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Physiological and Hormonal Effects of Titanium Dioxide Nanoparticles on Thyroid Function and the Impact on Bodyweight in Male Rats

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Abstract:

Fifty-four Sprague-Dawley albino adult male rats were classified into three main groups each of 18 rats treated for a particular duration (1,2, and 4) weeks respectively. Each group was subdivided into three subgroups each of six rats treated as follows; group (1) serve as normal control, group (2, and 3) intra-peritoneal treated with TiO_2NPs (50,200) mg/kg respectively, body *weight of all rats was measured before and after the experiment, then rats were dissected at the end of each experiment and the weights of the thyroid was measured. The result showed a highly significant decrease ($p<0.01$) in thyroid gland weight, a highly significant increase ($p<0.01$) in body weights and TSH, while a highly significant decrease ($p<0.01$) inT3 and T4 was observed in all different doses (50,200) mg/kg at durations 1,2 and 4 weeks. So, this study confirms body weight gain is associated with thyroid dysfunction.

Keywords: Body weight, Nanoparticle, Rats, Thyroid gland, TiO_2NPs.

Introduction:

Nanoparticles: are small size particles (≤ 100 nm) with one or more external dimensions, because of their great scientific advantage used in various industries and enter the field of nanotechnology and biomedical projects such as cancer treatments, used in food manufacture, environmental gases filtration, especially in air pollution, and nutrients, food packaging and in various lifestyle. Titanium dioxide nanoparticles (TiO2-NPs) are the most widely incorporated nanomaterial into many consumer products, which may have adverse health effects after entering the body. Nanoparticles are defined as small substances that have at least one dimension in the range of (1–100) nm, the small size and high surface area of nanoparticles make them their principal participants in all features of modern life applications [1]. One of the unique characteristics of TiO2 particle is can enter the human body quickly and then imposes potential health risks on human [2,3]. Nanoparticles exist naturally in a form of volcanic ash, ocean spray, storm dust, and engineered NPs that include carbon-based (fullerenes, carbon nanotubes), inorganic NPs as metals like (silver, iron, copper, manganese), metal oxides as (titanium dioxide, zinc oxide, copper oxide, silicon oxide) and quantum dots like cadmium and selenium [4]. TiO_2 NPs can be absorbed into the human body by inhalation, ingestion, and dermal penetration because of their small size[5]. The thyroid gland is a large endocrine gland that locates in the lower part of the neck, it secretes two main thyroid hormones (T3) and (T4) which are responsible for regulating cell metabolism in the human body[6]. This study was designed to reveal the dose and time-dependent effect of TiO_2-NPs on body weight, and thyroid in male rats.

Material and Methods:

Preparation of titanium dioxide nanoparticles (TiO_2NPs) solution

TiO_2NPs used in this study were obtained from Skyspring Nanomaterials, they were in white powder Rutile 99.9 % purity, Particle size (30nm) diameter.

The stock suspension was prepared according to [7] by dissolving 1gram of powder TiO_2NPs in 10 ml of distilled water and then mixed by vortex for 10 min to prevent agglomeration, from this stock

suspension, two additional diluted TiO_2NPs suspensions (low and high) doses were prepared:
Group of 200 mg/kg of TiO_2NPs (high dose)
Group of 50mg/kg of TiO_2NPs (low dose)

Animals

The study was conducted on (54) adult male Sprague-Dawley albino rats (*Rattus norvegicus*) with the age of about (2.5-3) months as mammalian models and an average body weight of (250-260) gm. The animals were obtained from the Iraqi Center for Cancer and Medical Genetic Research and then transferred to the animal house of the college of science, Mustansyria University. The males were kept for 10 days for acclimation before starting treatment in clean plastic cages with a metal network cover, rats have kept under climate-controlled conditions in the animal house with 22-25 temperature, Animals were allowed to feed standard rat pellets with free access to tap water

Experimental design

54male rats were randomly divided into nine groups each of six rats treated at different durations of 1 week, 2 weeks, and 4 weeks as follows:

Group 1, 2, and 3 (control groups); Respectively received an intraperitoneal injection of distilled water for different durations (1, 2, and 4) weeks.

Group 4, 5, and 6 (the experimental groups); The rats respectively received intraperitoneal dose (50mg/kg) of (TiO_2 NPs) for different durations (1, 2, and 4) weeks.

Group 7, 8, and 9: (the experimental groups); The rats respectively received intraperitoneal dose (200mg/kg) of (TiO_2 NPs) for different durations (1, 2, and 4) weeks.

Collection of Blood Samples and the Dissection of the Animals.

The weighting of the animals was done at the end of each experiment, they were completely anesthetized by diethyl ether for several minutes and blood samples were obtained by heart puncture were collected into non-heparinized tubes used for hormonal examination. 5 ml of blood for the hormonal test collected from each rat was used to obtain sera (1.0-1.5) ml separated by centrifugation at 3000 rpm for 10 min, then they were kept at -20ºC until analysis. The thyroid gland was removed, then washed with normal physiological saline 0.9% (NaCl) to remove blood, blotted with filter paper, and weighted.

Result and Discussion:

Thyroid weight and Functions

Results (Mean ± Standard error) showed that TiO_2 -NPs had effects on thyroid weights as it was demonstrated in Table .1 rats exposed to TiO_2 -NPs for 1 week demonstrated a highly significant decrease($p<0.01$) in thyroid weight of treated groups with doses (50 and 200) mg/kg (0.200±0.015, 0.180±0.005) gm respectively compared to control groups (0.270±0.009) gm, as well as, there was a highly significant decrease ($p<0.01$) in thyroid weights of experimental groups treated with TiO_2 NPs for 2 weeks in doses (50 and 200)mg/kg (0.178±0.009), (0.141± 0.020) gm respectively when compared to control groups(0.260 ± 0.008) gm, also at 4weeks period there was a highly significant decrease($p<0.01$) in thyroid weights (0.126±0.006),(0.100±0.005)gm respectively compared with control groups (0.271±0.009)gm.

A high significant decrease was observed when comparing between treated groups themselves depending on the concentrations as fixed factors while days were the variable factors in the concentrations (50 and 200) mg/kg exposure to TiO_2 -NPs with the increase of experimental duration 1, 2 and 4 weeks respectively

Table 1. Effect of Dose and Time of TiO_2 -NPS in Thyroid weight

	Mean ± SE of Thyroid weight (gm)			LSD value
Dose	**1 Week**	**2 Week**	**4 Week**	
Control	**0.270 ± 0.009 A a**	**0.260 ± 0.008 A a**	**0.271 ± 0.009 A a**	**0.027 NS**
Low (50 g/kg)	**0.200 ± 0.015 B a**	**0.178 ± 0.009 B b**	**0.126 ± 0.006 B c**	**0.033 ****
High (200 g/kg)	**0.180 ± 0.005 B a**	**0.141 ± 0.020 C b**	**0.100 ± 0.005 C c**	**0.038 ****
LSD value	**0.033 ****	**0.041 ****	**0.022 ****	**---**

** (P<0.01).
A,B,C) represent the significant difference among groups with days as the fixed factors and concentrations as the variable factors.
(a,b,c) represent the significant difference among groups with concentrations as the fixed factors and days as the variable factors.

Statistical analysis of the present study for the effect of TiO_2 -NPs on thyroid hormones (Mean ± Standard error) that include TSH, T3, and T4 in Table.2, 3, 4, Sequential reveals that:

The values of TSH(µlU/ml) showed high significant increase (p>0.01) at different treatment durations (1, 2, 4) weeks exposing to TiO_2 -NPs at (50, 200) mg/kg (0.600 ± 0.015), (0.841± 0.037),(0.990 ± 0.003) ,(1.50 ± 0.013),(2.11 ± 0.013, (2.83± 0.16) (µlU/ml) respectively when compared to control groups (0.051 ± 0.004),(0.143 ± 0.091),(0.060 ± 0.005) (µlU/ml) respectively, demonstrated in table (2). High significant increase in the level of (TSH) (µlU/ml) also was observed when comparing between treated groups themselves depending on the concentrations as fixed factors while days were the variable factors in the concentrations (50 and 200) mg/kg exposed to TiO_2 -NPS with the increase of experimental duration 1, 2 and 4 weeks respectively.

Table 2. Effect of Dose and Time of TiO_2 –NPS in the level of TSH

	Mean ± SE of TSH µlU/ml			**LSD value**
Dose	**1 Week**	**2 Week**	**4 Week**	
Control	**0.051 ± 0.004 C a**	**0.143 ± 0.091 C a**	**0.060 ± 0.005 C a**	**0.159 NS**
Low (50 g/kg)	**0.600 ± 0.015 B c**	**0.990 ± 0.003 B b**	**2.11 ± 0.013 B a**	**0.036 ****
High (200 g/kg)	**0.841 ± 0.037 A c**	**1.50 ± 0.013 A b**	**2.83 ± 0.16 A a**	**0.288 ****
LSD value	**0.071 ****	**0.161 ****	**0.281 ****	**---**

** (P<0.01).
A,B,C) represent the significant difference among groups with days as the fixed factors and concentrations as the variable factors.
(a,b,c) represent the significant difference among groups with concentrations as the fixed factors and days as the variable factors.

A high significant decrease (p<0.01) in serum level of (T3) (ng/ml) in both treated groups (50, 200) mg/kg (1.260±0.012),(1.060±0.051) (ng/ml) respectively exposed to TiO_2 -NPs for 1 week compared to the control groups (1.490±0.017) (ng/ml), also there was a highly significant decrease(p<0.01) in the level of (T3) in both doses (50, 200) mg/kg at 2 weeks (0.980±0.004), (0.810±0.005) (ng/ml) in comparison to control groups (1.231 ± 0.023), and at 4 weeks (0.77± 0.014), (0.416±0.01) (ng/ml) in comparison to control groups (1.46 ± 0.006) (ng/ml) demonstrated in Table .3. High significant decrease due to TiO_2 -NPS in serum level of (T3) (ng/ml) was observed when comparing between treated groups themselves depending on the concentrations as fixed factors while days were the variable factors in the concentrations (50 and 200) mg/kg exposing to TiO_2 -NPS with the increase of experimental duration 1, 2 and 4 weeks respectively.

Table 3. Effect of Dose and Time of TiO_2 -NPS in the level of T3

	Mean ± SE of T3 ng/ml			**LSD value**
Dose	**1 Week**	**2 Week**	**4 Week**	
Control	**1.490 ± 0.017 A a**	**1.231 ± 0.23 A a**	**1.46 ± 0.006 A a**	**0.416 NS**
Low (50 g/kg)	**1.260 ± 0.012 B a**	**0.980 ± 0.004 AB b**	**0.77 ± 0.014 B c**	**0.029 ****
High (200 g/kg)	**1.060 ± 0.051 C a**	**0.810 ± 0.005 B b**	**0.416 ± 0.01 C c**	**0.092 ****
LSD value	**0.097 ****	**0.415 ***	**0.030 ****	**---**

** (P<0.01). *(p<0.05)
A,B,C) represent the significant difference among groups with days as the fixed factors and concentrations as the variable factors.
(a,b,c) represent the significant difference among groups with concentrations as the fixed factors and days as the variable factors.

values of T4(µg/dl) displayed non-significant decrease of treated groups (50) mg/kg (6.20±0.01) (µg/dl), but show significant decrease (p<0.05) of treated groups (200) mg/kg (5.08±0.79) (µg/dl) respectively at 1 week compared to control groups(6.91±0.01) (µg/dl), at week 2 also showed non- significant decrease(p<0.05) at dose (50) mg/kg ,(4.32±0.01) (µg/dl), while significant decrease (p<0.05) of treated groups (200) mg/kg (4.10±0.02) (µg/dl) when compared with control groups(5.97±0.90) (µg/dl), in addition to 4 weeks exposing to TiO_2 -NPS observed high significant decrease (p<0.01) of the level of T4 in different doses (50,200) mg/kg (3.77±0.01),(3.31±0.01) (µg/dl) compared to control groups (6.91±0.02) (µg/dl) demonstrated in Table .4. High significant decrease in the level of T4 was observed when comparing between treated groups themselves depending on the concentrations as fixed factors while days were the variable factors in the concentrations (50 and 200) mg/kg exposure to

TiO_2 -NPS with the increase of experimental duration 1, 2 and 4 weeks respectively

Table 4. Effect of Dose and Time of TiO_2 -NPS in the level of T4

	Mean ± SE of T4 µg/dl			LSD value
Dose	**1 Week**	**2 Week**	**4 Week**	
Control	**6.91 ± 0.01 A a**	**5.97 ± 0.90 A a**	**6.91 ± 0.02 A a**	**1.567 NS**
Low (50 g/kg)	**6.20 ± 0.01 AB a**	**4.32 ± 0.01 AB b**	**3.77 ± 0.01 B c**	**0.034 ****
High (200 g/kg)	**5.08 ± 0.79 B a**	**4.10 ± 0.02 B ab**	**3.31 ± 0.01 C b**	**1.384 ***
LSD value	**1.383 ***	**1.566 ***	**0.049 ****	---

* (P<0.05), ** (P<0.01).
A,B,C) represent the significant difference among groups with days as the fixed factors and concentrations as the variable factors.
(a,b,c) represent the significant difference among groups with concentrations as the fixed factors and days as the variable factors.

The size, weight, and histology of the thyroid gland were known to be influenced by its functional condition and production of thyroid hormone, where some disorders of thyroid glands, the weight, size, and histology of thyroid gland affected by the production of thyroxin and its functional status, also some disorder of thyroid gland such as overactive or underactive thyroid gland are established by enlargement of the thyroid gland as a part of compensatory mechanism to maintain of thyroid hormone homeostasis [8]. The function of the thyroid gland is often preserved by a negative feedback mechanism, which involves the interplay between the hypothalamus (through the TRH release) and the TSH released from the pituitary gland, this regulatory effect detects the levels of the circulating thyroid hormones T3 and T4 in serum [9]. [10] reported that, the reduction in T4 levels and increases thyroid weight following exposure to long time exposure to high doses of AgNPs. Researches display that TiO_2 -NPS affects different body organs. [11] suggests that TiO_2 NPS significantly decreases the TSH and T4 in mice, concerning the effect of TiO_2 -NPS on thyroid hormones level, there was no significant increase in the serum TSH, and T3 while T4 showed no significant decrease. These results may illustrate after oral administration of TiO_2 -NPS (5 g / kg BW) for (65 days) in male rats, lead to the TiO_2 NPS toxic effect became non-significant in the function of the thyroid gland, the difference may be due to the short duration, high dose and the surface area of the particles used [12]. Exposure to a high dose (50 mg/kg) of AgNPs for 20 and 30 days produced a significant ($p<0.05$) increase in the weight of the thyroid gland compared with control groups, while non-significant changes were observed with the doses (12.5 and 25 mg/kg). Moreover, short-term exposure of 10 days to any of three doses of AgNPs has no significant effect on the thyroid gland [13]. Results show that nano- TiO_2 -NPS decreased the total T4 and T3 contents in the zebrafish larvae [14]. Different studies observed changes in TSH, T4, and T3 levels, according to dose and time of exposure displayed no significant changes in the serum levels of T3 and TSH among all groups exposed to AgNPs (12.5, 25, and 50 mg/kg) at different period, while, a highly significant reduction ($p<0.01$) in the mean values of the T4 achieved after the long and intermediate duration of exposure (30 days) to 50 mg/kg of AgNPs, the exposure to 25 mg/kg showed a similar result only after 30-day duration contrast with the control group and the other exposed groups [13]. T3 serum levels were reduced at both doses of 1 and 2 mg/kg body weight per day in males and since the largest part of serum T3 is derived from peripheral deiodination of T4 this finding may suggest effecting on peripheral deiodinase 1 activity by TiO_2 NPS nanoparticles [15, 16], suggested that the iron oxide nanoparticles significantly increased serum levels of T4 and TSH serum levels are significantly reduced. The small particle size of NPs including AgNPs contributes to extensive tissue penetration, it can be supposed that they may damage the structure and function of the thyroid gland [17]. These thyroid hormones play critical roles in the metabolic and developmental functions of the body; therefore, any alteration in the levels of these hormones will negatively affect the processes of development and differentiation [18]. The appearance of symptoms of acute toxicity with increased doses of NPs, which show passive behavior, loss of appetite, tremor, and lethargy, by using 50 nm TiO_2 -NPS [19,5].

The duration and dose-dependent of TiO_2 -NPS reduces thyroid weight, with the increase in time and doses of NPs, the results of the present study reflect a significant decrease in serum level of T4 and T3 with the exposure to TiO_2 NPS.

Bodyweight

The statistical analysis of the present study in Table .5 (Mean ± Standard error) showed an increase in the body weight of animal groups exposed to TiO_2 NPs compared to control groups. 1

week exposing to TiO_2 -NPS demonstrated a highly significant increase ($p<0.01$) in body weights of experimental treated groups with different doses (50 and 200) mg/kg (260.00±1.86), (300.00±1.39) gm respectively compared with the control (254.10±0.61) gm. As well, there was a highly significant increase($p<0.01$) in body weights exposed to TiO_2-NPs for 2 weeks of experimental treated groups with doses (50 and 200) mg/kg (320.00±0.77), (423.67±0.42) gm respectively comparing with the control groups (255.13±0.54) gm, also there was a highly significant increase ($p<0.01$) in body weights exposed to TiO_2 -NPs with doses (50 and 200) mg/kg for 4 weeks (371.67±0.56), (500.00±0.68) gm in comparison with control groups(255.16±0.83)gm.

A high significant increase ($p<0.01$) in rat body weights was revealed with the increase of the experimental duration in concentrations (50, 200) gm/kg of TiO_2 -NPs when comparing between experimental treated groups themselves.

Table 5. Effect of Dose and time of TiO_2 -NPS in Rat weight

	Mean ± SE of Rat weight (gm)			LSD value
Dose	**1 Week**	**2 Week**	**4 Week**	
Control	**254.10 ± 0.61 B a**	**255.13 ± 0.54 C a**	**255.16 ± 0.83 C a**	**2.19 NS**
Low (50 g/kg)	**260.00 ± 1.86 B c**	**320.00 ± 0.77 B b**	**371.67 ± 0.56 B a**	**3.64 ****
High (200 g/kg)	**300.00 ± 1.39 A c**	**423.67 ± 0.42 A b**	**500.00 ± 0.68 A a**	**2.79 ****
LSD value	**17.22 ****	**1.802 ****	**2.11 ****	**---**

** ($P<0.01$).
A,B,C) represent the significant difference among groups with days as the fixed factors and concentrations as the variable factors.
(a,b,c) represent the significant difference among groups with concentrations as the fixed factors and days as the variable factors.

The obtained results of the present study about the increase in body weights agreed with a previous study by 20 who realized the increase in body weight of male mice treated orally with TiO_2 -NPS (5-6 nm) 2.5, 5, and 10 mg/kg/day for 90 days. [21] suggests a significant rise in body weight of rats treated with different doses of AgNPs (1000 and 5000) mg/Kg for 14 days and 21 days respectively. About adding ZnO into the basal diet at (0, 50, 500, and 5000) mg/kg, results displayed a rise in body weight occurred at the concentrations (50 and 500) mg/kg nano-ZnO [22]. Results of the present study disagreed with a previous study by [23] who showed that oral exposure to mice with 250 mg/kg/day TiO_2 NPS (25 nm) for 42 days significantly decreased the body weight gain of mice. Another study by [24] male rats treated orally with 4 mg/kg body weight TiO_2 -NP S for 90 days resulted in a significant decrease in their body weight. A result from another study on male albino rats who were fed with TiO_2 NPS 1% and 2% for 65 days had shown reduce in body weights compared to the control group[25]. In another experiment, study results disagreed with the present study using different experimental animals, reduced body weight in all species and in all groups which exposed to TiO_2 NPs for 6 hours per day and 5 days per week for 13 weeks with doses (10, 50 or 250) mg/m³ on six weeks old female mice, rats, and hamsters [26]. Reduced body weight was confirmed with results observed by [5] who suggested that acute oral administration of a single oral gavage of 5g/kg TiO2 -NPS decreased the body weight of mice. While [27] reported that after oral administration of 300 mg/kg TiO_2 NPS on mice for 35 days, no significant changes occurred in body weights. So did an oral administration of TiO_2 -NPS (50, 120 nm, 5 g/kg to mice for 1 week does not affect their body weights [28]. Physiological changes may occur via injecting TiO2 NPS intraperitoneally such as changes in weight in treated rats [29]. The lack of thyroid hormones (TH)is thought to reduce energy expenditure, influence circulating leptin levels indirectly by regulation of adipose tissue mass and increase the fat mass and possibly increase body weight because TH is assumed to play a role in the regulation of body and fat weight homeostasis by decreasing the body fat content [30]. The variations in the results about increasing or reduction in body weight due to differences in experimental conditions such (as different properties of TiO_2 NPS, type of exposure to TiO_2 NPS, dose, time, room temperature, increase in body weight due to TiO_2 -NP S may accumulate in different organs in animals and induce alteration in cellular functions, and consequently alters their metabolic rate. Men with hypothyroidism observed unexplained weight gain with reduced intake of food and loss of appetite [31]. In a previous study, it was evidenced a moderate increase in the weight of rats after being made hypothyroid [32]. Excess thyroid hormone leads to an elevation in metabolic rate and frequently presents with weight loss [33]. The link between

obesity and hypothyroidism the two common clinical conditions has become more relevant in the context of an unprecedented rise in obesity worldwide, reports indicate that changes in thyroid-stimulating hormone (TSH) could well be secondary to obesity, and the close relationship between obesity and thyroid autoimmunity with the leptin (adipocyte hormone) observing to be the key factor linking these two conditions [34]. Results support the use of serum TSH levels as the best test to detect abnormal thyroid function [35]. Thyroid disorders increase with the age of patients and females are more susceptible than males also results observed a correlation between thyroid disorders and high body weight [36]. An association between weight change and TSH change was present in a random sample of 4,649 persons aged 18–65 years from a general population, 2.102 individuals who participated in an 11-year follow-up, without current or former treatment for thyroid disease and with measurements of weight and TSH at both examinations, change in serum TSH and change in weight were significantly associated in both sexes, weight increased by 0.3 kg in women and 0.8 kg in men for every one unit TSH (mU/L) increase, but an association between weight change and TSH change was present[37]. In a previous study aimed to investigate the relationship between thyroid function and different obesity phenotypes over nine years of follow-up, conducted on 1938 individuals from an ongoing population-based cohort study in Tehran, participants were classified into four obesity phenotypes based on metabolic status and body mass index, results showed significant positive association was found between serum thyrotropin levels and development of the metabolically unhealthy normal weight phenotype, serum-free Thyroxine (fT4) concentrations within the reference range are associated with the development of some obesity phenotypes, including the metabolically healthy normal weight and metabolically healthy obese phenotypes, after consideration of potential confounders[38]. Thyroid function has been extensively investigated in obese subjects to relate the elevation in body weight with thyroid disturbance, thyroid diseases, and obesity are common disorders in the general population, thyroid hormone is an important determinant of energy expenditure and contributes to appetite regulation, while hormones and cytokines from the adipose tissue act on the central nervous system(CNS) to inform on the number of energy stores, the continued interaction between the thyroid hormone and regulatory mechanisms localized in the brain and adipose tissue is important for human body weight control and maintenance of optimal energy balance [39]. Abdominal obesity is defined as one of the metabolic syndromes (MetS), which represents one of the most frequent endocrine disorders, particularly in a society with increasing weight problems, evidence has accumulated that thyroid hormones affect components of the MetS, and results revealed a significant interaction between thyroid hormone status and MetS, as animal data demonstrate a strong interaction between Thyroid hormone and skeletal muscle metabolism as well as liver and lipid metabolism [40]. Thyroid hormone regulates metabolism in both humans and animals, as there is a complex relationship between thyroid disease, body weight, and metabolism, studies showed low thyroid hormone levels were related to low basal metabolic rate (BMRs) and high thyroid hormone levels with basal metabolic rate BMRs, the decrease in BMR due to hypothyroidism is usually much less dramatic than the marked increase seen in hyperthyroidism, leading to more modest alterations in weight due to the underactive thyroid, the weight gain in hypothyroid patients is not always related to excess fat accumulation, the extra weight gained related to excess accumulation of salt and water. Massive weight gain is rarely associated with hypothyroidism, thyroid hormones help break down body fat by the metabolism of stored calories to be used for energy, diminished thyroid function causes the body to hold on to calories, storing them as fat, which is particularly not easy to burn off and metabolize.

Conclusion:

In summary, this study confirmed that body weight gain is associated with thyroid dysfunction, as an unexplained weight change is one of the most common signs of a thyroid disorder, In a condition known as hypothyroidism usually occurs in patients and causes weight gain, as weight gain may signal low levels of thyroid hormones. Thyroid hormones that are released from the thyroid gland helps regulate metabolism, while decreased levels of thyroid hormones cause metabolism to slow down, which results from less burning of calories, so weight change seems to be associated with thyroid hormone levels.

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Authors' declaration:

- Conflicts of Interest: None.

- We hereby confirm that all the Figures and Tables in the manuscript belong to us. Besides, the Figures and images, which don't belong to us, have been given permission for re-publication attached with the manuscript.
- The author has signed an animal welfare statement.
- Ethical Clearance: The project was approved by the local ethical committee at Mustansiriyah University.

Authors' contributions statement:

Both authors N. M. L. and R. A. M. conceived and planned the experiment, experimented, and contributed to sample preparation. N. M. L. contributed to the interpretation of the results. R. A. M. took the lead in writing the manuscript. Both authors provided critical feedback and helped shape the research, analysis, and manuscript.

Ethics Approval

The researchers are demonstrating that they have adhered to the accepted ethical standards of a genuine research study. Ref. No.:BCSMU/1221/0002Z

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التأثيرات الفسيولوجية والهرمونية لجسيمات ثاني أكسيد التيتانيوم النانوية على وظائف الغدة الدرقية في ذكور الجرذان

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الخلاصة:

تم استخدام 54 ذكر من الجرذان البيضاء وتم تصنيفها الى ثلاثة مجاميع رئيسية (3,2,1) كل مجموعه تتضمن 18 جرذ عوملت بثلاث فترات زمنية مختلفة (4, 2, 1) أسابيع على التوالي .وتم تقسيم هذه المجاميع الى ثلاث مجاميع فرعية كل منها تتضمن ست حيوانات تمت معاملتها على النحو التالي : (1) سيطرة , المجموعة (3, 2) حقنت بالتجويف البريتوني بجرعات متزايدة من دقائق التيتانيوم النانوية (50 ,200) ملغ / كغم على التوالي. تم احتساب وزن الجسم للحيوان قبل وبعد اجراء التجربة , في نهاية التجربة شرحت الجرذان وتم حساب وزن االغدة . النتائج اظهرت انخفاض معنوي عالي ($p\leq 0.01$) في وزن الغدة الدرقية وارتفاع معنوي عالي ($p\leq 0.01$) في وزن الجسم ومستوى هرمون TSH بينما انخفاض معنوي عالي في مستويات هرمون T3 و T4 المعاملة بجرعات مختلفة من TiO_2 (200, 50) ملغم / كغم في جميع الفترات الزمنية (4,2,1) اسابيع .

الكلمات المفتاحية: وزن الجسم، دقائق نانويه، جرذان، الغده الدرقيه ، دقائق ثنائي اوكسيد التيتانيوم النانويه.