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Cardiac and testicular alterations induced by acute exposure to titanium dioxide nanoparticles: Histopathological study

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Abstract

Titanium dioxide nanoparticles (TiO_2 NPs) have novel application and are used in many household application, nanomedicine, agriculture, industries and pharmaceutical products. These applications may be accompanied with potential risk in human health and the ecosystems. The current study was carried out to find out the acute damage that might be induced by TiO_2 NPs in the heart and testis. Three groups of Wistar albino rats (*Rattus norvegicus*) were subjected to a single dose TiO_2 NPs (126, 252, 378 mg/kg bw). Cardiac and testicular biopsies from each animal under study were handled for histological and histochemical examination. Rats exposed to TiO_2 NPs demonstrated the following cardiac alterations: myofibres wavy appearance, myofibre disarray, partial cross striation, cardiomyocytes hydropic degeneration together with vacuolation and nuclear alterations. Moreover, acute exposure to TiO_2 NPs induced the following testicular alterations: spermatocytes degeneration, spermatids sloughing and interstitial edema. The presented cardiac and testicular alterations were dose dependent. From the findings of the present study, it might be concluded that TiO_2 nanomaterials are capable of inducing acute cardiac and testicular damage that is dose dependent and could adversely affect the function of the vital organs.

1 | INTRODUCTION

Titania nanoparticles (NPs) applications are widely seen in nanomedicine specially skin products, industry, optical fields, battery manufacturing, additives of foods and agriculture due to low production cost, photostability and high refractive index in solutions [1]. In addition, titanium dioxide (TiO_2) NPs have anticorrosive characteristic making them suitable for medical, biological and commercial applications [2]. Moreover, these nanomaterials have variable sizes, shapes and crystalline structures giving them unique characterizations appear in their functionalization and stability, enabling them to be invested in various sectors of our life activities [3].

The world market is crowded with NPs products with thousands of tons of TiO_2 NPs are invested annually in many commercial applications such as plastics, pains and covers of consuming products especially in foodstuffs and cements [4]. Moreover, TiO_2 NPs are used in drug delivery, cosmetics, toothpaste, agriculture, engineering, electronics and imaging agent [5]. In addition, TiO_2 NPs are widely invested in diseases diagnosis, nanotherapeutics such as antimicrobial drugs, photodynamic therapy, and skin care products [6]. It is predicted that most of the produced TiO_2 will be converted into nanoforms by the end of the year 2026 [7].

Studies have revealed the toxic impacts of TiO_2 NPs on various organs of human body [8]. Titanium oxide NPs are rapidly absorbed after injection, carried to organs and tissues and can pass into the cells [9]. These nanomaterials could be absorbed through inhalation, oral ingestion, intravenous injection and dermal penetration into the body, and accumulated in the vital organs [10]. Some *in vivo* studies showed that ultrafine anatase TiO_2 particles could induce bronchoalveolar lavage inflammation and inflammatory cells proliferation [11]. In addition, nanotitania materials have the potential to cross biological barriers such as blood–brain barrier and

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blood–placenta barrier [12]. Several reports indicated that TiO_2 NPs could accumulate in several organs mainly in the liver, kidneys, spleen, lymph node, lungs, and heart, and could not leave the body before 15 days after administration [13]. Hepatic injury was reported in female mice subjected to TiO_2 NPs, including hydropic degeneration, hepatocytes spotty necrosis; renal damage including swelling of the renal glomeruli [8]. Chang et al. [14] review on 347 reports on TiO_2 NPs toxicity indicated the presence of nano-TiO_2 in various vital organs especially the liver, kidney, spleen and brain. The testis of mice subjected to chronic exposure to titania NPs demonstrated seminiferous tubules injury, reduction in sperm motility and sperm morphological abnormalities together with hormonal alterations of testosterone, LH and FSH [15].

Thousands of tons of TiO_2 NPs are invested annually in many commercial applications especially in foodstuffs, drug delivery, cosmetics, toothpaste and agriculture. Titanium dioxide NPs are used as a common additive in whitening a variety of foodstuffs. It is predicted that most of the produced TiO_2 will be converted into nanoforms by the end of the year 2026. One food additive E171 (TiO_2 NPs) is consumed globally in high proportion everyday by the general population as it is commonly used in some medicines and hundreds of food products as a whitening agent [16].

This increased occupational exposure to titania NPs put persons manufacturing and handling these NMs and their containing products at risk [17]. Little is known about the acute toxicity of nanotitania materials on the cardiac and testicular tissues. Accordingly, the present study aims to find out the histological and histochemical alterations that might be induced by TiO_2 nonmaterial on the heart and testis.

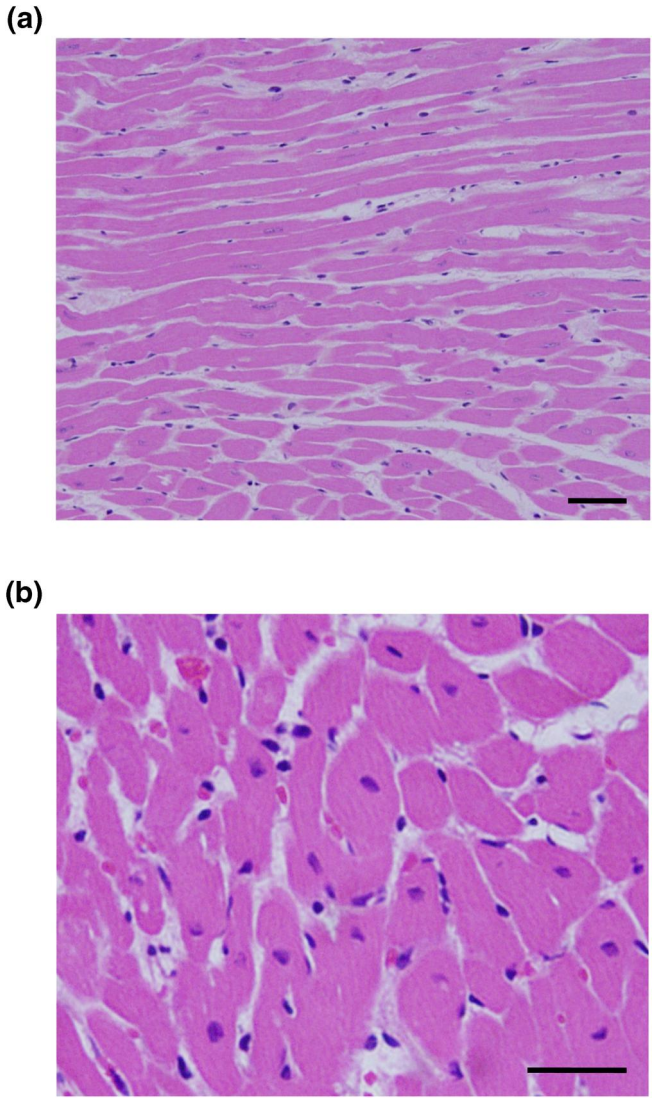

FIGURE 1 Light micrograph of section in the heart of control rat demonstrating: (a) Normal cardiac histological architecture with myofibres, arranged in bundles and (b) Normal oval nuclei. H&E stain (scale bar 50 μm)

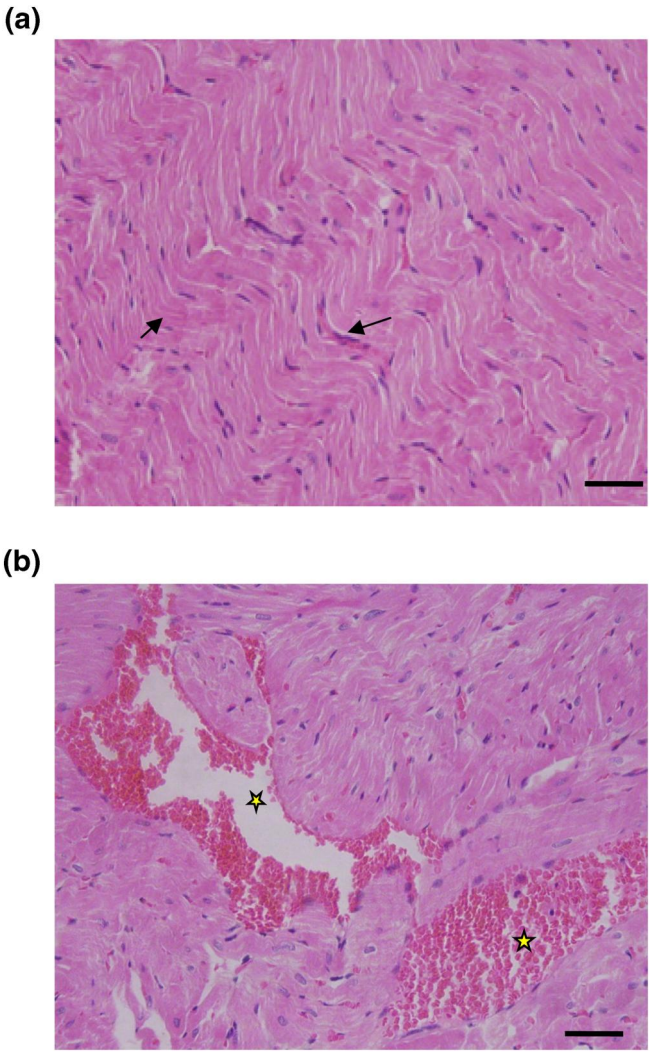

FIGURE 2 Light micrograph of section in the cardiac muscle of TiO_2 NPs-treated rat demonstrating: (a) Appearance of myocardial fibres (arrows) with dilatation and (b) Congestion of blood capillaries in interstitial tissue (stars). 378 mg/kg bw of TiO_2 NPs, H&E stain (scale bar 50 μm)

2 | MATERIALS AND METHODS

2.1 | Nanoparticles

Titanium oxide nanopowder (99.7% with an average particles size of 25 nm and surface area of 45–55 m^2/g) was purchased from Sigma–Aldrich (USA). The particles were dispersed in normal saline and sonicated for 15 min. Each suspension was vortexed before every use to obtain homogenized suspension.

2.2 | Animals and conditions

Forty healthy adult male Wistar albino rats (*Rattus norvegicus*) of the same age weighing 220–250 g were used in the present study.

2.3 | Experimental protocol

Three doses of TiO_2 NPs were used in the current study (126, 252 and 378 mg/kg bw). These doses were selected according to previous reports elsewhere [2,18]. The rats were distributed into four groups (10 rats each), and received the nanomaterials intraperitoneally (ip) during 12 h as follows:

Group I: Each member of this group received 12 ml of normal saline during 12 h.

Group II: Each member of this group received 12 ml of normal saline contained 126 mg/kg TiO_2 NPs during 12 h.

Group III: Each member of this group received 12 ml of normal saline contained 252 mg/kg TiO_2 NPs during 12 h.

Group IV: Each member of this group received 12 ml of normal saline contained 378 mg/kg TiO_2 NPs during 12 h.

All the experiments were carried out in accordance with the standard animal ethics and the study protocol was reviewed and approved by the Ethical Committee at King Khalid University, Saudi Arabia.

2.4 | Histopathological investigation

The rats of all groups (control and SiO_2 NPs-treated rats) were euthanized after 48 h of the post-exposure to TiO_2 NPs for histological processing and examination. The rats were dissected and the heart with the right testis of each rat was removed rapidly. Following excision, the heart was perfused

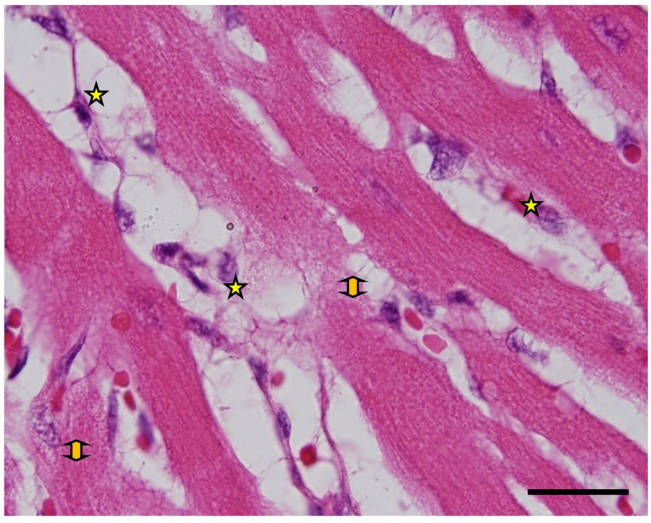

FIGURE 3 Light micrograph of section in the cardiac muscle of TiO_2 NPs-treated rat demonstrating marked hydropic degeneration (ballooning [stars]) and cardiomyocytes necrosis (up-down arrow). 378 mg/kg bw of TiO_2 NPs, H&E stain (scale bar 50 μm). TiO_2 NP, titanium dioxide nanoparticles

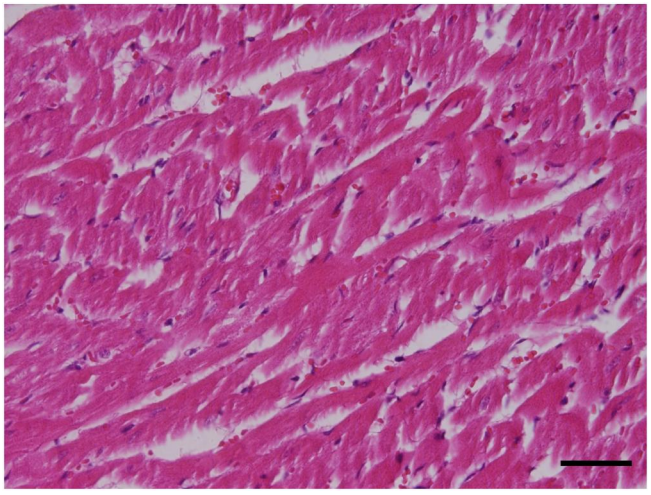

FIGURE 4 Light micrograph of section in the cardiac muscle of TiO_2 NPs-treated rat demonstrating marked cardiac myofibre disorganization (disarray of muscle fibres). H&E stain (scale bar 50 μm). 378 mg/kg bw of TiO_2 NPs. TiO_2 NP, titanium dioxide nanoparticles

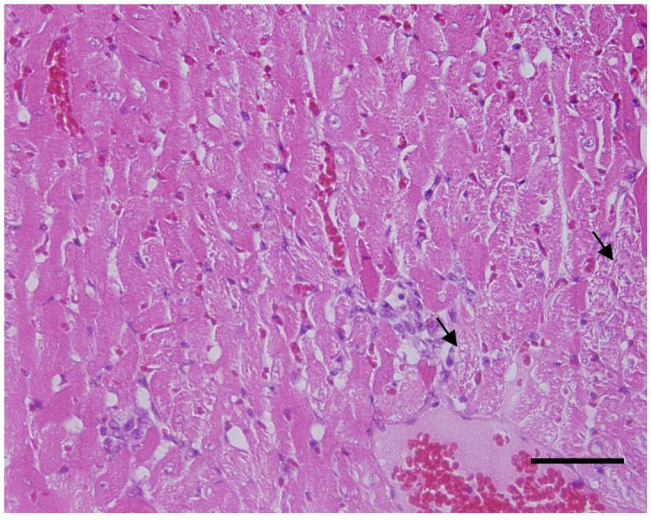

FIGURE 5 Light micrograph of section in the cardiac muscle of TiO_2 NPs-treated rat demonstrating myocytes hypertrophy and disorganization of muscle fibres with focal necrosis (arrows). H&E stain (scale bar 50 μm), 378 mg/kg bw of TiO_2 NPs. TiO_2 NP, titanium dioxide nanoparticles

with 10% neutral buffered formalin (NBF) injection through the aortic cannula. By then, the endomyocardial biopsies were obtained by slicing the heart into two longitudinal halves from the apex through to the base exposing the atria and the ventricles. On the other hand, The right testis obtained from each rat under study was immersed in NBF for 30 min before a longitudinal section through the rete testis was made.

The tissue blocks were fixed in NBF, dehydrated, with ascending grades of ethanol (70%, 80%, 90%, 95% and 100%) and cleared in xylene. Tissue samples were then impregnated with molten paraffin wax (melting point 58°C), embedded and blocked out. Serial sections (4 μm) were taken from each tissue block, processed for histopathological examination and stained with haematoxylin and eosin stain. Stained tissue sections were examined blindly by histopathologist and the photos were taken using optical microscope (Olympus, BX51 with Digital Camera, Japan).

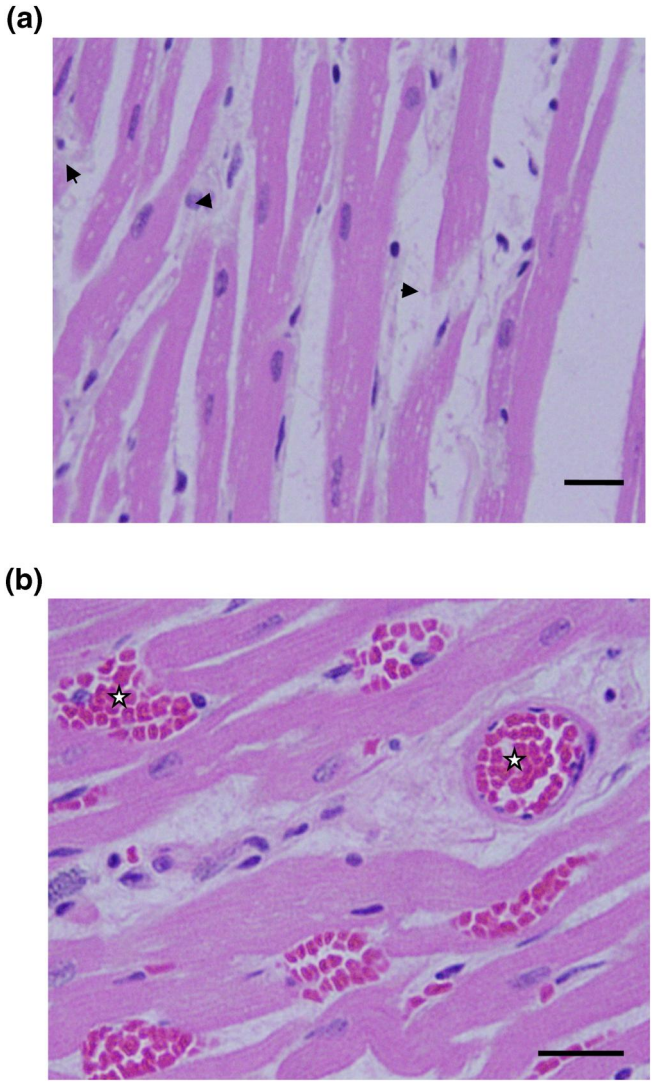

FIGURE 6 Light micrograph of section in the cardiac muscle of TiO_2 NPs-treated rats demonstrating: (a) Degenerative foci accompanied with hyaline degeneration (arrow heads) and (b) Vacuolization of cytoplasm of muscle fibre, dilatation and congestion of blood capillaries (*). H&E stain (scale bar 50 μm). 252 mg/kg bw of TiO_2 NPs. TiO_2 NP, titanium dioxide nanoparticles

3 | RESULTS AND DISCUSSION

3.1 | Histological alterations

The heart of all control rats demonstrated normal branched myocardial fibres arranged in parallel bundles and anchored to each other by intercalated discs. The myocardial fibres were separated by connective tissue crowded with blood capillaries. In addition, the myocardial fibres of the control rats showed normal cross striation and oval nuclei (Figure 1a-b).

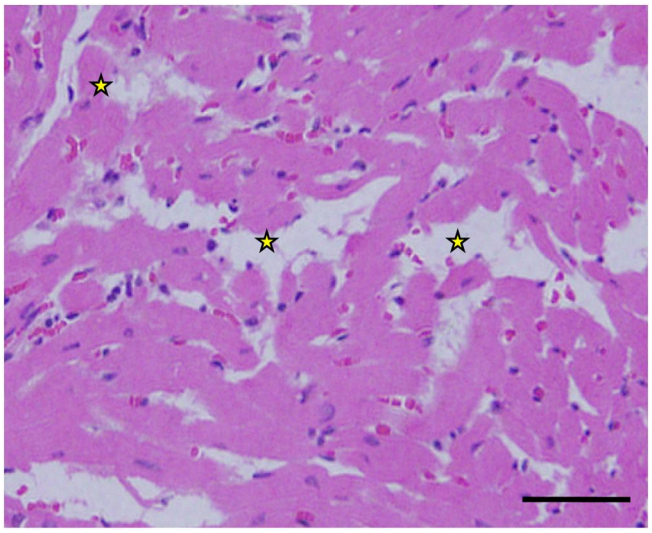

FIGURE 7 Light micrograph of section in the cardiac muscle of TiO_2 NPs-treated rat demonstrating myofibre vacuolization (stars). H&E stain (scale bar 50 μm), 126 mg/kg bw of TiO_2 NPs. TiO_2 NP, titanium dioxide nanoparticles

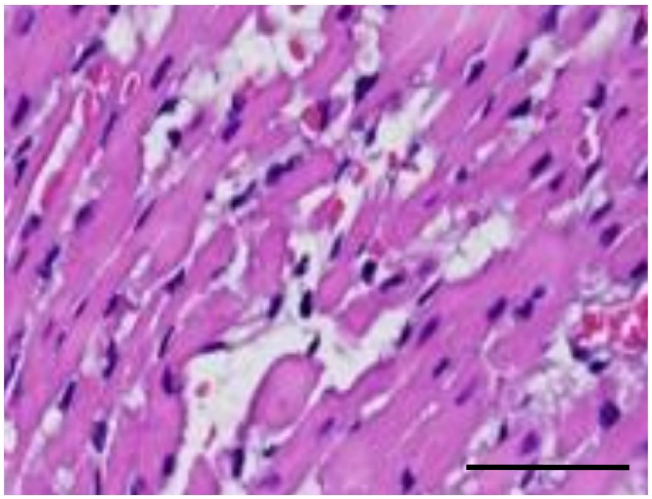

FIGURE 8 Light micrograph of section in the cardiac muscle of TiO_2 NPs-treated rat demonstrating cardiomyocytes pyknosis and irregular nuclei together with cytoplasmic vacuolization. H&E stain (scale bar 50 μm). 252 mg/kg bw of TiO_2 NPs. TiO_2 NP, titanium dioxide nanoparticles

In contrast, the following histological alterations were seen in the cardiac tissues of all TiO_2 NPs-treated rats.

3.1.1 | Wavy myocardial fibres appearance

This alterations appeared in the cardiac tissues of rats exposed to 252 mg/kg bw and more and to the lesser extent in those received 126 mg/kg bw of TiO_2 NPs (Figure 2a-b). Myocardial fibre wavy appearance may indicate an impact on the heart pump and is considered as myocardial degeneration towards heart attack. This alteration was accompanied with dilatation and congestion of blood vessels was seen in the cardiac interstitial tissues. This finding may indicate that TiO_2 NPs could affect the cell membrane permeability of blood vessels endothelial [19].

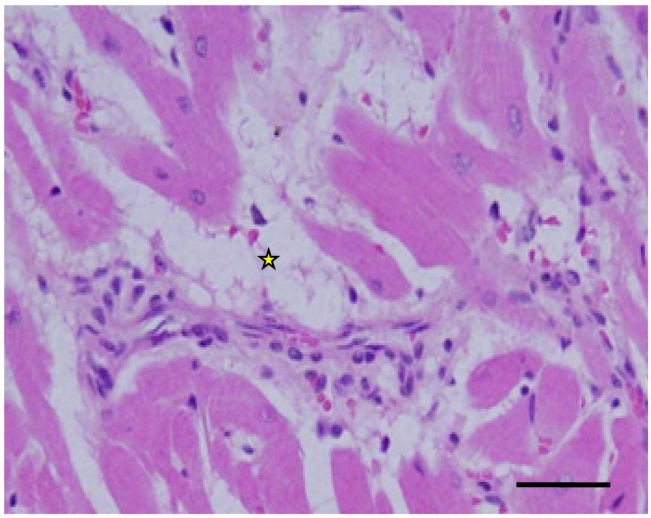

FIGURE 9 Light micrograph of section in the cardiac muscle of TiO_2 NPs-treated rat demonstrating marked oedema (star). H&E stain (scale bar 50 μm), 126 mg/kg bw of TiO_2 NPs. TiO_2 NP, titanium dioxide nanoparticles

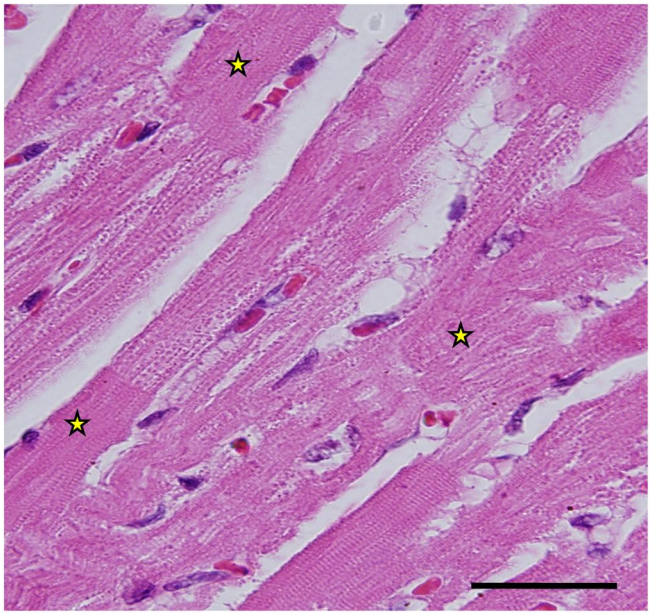

FIGURE 10 Light micrograph of section in the cardiac tissues of TiO_2 NPs-treated rat demonstrating partial cross striation loss (stars). H&E stain (scale bar 50 μm), 378 mg/kg bw of TiO_2 NPs. TiO_2 NP, titanium dioxide nanoparticles

3.1.2 | Hydropic degeneration

Marked cardiomyocytes hydropic degeneration was observed in the cardiac tissues of this group of rats (Figure 3). This alteration might be resulted from a disturbance of ion and fluid homeostasis induced by TiO_2 nanomaterials that lead to an

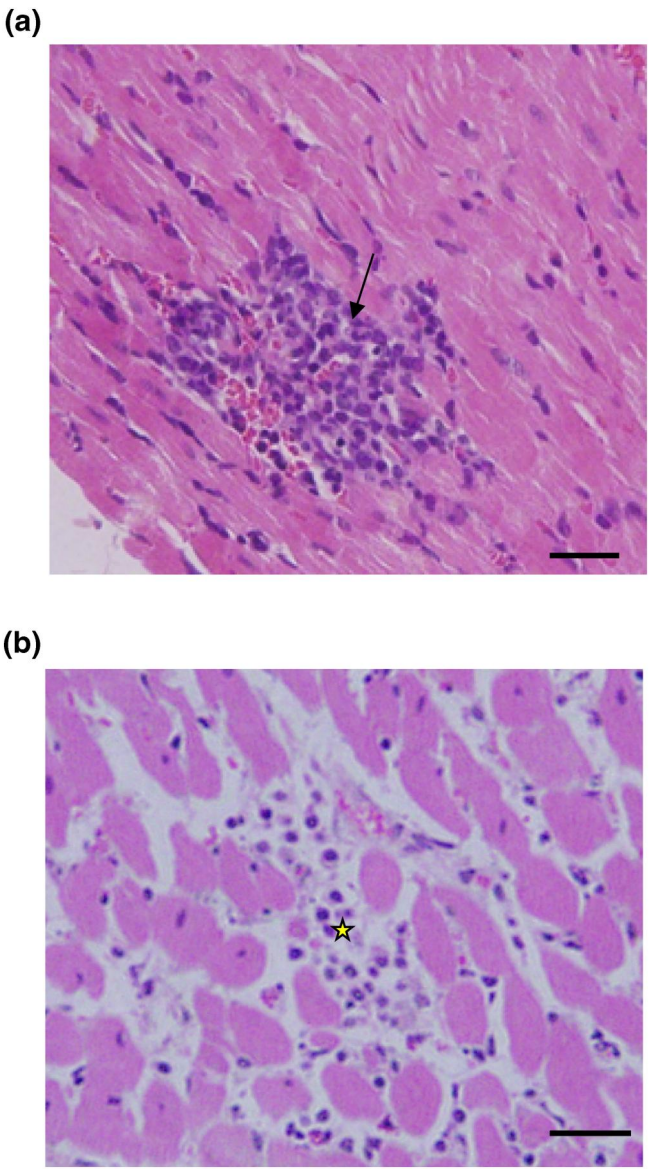

FIGURE 11 Light micrograph of section in the cardiac tissues of TiO_2 NPs-treated rat demonstrating: (a) Lymphocytes (arrow) and (b) Neutrophils (star) infiltration. H&E stain (scale bar 50 μm), 378 mg/kg bw of TiO_2 NPs. TiO_2 NP, titanium dioxide nanoparticles

increase of intracellular water leading to vacuoles formation [20]. Vacuolated swelling of the sarcoplasm of cardiomyocytes may indicate acute heart injury induced by these nanomaterials.

3.1.3 | Cardiac myofibres disarray

Marked cardiac myofibres disorganization was exhibited by the heart of rats subjected to 378 mg/kg bw of TiO_2 NPs and to the lesser extent in the hearts of rats received 126 nm or 252 nm TiO_2 NPs. The fibres appeared as if they lost their normal parallel alignment to a non-parallel arrangement (Figure 4). This alteration might be resulted from the formation of non-contractile scar tissue and considered a feature of hypertrophic cardiomyopathy [21].

3.1.4 | Myocytes hypertrophy

The heart of the rats received 378 mg/kg bw demonstrated individual eccentric myofibres enlargement (Figure 5). This increase in the size of muscle fibres may indicate maladaptive to adverse load condition induced by TiO_2 NPs [22]. Myocytes hypertrophy is usually accompanied by increased nuclear size from oval to boxcar shaped nuclei.

3.1.5 | Hyaline degeneration

Degenerative foci accompanied with hyaline degeneration, vacuolization of cytoplasm of muscle fibre, dilation and congestion of blood capillaries were seen in myofibre of rats received 252 mg/kg bw and more of TiO_2 NPs (Figure 6a-b). Histopathological studies indicated fibrosis associated with cardiac hyalinization, in cardiomyocytes [23].

3.1.6 | Myofibre vacuolization

This alteration was seen in rats exposed to 126 mg/kg bw of TiO_2 NPs and more (Figure 7). Diffuse myocardial vacuolization is considered as an indication of cardiotoxicity [24].

3.1.7 | Cardiomyocytes nuclei alterations

Pyknotic cardiomyocytes with irregular nuclei and vacuolization of cytoplasm of the myofibres were seen in the cardiac

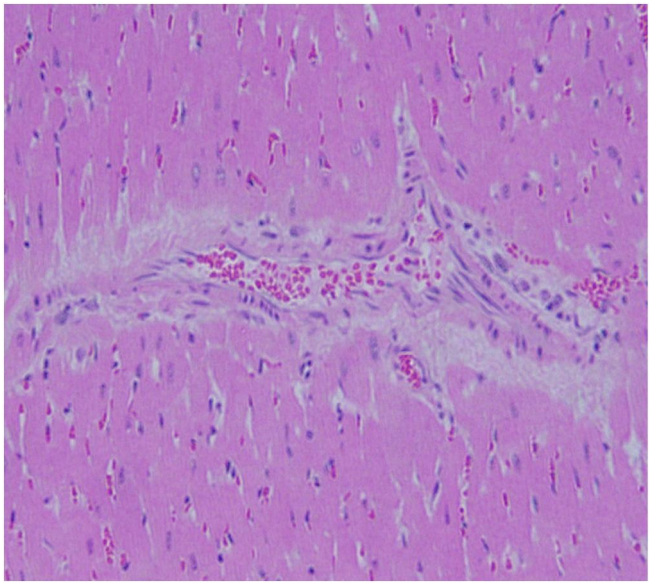

FIGURE 12 Light micrograph of section in the cardiac tissues of TiO_2 NPs-treated rat showing fibrocytes proliferation in the interstitial connective tissue surrounding blood vessel (arrow). H&E stain (scale bar 50 μm), 252 mg/kg bw of TiO_2 NPs. TiO_2 NP, titanium dioxide nanoparticles

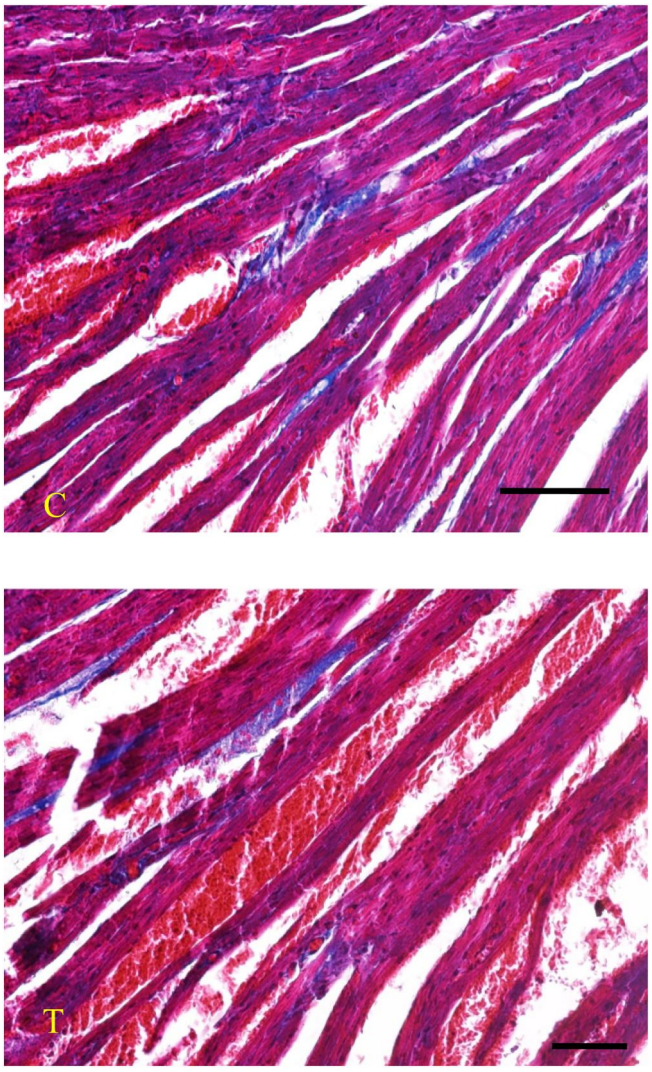

FIGURE 13 Light micrographs of sections in the cardiac tissues of control (C) and TiO_2 NPs-treated rats (T) stained with Masson trichrome stain for collagen fibres demonstration. Note that the density of the interstitial collagen fibres was not affected in 378 mg/kg bw TiO_2 NPs-treated rats. Masson trichrome stain (scale bar 50 μm). TiO_2 NP, titanium dioxide nanoparticles

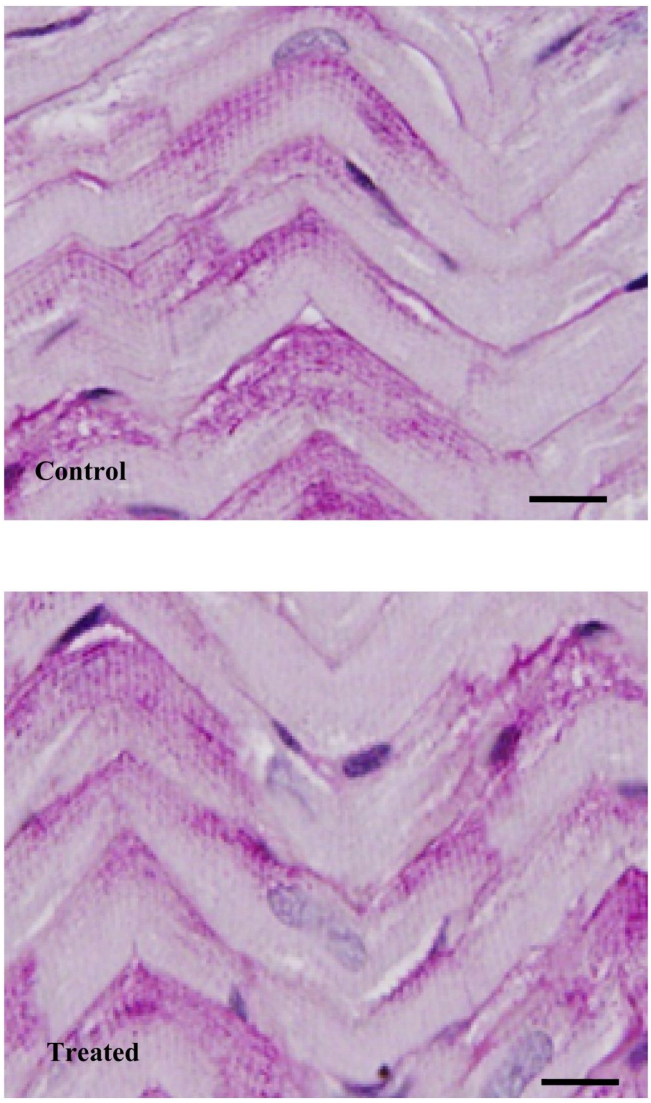

FIGURE 14 Light micrographs of sections in the cardiac tissues of control and TiO_2 NPs-treated rats stained with PAS stain. No change was seen the glycogen content in the myofibres of rats exposed to TiO_2 NPs in comparison with the control rats. PAS stain (scale bar 50 μm). PAS, periodic-acid-Schiff; TiO_2 NP, titanium dioxide nanoparticles

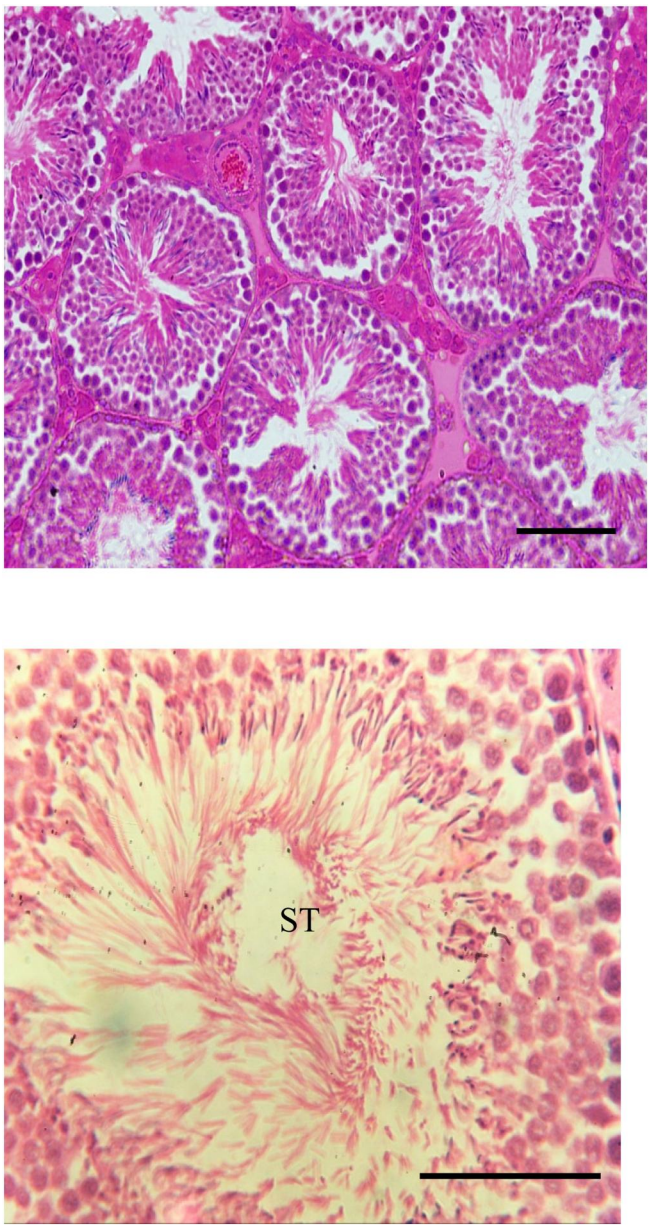

FIGURE 15 Light micrographs of sections in the testicular tissues of control rat demonstrating: (a) Normal architecture of the testicular tissue and (b) Normal spermatogenesis in ST and interstitial tissues. H&E stain (scale bar 200 μm). ST, seminiferous tubule

tissues of rats exposed to 252 mg/kg bw of TiO_2 NPs and more (Figure 8). Moreover, cardiomyocytes nuclei demonstrated anisokaryosis, accompanied with hydropic degeneration. These findings may indicate myocytes injury. The induced cardiomyocytes nuclei alterations might be associated with probable developing cardiomyopathy [25].

3.1.8 | Interstitial oedema

Considerable oedema accompanied with hyaline degeneration were exhibited by the cardiac tissues of rats exposed to 126 mg/kg bw of TiO_2 NPs and more (Figure 9). This alteration may indicate that heart became unable to meet the requirements of the body for oxygen. Some studies showed that the heart is unable to function effectively in the presence of myocardial oedema [26].

3.1.9 | Cross striation loss

Most of the myocardial fibres demonstrated partial cross striation loss (Figure 10). This cardiac change may indicate insufficient myocardial blood supply and irregular bands contraction leading to arrhythmia. Loss of cross striation within myocardial fibres is an indication of myocardial infarction [27].

3.1.10 | Inflammatory cells infiltration

Occasional inflammatory cells infiltration of lymphocytes, neutrophils and plasma cells was demonstrated in the interstitial cardiac tissues of rats exposed to 378 mg/kg bw of TiO_2 NPs (Figure 11a-b). This alteration may indicate the ability of TiO_2 NPs to interact with the cardiac tissue components. Infiltration of the inflammatory cells may induce oxidative stress generating inflammatory immune-mediated injury and reactive oxygen species as an immune response [28].

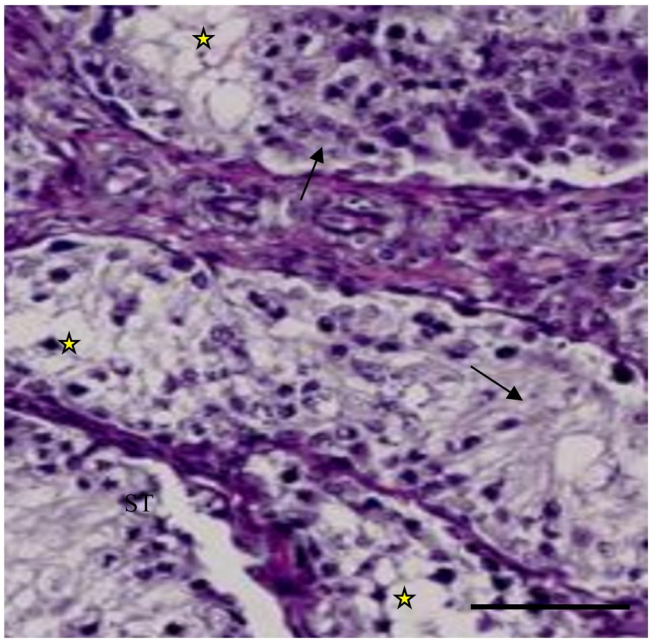

FIGURE 16 Light micrograph of section in the testicular tissues of TiO_2 NPs-treated rats demonstrating spermatocytes degeneration (arrows) and vacuolization (stars). H&E stain (scale bar 200 μm), 378 mg/kg bw of TiO_2 NPs. TiO_2 NP, titanium dioxide nanoparticles

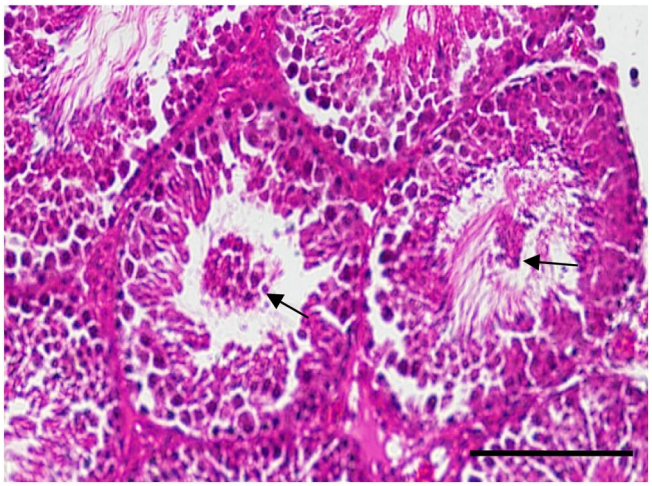

FIGURE 17 Light micrograph of section in the testicular tissues of TiO_2 NPs-treated rats demonstrating sloughing of spermatogenic cells to the lumen of seminiferous tubules (arrows) H&E stain (scale bar 200 μm), 378 mg/kg bw of TiO_2 NPs. TiO_2 NP, titanium dioxide nanoparticles

3.1.11 | Fibrocytes proliferation

Fibrocytes proliferation in the interstitial tissue surrounding some blood vessel of rats exposed to 252 mg/kg bw of TiO_2 NP and more were seen (Figure 12). Fibrocytes proliferation is contributed to fibrosis in many cardiac diseases as a result of interleukin-34 promotion [29].

On the other hand, no alteration in the density and arrangement of the collagen fibres was detected in the cardiac interstitial tissue of all rats subjected to any used dose of TiO_2 NPs (Figure 13). In addition, we could not detect any change in the glycogen content of the cardiac myofibres in all rats subjection to TiO_2 NPs treatment (Figure 14).

3.2 | Testicular alterations

Control rats demonstrated normal histological architecture of the testicular tissue and seminiferous tubules together with normal spermatogenesis and interstitial tissues (Figure 15a-b).

In comparison with the control rats, the following histological alterations were seen in the testicular tissues of TiO_2 NPs-treated rats.

3.2.1 | Spermatocytes degeneration

Occasional vacuolization of spermatocytes was demonstrated by the testis of treated rats (Figure 16). This alteration was seen in rats subjected to 252 mg/kg bw of TiO_2 NPs and more.

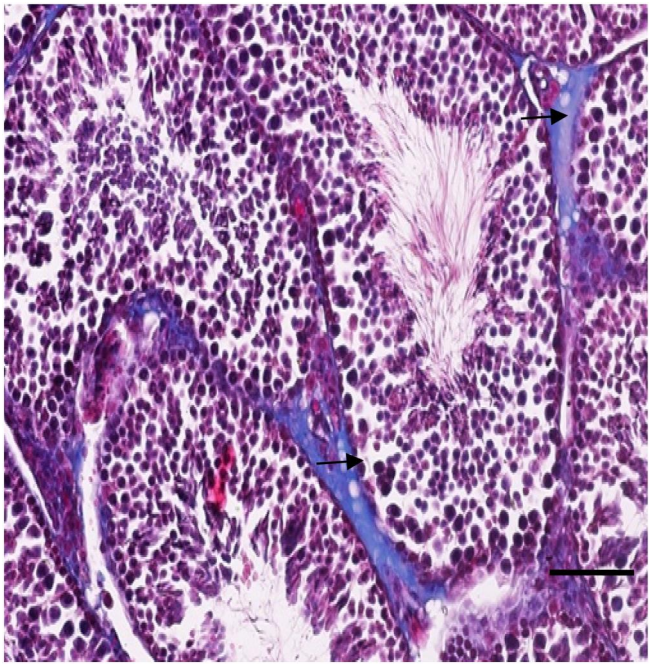

FIGURE 18 Light micrograph of section in the testicular tissues of TiO_2 NPs-treated rats demonstrating interstitial testicular tissue. Oedema (arrows). Mallory trichrome stain (scale bar 500 μm), 252 mg/kg bw of TiO_2 NPs. TiO_2 NP, titanium dioxide nanoparticles

TABLE 1 Cardiac and testicular histological alterations induced by 25 nm TiO_2 NPs

	Cardiac histological alterations										Testicular histological alterations	
	Parameters											
Group	1	2	3	4	5	6	7	8	9	10	11	12
Control rats	−	−	−	−	−	−	−	−	−	−	−	−
Rats received TiO_2 NPs (126 mg/kg bw)	±	+	±	−	−	+	−	±	−	−	−	−
Rats received TiO_2 NPs (252 mg/kg bw)	+	+±	+	±	+	+±	+	+±	±	+	±	−
Rats received TiO_2 NPs (387 mg/kg bw)	+±	++	++	+	+±	++	+±	++	+±	++	+	+

Note: 1, Wavy myocardial fibres appearance; 2, Hydropic degeneration; 3, Cardiac myofibres disarray; 4, Myocytes hypertrophy; 5, Hyaline degeneration; 6, Myofiber cytoplasmic vacuolization; 7, Cardiomyocytes nuclei alterations; 8, Interstitial oedema; 9, Cross striation loss; 10, Spermatocytes degeneration; 11, Spermatogenic cells sloughing; 12, Testicular oedema. Alteration degree: −, absent; ±, occasional; +, moderate; ++, strong.

Abbreviations: NA, not applied; TiO_2 NPs, titanium oxide nanoparticles.

Spermatocytes degeneration may lead to spermatogenesis disturbance and/or may be related to changes in Leydeg cells population.

3.2.2 | Spermatogenic cells sloughing

The lumen of seminiferous tubules in the testicular tissues of rats subjected to 252 mg/kg bw of TiO_2 NPs or more demonstrated spermatids sloughing (Figure 17). This finding may indicate spermatocytes cytoskeleton disruption of the physical interaction of spermatocytes due to nanotitania toxicity [30].

3.2.3 | Testicular oedema

Oedema was demonstrated in the testicular interstitial connective tissue of rats exposed to 378 mg/kg bw TiO_2 NPs (Figure 18). Testicular oedema is an alteration that might be associated spermatogonial arrest Porter et al. [31].

In addition, some studies have linked interstitial testicular oedema to alterations in the testicular tissues such as testosterone [32].

Semi-quantitative assessment of the cardiac and testicular alterations induced by acute exposure to titanium dioxide NPs is tabulated in Table 1. These testicular alterations may together indicate that exposure to TiO_2 NPs could induce toxicological impact on spermatogenesis with potential sequences of reproduction and fertility.

The present study demonstrated nanotoxic cardiac and testicular histological alterations due to acute TiO_2 NPs exposure suggesting damage of the heart and testis. The toxicity of titania NPs might be due to their ability to produce reactive oxygen species. These findings with other reports demonstrated alterations in the structure and function of other vital organs. Respiratory chronic exposure to ultrafine TiO_2 aerosols (0.8 μm, 10 mg/m^3) for one year caused damage of liver, kidneys and heart [33]. Titania NPs were observed by other studies to translocate into the blood, following oral exposure, and thereafter distributed to secondary targets, including liver, heart, spleen, lungs and kidneys [34].

4 | CONCLUSIONS

It is concluded from the findings of the present investigation that these nanomaterials could cause marked injury to the heart and the testis affecting the functions of these vital organs. The induced damage might be resulted from the oxidative stress induced by these NPs due to the interaction with the membrane structure, and macromolecules of the myocytes and spermatocytes. More investigations are recommended on the nanotoxicity of these particles with a need to understand their ecotoxicity and persistency.

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REFERENCES

1. Seeger, E., Baun, A., Kästner, M., et al.: Insignificant acute toxicity of TiO_2 nanoparticles to willow trees. J. Soil. Sediment. 9(1), 46–53 (2009)
2. Al-Doaiss, A., Ali, D., Ali, B., Jarrar, B.: Renal histological alterations induced by acute exposure of titanium dioxide nanoparticles, Int J Morphol. 37(3), 1049–1057 (2019)
3. Li, J., Muralikrishnan, S., Ng, C., Yung, C., Bay, B.: Nanoparticle-induced pulmonary toxicity. Exp Biol Med. 235,1025–1033 (2010)
4. Davis, J.: Oversight of next generation nanotechnology. Project of the Emerging Nanotechnologies, pp. 1–39. Woodrow Wilson International Center for Scholars, Washington, DC (2009)
5. Yang, Y., Qin, Z., Zeng, W., et al.: Review: toxicity assessment of nanoparticles in various systems and organs. Nanotechnol. Rev. 6(3), 279–289 (2017)
6. Yuan, Y., Ding, J., Xu, J., Deng, J., Guo, J.: TiO_2 nanoparticles co-doped with silver and nitrogen for antibacterial application. J. Nanosci. Nanotechnol. 10, 4868–4874 (2010)
7. Galletti, A.: Toxicity evaluation of TiO_2 nanoparticles embedded in consumer products, MSc Thesis of Science, University of Miami (2016)
8. Fartkhooni, F., Noori, A., Mohammadi, A.: Effects of titanium dioxide nanoparticles toxicity on the kidney of male rats. Int. J. Sci. 10(1), 65–69 (2016)
9. Mahdieh, Y., Sajad, S., Mahmoudreza, G., et al.: The effects of titanium dioxide nanoparticles on liver histology in mice. J. Chem. Pharm. Res. 8(4), 1313–1316 (2016)

10. Shakeel, M., Jabeen, F., Shabbir, S., Asghar, M., Khan, M., Choudhry, A.: Toxicity of nano-titanium dioxide (TiO_2-NP) through various routes of exposure: a review. Biol Trace Elem. Res. 172(1), 1–36 (2016)
11. Warheit, D., Webb, T., Reed, K., Frerichs, S., Sayes, C.: Pulmonary toxicity study in rats with three forms of ultrafine TiO_2 particles: differential responses related to surface properties. Toxicology. 230, 90–104 (2007)
12. Song, B., Liu, J., Feng X., Wei, L., Shao, L.: A review on potential neurotoxicity of titanium dioxide nanoparticles. Nanoscale Res. Lett. 10(1), 342 (2015)
13. Li, Y.F., Chen, C.: Fate and toxicity of metallic and metal-containing nanoparticles for biomedical applications. Small. 7(21), 2965–2980 (2011)
14. Chang, X., Zhang, Y., Tang, M., Wang, B.: Health effects of exposure to nano-TiO_2 : a meta-analysis of experimental studies. Nanoscale Res Lett., 8(51), 1–10 (2013)
15. Abdulla, I.: Histological effects of titanium dioxide nanoparticles size 10 nm in mice testes. Sci. J. Univ. Zakho. 5(2), 158–161 (2017)
16. Pinget, G., Tan, J., Janac, B., et al.: Impact of the food additive titanium dioxide (E171) on gut microbiota-host interaction. Front. Nutr. 14(6), 57 (2019)
17. Yang, Y., Qina, Z., Zeng, W., et al.: Toxicity assessment of nanoparticles in various systems and organs. Nanotechnol. Rev. 6(3), 279–289 (2016)
18. Alarifi, S., Ali, D., Al-Doaiss, A., Ali, B., Ahmed, M., Al-khhairy, A.: Histologic and apoptotic changes induced by titanium dioxide nanoparticles in the livers of rats. Int J Nanomed. 8, 3937–3943 (2013)
19. Johnson, C.E.: Effects of fluid imbalances. In: Michael P., Conn J.B. (eds.) Neurosciences in Medicine, pp. 881–894. Lippincott Company, New Jersey (1995)
20. Schrand, A.M., Rahman, M.F., Hussain, S.M., Schlager, J.J., Smith, D.A., Sayed, A.F.: Metal-based nanoparticles and their toxicity assessment. Nanomed Nanobiotechnol. 2(5), 544–568 (2010)
21. Francalanci, P., Gallo, P., Bernucci, P., Silver, M., Amati, G.: The pattern of desmin filaments in myocardial disarray. Hum Pathol. 26(3), 262–266 (1995)
22. van Empel, V.P., De Windt, L.J.: Myocyte hypertrophy and apoptosis: a balancing act. Cardiovas. Res. 63(3), 487–499 (2004)
23. Yumusak, N., Yigin, Y., Polat, P., Hitit, M., Yilmaz, R.: Expression of ADAMTS-7 in myocardial dystrophy associated with white muscle disease in lambs. Polish J Veter Sci. 21(1), 119–126 (2018)
24. Jokinen, M.P., Lieuallen, W.G., Boyle, M.C., Johnson, C.L., Malarkey, A. N., Nyska, A.: Morphologic aspects of rodent cardiotoxicity in a retrospective evaluation of National Toxicology Program studies. Toxicol Pathol. 39(5), 850–860 (2011)
25. Kong, J.Y., Rabkin, S.W.: Palmitate induces structural alterations in nuclei of cardiomyocytes. Tissue Cell. 31(5), 473–479 (1999)
26. Dongaonkar, R.M., Stewart, R.H., Geissler, H.J., et al.: Myocardial microvascular permeability, interstitial oedema, and compromised cardiac function. Cardiovasc. Res. 87(2), 331–339 (2010)
27. Hashmi, S., Al-Salam, S.: Acute myocardial infarction and myocardial ischemia-reperfusion injury: a comparison. Int. J. Clin. Exp. Pathol. 8(8), 8786–8796 (2015)
28. Al-Doaiss, A., Jarrar, Q., Moshawih, S.: Hepatic histopathological and ultrastructural alterations induced by 10nm silver nanoparticles. IET Nanobiotechnol. 14(5), 405–411 (2020)
29. Gakllgan, C.L., Fish, E.N.: Interleukin-34 promotes fibrocyte proliferation. J. Interferon Cytokine Res. 37(10), 440–448 (2017)
30. Almansour, M., Jarrar, Q., Battah, A., Jarrar, B.: Histomorphometric alterations induced in the testicular tissues by variable sizes of silver nanoparticles. J Rep Med. 62(3), 17–23 (2017)
31. Porter, K.L., Shetty, G., Meistrich, M.L.: Testicular edema is associated with spermatogonial arrest in irradiated rats. Endocrinology. 147(3), 1297–1305 (2006)
32. Maina, M.B., Garba, S.H., Jacks, T.W.: Histological evaluation of the rats testis following administration of a herbal tea mixture. J. Pharm. Toxicol. 3(6), 464–470 (2008)
33. Wang, J., Zhou, G., Chen, C., et al.: Acute toxicity and biodistribution of different sized titanium dioxide particles in mice after oral administration. Toxicol. Lett. 168(2), 176–185 (2007)
34. Johnston, H.J., Hutchison, G.R., Christensen, F.M., et al.: Identification of the mechanisms that drive the toxicity of TiO_2 particulates: the contribution of physicochemical characteristics. Part. Fibre Toxicol. 6(1), 33 (2009)

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