice for 5 days; they observed that there was no significant change in the body weight of animals when compared with the control groups.

Several mechanisms indicate that increases or loss in body weight are associated with declines and increases in energy expenditure (EE), which mainly follow changes in the metabolically active component of the body [29]. One of the essential things responsible for metabolic activity is the thyroid function, so the thyroid hormones (THs) are potent regulators of metabolism with significant effects on body weight, cholesterol, and liver fat [30]. Therefore, any disturbance in the levels of thyroid hormones hurts body weight [31]. A slight rise in the weight of rats after being treated hypothyroid was seen in a prior study [32]. On the other hand, other researchers reported that the exposure to AgNPs in mice suppresses browning gene programs in subcutaneous fat, leading to decreased energy expenditure and increased adiposity in mice [33].

Research has revealed that the physicochemical features of nanoparticles (surface area, particle size, oxidant generation potential, chemical properties, charge, solubility, shape, and degree of agglomeration) may influence their properties on biological systems [45]. By crossing biological barriers to cell membranes and interacting with intracellular structures, the mechanisms of their toxicity were observed to be due to ionic toxicity [46]. Therefore, any chemical or compound that interferes with any stage of thyroid hormone production from iodine uptake can cause a profound imbalance in the feedback loop and induce morphological alterations, including pituitary and thyroid gland neoplasms [47]. On the other hand, other previous studies showed that exposure to the nanoparticles caused a decrease in levels of transcriptions encoding the TH-induced receptor [48].

Conclusion

The study revealed that Exposure to Sio2NPs at different concentrations caused structural and functional in the thyroid gland, characterized by and decrease in T3 and T4 hormone levels, and caused hypothyroidism. This led to a decrease in the metabolism process, and thus, the body weight of animals significantly increased.

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