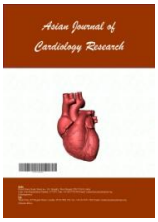

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Silver Nanoparticles Induced Cardiac Toxicity

Yasmeen M. Amer[1], Afaf Elatrash[1] and Ehab Tousson[1*]

[1]Department of Zoology, Faculty of Science, Tanta University, Tanta, Egypt.

Authors' contributions

This work was carried out in collaboration among all authors. Authors AE and ET designed the study, performed the statistical analysis and wrote the protocol. Author YMA wrote the first draft of the manuscript, managed the analyses of the study and managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aim: Silver nanoparticles (Ag NPs) have been utilized in a wide assortment of uses as antimicrobial specialists and have been fused into a few items as mechanical and food items not withstanding natural and clinical applications. Inordinate utilization of nanoparticles might be dangerous to human wellbeing and the climate. No sufficient information present about the toxic effect of silver nanoparticles on heart. Accordingly, The current study aimed to investigate the cardiac toxicity of silver nanoparticles.
Study Design: A total 20 male Wistar rats were divided into 2 equivalent groups (Group 1, control; group 2, Ag NPs).
Results: Current results revealed that; Ag NPs induced a significant decrease in serum e kinase myoglobin (CK-MB), phosphokinase (CPK), myoglobin, alkaline phosphatase (ALP) and aspartate aminotransferase (AST), cholesterol, triglycerides, and low-density lipids (LDL) while they cause a significant depletion in the levels of high-density lipids (HDL) in the sera of Ag NPs group (Gp2) when compared with the control group (Gp1).
Conclusion: The present study confirmed that; silver nanoparticles (Ag NPs) induced cardiac toxicity in rats.

Keywords: Silver nanoparticles; heart; cardiac enzymes; lipid profiles; rats.

**Corresponding author: Email: toussonehab@yahoo.com;*

1. INTRODUCTION

Nanotechnology is a quickly developing science by creating nanoproducts and nanoparticles (NPs) that can have novel and size-related Physico-compound properties contrasting fundamentally from bigger issue [1]. The epic properties of NPs have been abused in a wide scope of expected applications in medication, beauty care products, sustainable power sources, ecological remediation, and biomedical gadgets [2,3,4,5].

Among these nanoparticles, silver nanoparticles (Ag NPs or nanosilver) have pulled in expanding interest because of their novel physical, substance, and organic properties contrasted with their full scale scaled partners [6]. Ag NPs have particular Physico-synthetic properties, including a high electrical and warm conductivity, surface-upgraded Raman dispersing, compound solidness, synergist movement, and nonlinear optical conduct [7]. Because of their bactericidal properties, silver nanoparticles (AgNP) are the most habitually applied nanomaterials. They are utilized in materials, beautifiers, as items for homegrown cleaning, air cleaners, food bundling, covering for coolers, water sterilization, truth be told, in each application where microorganisms may apply a destructive impact. Specifically, a significant use is that in emergency clinics and general clinical practice, in clinical gadgets, and dressings for the treatment of wounds, consumes, and ulcers [8,9]. Studies have discovered that silver nanoparticles show antimicrobial action bringing about their broad use in bedding, washers, water decontamination, toothpaste, cleanser and flush, baby areolas and nursing bottles, textures, antiperspirants, channels, kitchen utensils, toys, and humidifiers [10]. It is additionally utilized for the treatment of wounds and consumes [11]. On the other hand, excessive use of nanoparticles may be hazardous to human health and the environment. Exposure to nanoparticles can occur via water, food, cosmetics, drugs, and drug delivery devices, and lead to various toxicological effects [9,12]. NPs may cause inflammation, cytokine production, cytoskeletal changes, altered vesicular trafficking, oxidative stress, apoptosis, and changes in gene expression and cell signaling [13]. Because of the far reaching use of AgNPs in medicine and commercial products and the possibility of their potential side effects, the present study was designed to investigate the conceivable toxic impact of silver nanoparticles on the heart rats.

2. MATERIALS AND METHODS

2.1 Chemicals

2.1.1 Silver nanoparticles

Silver nanopowder with a particle size range 45±5 nm and a 99.9% trace metals basis was purchased from Sigma-Aldrich Chemicals, Cairo, Egypt. AgNPs have been dissolved in 0.5% aqueous carboxymethyl-cellulose (Sigma-Aldrich) were coated with carbon, mounted on an electron microscope grid (200 mesh), and visualized using a transmission electron microscope ([TEM]; JEM-100CXII, JEOL Ltd., Tokyo, Japan) operating at 80 kV. However, AgNPS in the injected doses should be distributed more uniformly by sonication for 10 minutes just before injection, to be taken by systemic circulation [14].

2.2 Animals and Experimental Design

Twenty healthy male Wistar rats (weighing 190±10 gram and 13±1 weeks age), supplied from the accredited breeding and experimental laboratory in zoology departments, Tanta Univ., Egypt) were used for this study. As endorsed by the Institutional Animal Care and Use Committee (IACUC-SCI-TU-0153). After two weeks of acclimation, animals were divided into 2 equal groups:

Group 1 (Control) served as control.

Group 2 (Ag NPs) was injected intraperitoneally with AgNPs (50 mg/kg BW; >100 nm) for 6 weeks [9].

2.3 Blood and Tissue Preparation

At the end of the experiment, the rats were fasted for 10-12 hours and were anesthetized using sodium pentobarbital and dissected. Blood samples were individually collected from the inferior vena cava of each rat in non-heparinized glass tubes for the estimation of cardiac biomarkers.

2.4 Measurement of Cardiac Biomarkers

Serum creatine kinase MB (CK-MB) and myoglobin levels were detected according to [15,16], respectively. Creatine phosphokinase (CPK) levels were measured by a kinetic method according to a method described by [17]. The

activities of serum AST and ALP were assayed by the colorimetric method, according to [18,19], respectively.

2.5 Measurement of Lipid Profiles

Cholesterol, triglyceride, high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C) levels were determined with Kits from ELLTECH, according to [20,21].

2.6 Histopathological Examination

Rats were decapitated before dissection, and heart extraction. Hearts were washed with 0.9% saline solution, fixed in 10% neutral buffered formalin, and then stained with Ehrlich's hematoxylin, as described by [22,23] For silver nanoparticles detection in the heart sections, semi thin sections were prepared on glass slides through cutting at 1-um using an ultra-microtome (EM UC7 from Leica Microsystems). Following this preparation, the sections were stained with Toluidine blue for 25 s and examined by a light microscope.

2.7 Statistical Analysis

Data were reported as mean values ± SE and one-way ANOVA were used to detect significant differences between treatment groups. For biochemical results, the criterion for statistical significance was set at $p<0.05$ for the biochemical data.

3. RESULTS

3.1 Effect of Agnps and Cur Nps on Cardiac Biomarkers

Table.1 revealed that; a significant ($P<0.05$) elevation in creatine kinase myoglobin (CK-MB), phosphokinase (CPK), myoglobin, alkaline phosphatase (ALP), and aspartate aminotransferase (AST) activities in sera in AgNPs group (Gp2) when compared with control (Gp1). It also shows a significant ($P<0.05$) elevation in the levels of cholesterol,

Table 1. Variations in the serum cardiac biomarkers (creatine kinase myoglobin, phosphokinase, and myoglobin), serum alkaline phosphatase, and aspartate aminotransferase and the lipid profile (cholesterol, triglycerides, high-density lipids (HDL) and low-density lipids (LDL) levels in different groups

	Control	Ag NPs
CPK (U/l)	2457 ± 105.5	4746* ± 80.43
CK-Mb (µg/ml)	0.139 ± 0.003	0.304* ± 0.0056
Myoglobin (ng/ml)	13.7 ± 0.1528	16.8* ± 0.3786
AST (U/L)	135.7 ±2.603	268.3*± 6.936
ALP (U/L)	86.33 ± 4.485	160.7*±4.702
Cholesterol (mg/dl)	136.7± 4.410	208.3*±3.480
Triglyceride (mg/dl)	122.3 ± 1.856	197.3* ± 1.764
High density lipoproteins (HDL) (mg/dl)	43.17 ± 1.014	22.67* ± 1.302
Low density lipoproteins (LDL) (mg/dl)	69.70 ± 3.308	147.0* ± 4.386

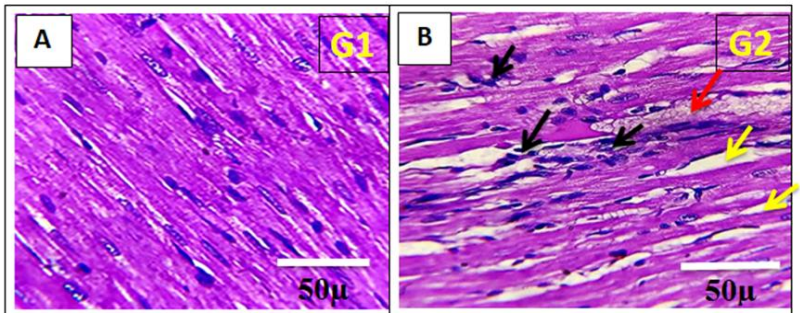

Fig. 1. Heart sections photomicrographs stained with H&E. A) Heart section in control rat groups showed normal myofibrillar structure with striations. B) Heart sections in treated rats with Ag NPs revealed moderate to marked myocardial hypertrophy (yellow arrows), cytoplasmic vacuoles (red arrows), and leukocytic infiltration (black arrows) 200X

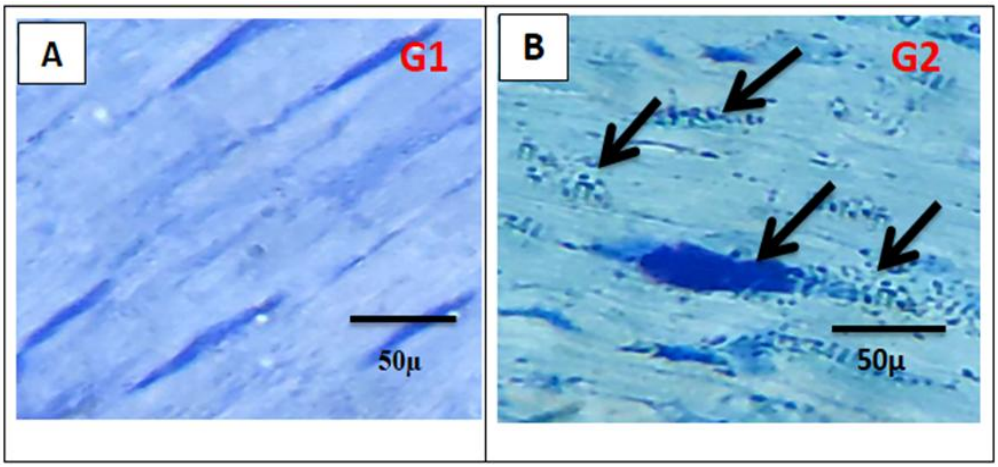

Fig. 2. Heart sections photomicrographs stained with toluidine blue. A) Heart section in the control rat group showed no deposition of AgNPs inside cardiomyocytes. B) Heart sections in treated rats with Ag NPs revealed moderate to marked deposition of AgNPs in cardiomyocytes as fine to small granules, Sometimes these granules aggregate form large masses (black arrows) 200X

triglycerides, and low-density lipids (LDL) while a significant (P<0.05) depletion in the levels of high-density lipids (HDL) in the sera of AgNPs group (Gp2) when compared with the control group (Gp1).

Data are expressed as mean ± SE of 10 observations. The significance of difference was analyzed by one–way ANOVA and Dunnett test (compare all vs. Ag Nps group) using a computer program. Values are expressed as means ± SEM. one – way ANOVA was significant at P < 0.05. Dunnett test was significant from corresponding Ag Nps group value at P < 0.05, P < 0.0001.

3.2 Histopathology Results

Heart section in control rat group showed normal myofibrillar structure with striations. On the other hand; heart sections in treated rats with Ag NPs revealed moderate to marked myocardial hypertrophy (yellow arrows), cytoplasmic vacuoles (red arrows), and leukocytic infiltration (Fig. 1).

3.3 Localization of Silver Nanoparticles (Ag Nps) in Cardiomyocytes

Heart sections stained with toluidine blue in treated rats with Ag NPs revealed moderate to marked deposition of AgNPs in cardiomyocytes as fine to small granules, sometimes these granules aggregate form large masses (Fig. 2).

4. DISCUSSION

Modernly, silver is utilized in mirrors, photography, and conductor instruments [24]. Since the coming of nanotechnology, the potential for utilizing silver nanoparticles (AgNPs) has expanded both in modern and biomedical applications, leading to an ascent in the quantity of buyer items containing these particles. AgNPs have gotten exceptional consideration in light of the fact that, at the nanoscale level, they show distinctive physical and synthetic properties, which have been utilized in optical, electrical, attractive, reactant, and organic applications [25].

Inferable from the disclosure of antiviral and antimicrobial properties offered by AgNPs, they have been fused into clinical supplies for the creation and improvement of natural apparatuses, for example, drugs, pacemakers, coupled antibodies to explicit particles, among others [11,26,27]. Nonetheless, (silver nanoparticles) SNP is as yet one of the most dubious materials because of its likely harmfulness in natural frameworks [28].

This examination intends to research the physiological and histological changes that may occur in the core of rodents after presentation to silver nanoparticles, though there isn't sufficient data on this field. The obtained results in this study indicated that; AgNPs treated rats show a significant elevation in creatine kinase myoglobin (CK-MB), phosphokinase (CPK), and myoglobin.

Elevated serum level of these enzymes is strong evidence for loss of sarcolemmal integrity due to injury to the myocardial cells. Our results don't agree with that obtained by Rathore et al. [29] who found no significant change in the levels of CP-MB was observed in the (Gold nanoparticles) GNP and (silver nanoparticles) SNP treated group. In the present study, we also found a significant elevation in the levels of cholesterol, triglycerides, and low-density lipids (LDL) while a significant depletion in the levels of high-density lipids (HDL) in the sera of AgNPs group when compared with the control group. Our results in the line of Sulaiman et al. [30], who find that; silver nanoparticle exposure in rats elevated the level of rat serum total cholesterol, triacylglyceride, free glycerol, low-density lipoprotein-cholesterol, and bilirubin ($p < 0.05$) when compared with the control. The level of high-density lipoprotein-cholesterol was depleted by nanoparticle exposure. According to our studies, alkaline phosphatase (ALP) and aspartate aminotransferase (AST) activities in sera in the AgNPs group were significantly increasing when compared with control. These data are supported by Adeyemi et al. [31], who reported that; AST and ALP levels in serum, kidney, and heart increase for the 14- and 21-day AgNPs treated groups.

This also agrees with Rathore et al. [29], who also found mild histopathological changes in the heart tissue of rats after oral administration of AgNPs (mild edema and separation of myofibrils).

5. CONCLUSION

The present study confirmed that; silver nanoparticles (Ag NPs) induced cardiac toxicity in rats. In this study, the histopathological examination of heart tissues of AgNPS treated rats demonstrated significant damage in the heart tissue (moderate to marked myocardial hypertrophy, cytoplasmic vacuoles, and leukocytic infiltration), which is in alignment with the previously mentioned physiological changes.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Animal Ethic committee approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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