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Biochemical and immunohistochemical evaluation of zinc oxide nanoparticles against experimental systemic amyloidosis in male rats

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Abstract

Forty male rats, two months old age were used in this experiment, divided into four groups, with ten animals per group. The first group was considered the control group. The second group was injected IP with nano zinc oxide at a dose of 5 mg/Kg B.wt. The third group was injected with 3 ml of 8% sodium caseinate the fourth group was treated with sodium caseinate and nano zinc oxide. The results of the histological examination of Sodium caseinate treated group kidneys showed coagulative necrosis in epithelial cells of the renal tubules with a Mesangial cells proliferation and deposition of amyloid in interstitial tissue and basement membrane of the epithelial cells and the wall of the blood vessels. The lesions were more severe after 60 days of treatment The GIV showed a clear improvement, especially after 60 days of treatment. In the spleen, the histological sections showed atrophy and deposition of amyloid in the red and white pulp in the GIII after 25 days of treatment, And the changes became more sever at the end of the experiment (60 days), which were represented by necrosis in the white and red pulp. The microscopic examination of the spleen samples of GIV showed a reduction in the pathological lesions. The results of histochemistry examination of kidney and spleen samples showed a positive reaction of amyloid deposition Immunohistochemistry examination, there was a strong reaction to the protein beta-amyloid in Kidneys and spleen in GIII a weak reaction in The GIV after 60 days of treatment.

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Introduction

Amyloidosis is a systemic disease described by the extracellular deposition of amorphous proteinaceous material in several tissues, especially spleen, liver, and kidney (1-3). This study was designed to determine the role of nano zinc oxide in reducing the lesions of experimentally induced systemic amyloidosis in male rats. Systemic amyloidosis, formerly known as primary amyloidosis, is a disorder described by the misfolding and deposition of proteins (4) related to a monoclonal gammopathy. The disorder primarily includes the production of immunoglobulin light chain fragments, mainly the lambda chain, by a monoclonal population of plasma cells in the bone marrow. In rare cases, the precursor protein may consist of an immunoglobulin heavy chain, termed AH amyloidosis, or may arise from an indolent B cell lymphoma (5). These precursor proteins undertake abnormal folding, resulting in the formation of fibrils with a beta-pleated sheet configuration. These fibrils interact with serum amyloid P protein (SAP) and other components, such as glycosaminoglycans, leading to the progress deposition of amyloid in extracellular tissues, which gradually accumulate and impair organ function. Although most monoclonal light chains do not demonstrate amyloidogenic properties, it remains impossible to prognosticate which ones will (6). Localized amyloid deposits are commonly found in the tracheobronchial tree, they can also affect the lungs, brain,

spleen, kidney and bladder, as well as the gastrointestinal tract, lymph nodes, skin, which may present as plaques and nodules (7). In the case of prostate deposits, they may represent localized AL amyloidosis or be associated with systemic transthyretin (TTR) amyloidosis (8). Nanotechnology has become a workable strategy in recent years (9,10), given that creative ways to treatment of many diseases. Zinc oxide nanoparticles (ZnO-NPs) have paid attention because of their adaptability and confirmed effectiveness in a different field (11). ZnO-NPs improve T cell activity and increase the rat serum's production of antigen-specific antibodies, particularly immunoglobulin E (IgE) and immunoglobulin G (IgG) (12). However, because ZnO-NPs inhibit growth of numerous bacteria, such as Streptococcus species, Staphylococcus species, *E. coli*, *B. subtiles*, and Pseudomonas fluorescens, they are regarded as strong antibacterial agents and antiparasitic (13,14). Although it is toxicity (15) zinc oxide ZnO-NPs have several uses in biological systems and can swiftly enter the bloodstream, where they circulate and propagate throughout various organs.

The study's aim to highlight the protective role of nano zinc oxide in reducing the development of amyloidosis lesions in the kidney and spleen of male rats.

Materials and methods

Ethical approval

Ethical approval reference number UM.VET.2024 for handling animals was awarded by Institutional Animal Care and Use Committee in University of Mosul, College of Veterinary Medicine.

Animals

Forty Albino male rats aged 2 months and weighing 250-300 grams were used. The Rats were housed under standard laboratory conditions, including a controlled temperature 22±2°C and a fixed dark / light cycle (12 hours dark / 12 hours light), with continuous access to food and water to ensure their well-being throughout the study.

Experimental design

Forty albino Rats divided to four experimental groups, each consisting of ten rats; Group I: Rat IP inoculated with normal saline (control group). Group II: Rat IP inoculated with ZnO-NPs 5 mg/kg (control +I) (16). Group III: Rat IP inoculated with 3.0 ml of sodium caseinate solution 8% (17). Group IV: Rat IP inoculated sodium caseinate with zinc oxide. The inoculation protocol was four days of injection and one day of rest. After 25 days of the experiment, half of the animals were sacrificed; at the end of the experiment (60 days), the other half were sacrificed, kidney and spleen. samples are stored in a neutral buffer, formalin, 10% for histopathological examination using routine stain and Congo red stain.

Histopathological examination

Samples from spleen and kidney were fixed in 10% neutral formalin for 48 hours, washed with running water, passed through ascending concentrations of ethyl alcohol, cleared by xylene, and finally embedded in paraffin wax. Four-micron-thick tissue sections were prepared, then stained with hematoxylin-eosin and examined under a light microscope (18,19). Congo red stain was used for the detection of amyloid, and the severity of lesions was scored according to Reiss *et al.* (20). And immunohistochemical examination (21) processing slides treated with beta Amyloid Polyclonal Antibody, for recognition of beta amyloid A.

Results

Histopathological changes

Histological sections of the kidneys of rats treated with sodium caseinate at a dose of 3 ml of 8% showed coagulative necrosis in epithelial cells lining renal tubules, and dense infiltration of mononuclear inflammatory cells around the blood vessels and in the renal interstitial tissue, with an increase in the glomerular cellularity and its shrinkage, and an expansion of Bowman's space, in addition to the deposition of a homogeneous red protein substance in the renal interstitial tissue, in basement membrane of the epithelial cells, and in the blood vessel wall. The pathological lesions were more severe after 60 days of treatment (Figures 1-4).

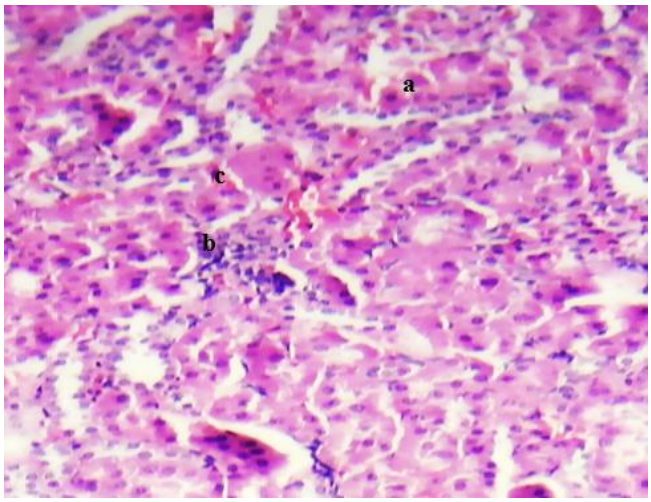

Figure 1: The histological section of the rat kidney was treated with sodium caseinate for 25 days, showing coagulative necrosis in epithelial cells of renal tubules (a) with infiltration of mononuclear inflammatory cells in interstitial tissue (b) in addition to the deposition of amyloid substance (c). H&E 100X.

Histological examination of kidney samples from the group of rats treated with sodium caseinate with zinc oxide nanoparticles at a dose of 5 mg /Kg B wt. showed a reduction in pathological lesions characterized by congestion of blood vessels with mild infiltration of mononuclear inflammatory cells and the presence of amyloid material in the interstitial tissue of the kidney (Figures 5 and 6).

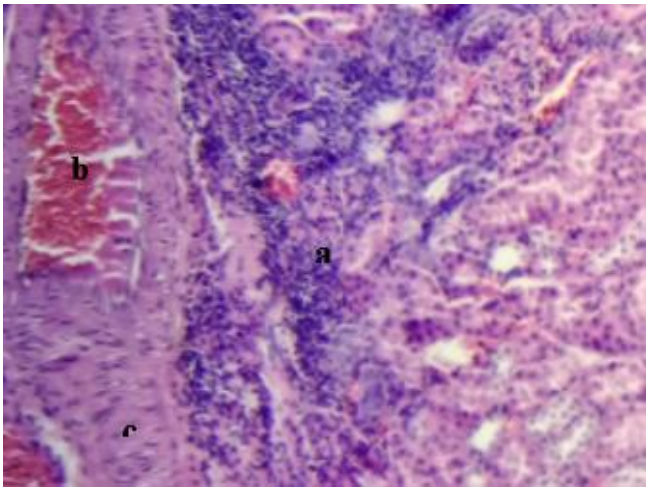

Figure 2: The histological section of the rat kidney was treated with sodium caseinate for 25 days, showing dense infiltration of mononuclear inflammatory cells in interstitial tissue (a) in addition to the deposition of amyloid substance congestion of blood vessels (b) thickening in the wall of blood vessel (c). H&E 100X.

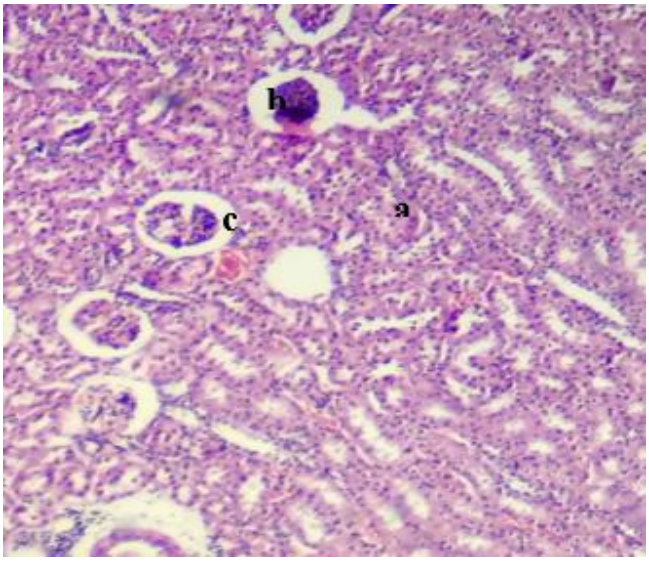

Figure 3: The histological section of the rat kidney was treated with sodium caseinate for 60 days, showing sever necrosis in renal tissue (a) atrophy in glomeruli (b) increase in cellularity of glomeruli (c). H&E 100X.

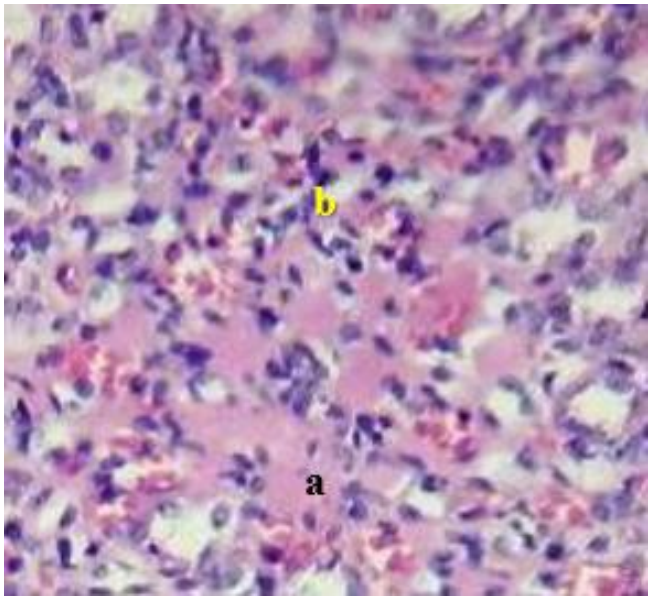

Figure 4: The histological section of the rat kidney was treated with sodium caseinate for 60 days, showing sever deposition of amyloid material in intestinal tissue and basement membrane (a) with infiltration of mononuclear inflammatory cells (b). H&E 400X.

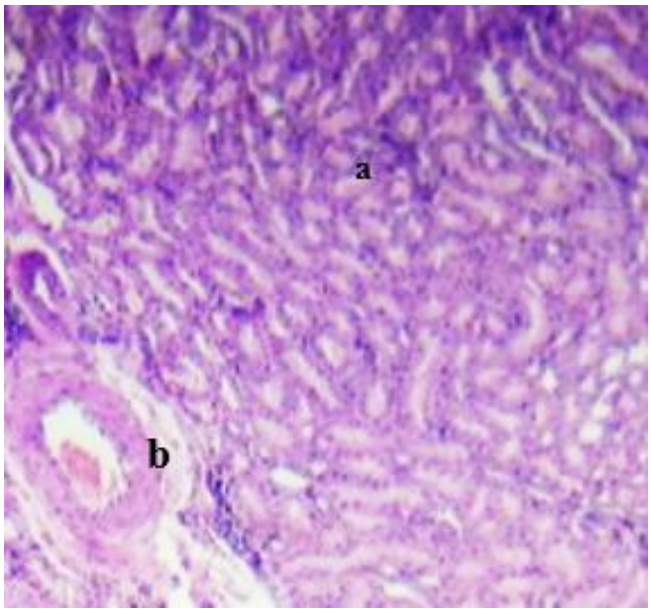

Figure 5: Histological section of rat kidney treated with sodium caseinate and zinc oxide nanoparticles for 60 days showing mild infiltration of mononuclear inflammatory cells (a) with congestion of blood vessels (b). H&E 100X.

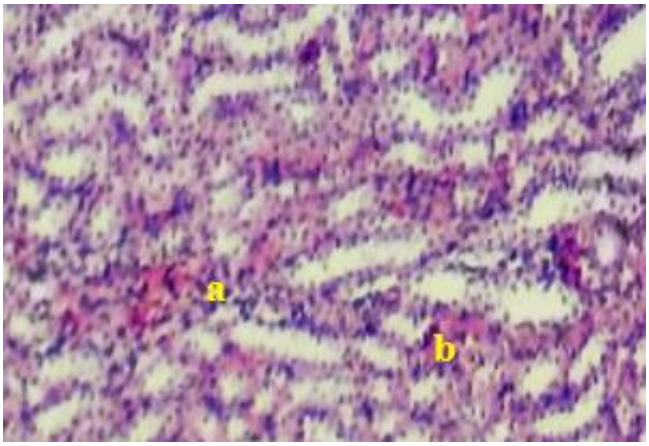

Figure 6: Histological section of rat kidney treated with sodium caseinate and zinc oxide nanoparticles for 60 days showing mild infiltration of mononuclear inflammatory cells (a) with shorthand in amyloid material (b). H&E 100X.

In the spleen, the histopathological lesions of the group of rats treated with sodium caseinate after 25 day of treatment were represented by atrophy in the white pulp and deposition of proteinaceous material under the capsule and in the white and red pulp (Figures 7 and 8), but after 60 days of the experiment, the lesions were more severe, characterized by severe necrosis of the white and red pulp, with severe deposition of proteinaceous material in the spleen tissue (Figure 9). There was an improvement in the histological image of the spleen when the rats were treated with sodium caseinate with nano zinc oxide, as the deposition of proteinaceous material was limited to the white pulp with slight infiltration of inflammatory cells (Figure 10).

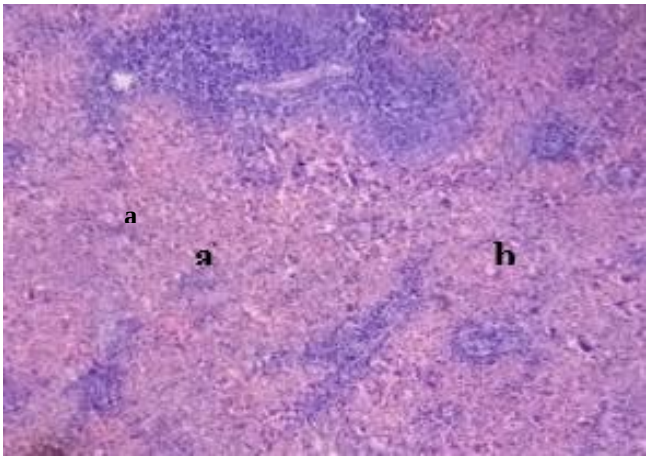

Figure 7: The histological section of the rat spleen was treated with sodium caseinate for 25 days, showing atrophy of white bulb (a) presence of amyloid material in red bulb (b). H&E 100X.

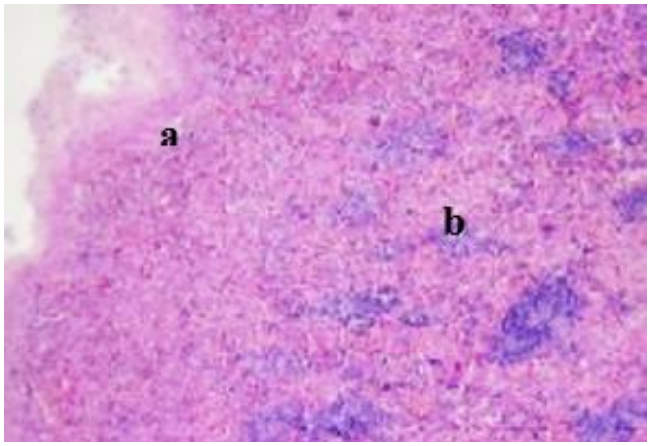

Figure 8: The histological section of the rat spleen was treated with sodium caseinate for 25 days, showing presence of amyloid material under the capsule (a) and in red bulb (b). H&E 100X.

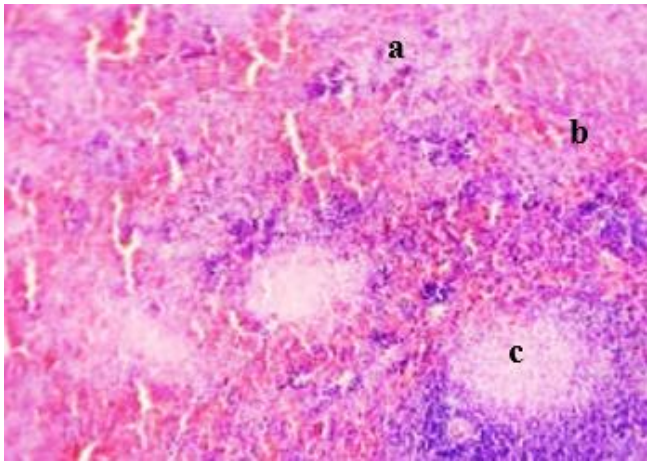

Figure 9: The histological section of the rat spleen was treated with sodium caseinate for 60 days, showing sever necrosis in splenic tissue (a) atrophy in white bulb (b) presence of amyloid material in white bulb (c). H&E 100X.

Histochemical analysis

Table 1 and 2 showed the results of microscopic examination of kidney and spleen of rats of different groups stained with Congo red stain showed a positive reaction represented by amyloid deposition with different intensity depending on the type and period of treatment, so in the kidney the deposition was of medium intensity (++) in the intestinal tissue, basement membrane of epithelial cell lining the kidney tubules, in the wall of blood vessels and glomerulus in the group of rats treated with sodium caseinate at a dose of 3 ml 8% for 25 days while the deposition was mild (+) in the intestinal tissue, basement membrane of epithelial cell lining the kidney tubules, around blood vessels and glomerulus in the group of rats treated with sodium

caseinate and nano zinc oxide at a dose of 5mg/kg wt After 60 days of treatment, the reaction was severe (+++) in all the above-mentioned kidney structures in the rats given sodium caseinate only while the reaction was of mild intensity (+) in interstitial tissue, blood vessels and glomerulus and medium (++) in the basement membrane in the group of rats treated with sodium caseinate with nano zinc oxide (Figure 11).

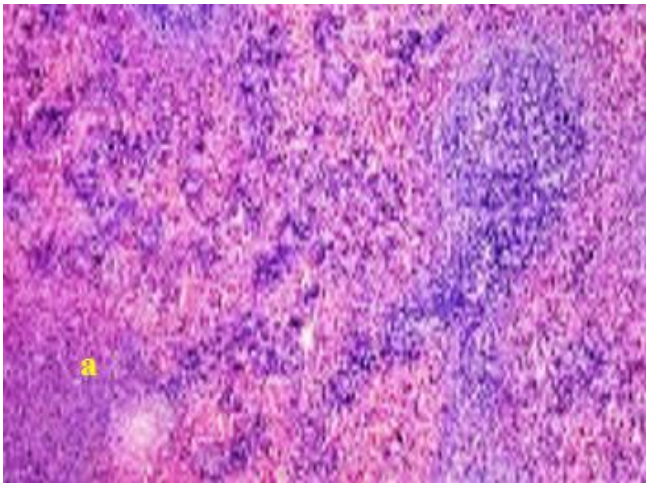

Figure 10: Histological section of rat kidney treated with sodium caseinate and zinc oxide nanoparticles for 60 days showing Improvement in the spleen image with a reduction in the amount of amyloid material, as it was limited to the white bulb (a). H&E 100X.

In spleen the deposition was in a medium intensity (++) in red and white bulb in the group of rats that treated with sodium caseinate at dose of 3ml 8% for 25 daysThe reaction became sever (+++) after 60 days of treatment). The reaction was mild (+) in GIV after 25 day of treatment while the reaction became moderate (++) in red bulb and mild (+) in white bulb after 60 days of treatment (Figure 12).

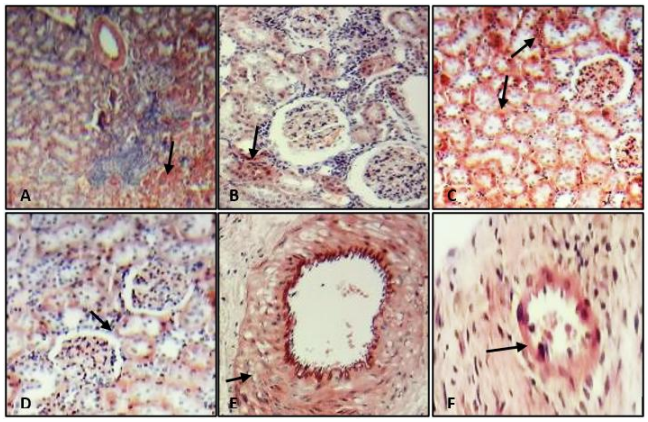

Figure 11: A: Histological section of rat kidney treated with 3 ml 8% sodium caseinate for 25 days, showing moderate amyloid deposition (++) black arrow (100X). B: The histological section of the rat kidney was treated with sodium caseinate and zinc oxide nanoparticles for 25 days, and mild amyloid deposition (+) black arrow (100X). C: Histological section of rat kidney was treated with 3 ml 8% sodium caseinate for 60 days, and sever amyloid deposition (+++) black arrow (100X). D: The histological section of the rat kidney was treated with sodium caseinate and zinc oxide nanoparticles for 60 days, and moderate amyloid deposition (++) black arrow (100X). E: Histological section of rat kidney was treated with 3 ml 8% sodium caseinate for 60 days, and sever amyloid deposition (+++) in wall of blood vessel black arrow (400X). The histological section of the rat kidney was treated with sodium caseinate and zinc oxide nanoparticles for 60 days, and moderate amyloid deposition (++) in wall of blood vessel black arrow (400X). Gongo red.

Table 1: Catalog score/grade system of amyloid deposition in kidney

Groups	After 25 days of experiment (Score/Grade)				After 60 days of experiment (Score/Grade)			
	I	BM	BV	G	I	BM	BV	G
GI	-/none.	-/none.	-/none.	-/none.	-/none.	-/none.	-/none.	-/none.
GII	-/none.	-/none.	-/none.	-/none.	-/none.	-/none.	-/none.	-/none.
GIII	++	++	++	++	+++	+++	+++	+++
GIV	+	+	+	+	+	++	++	+

Interstitial (I), Basement membrane (BM), Blood vessels (BV), Glomeruli (G).

Table 2: Catalog score/grade system of amyloid deposition in spleen

Groups	After 25 days of experiment (Score/Grade)		After 60 days of experiment (Score/Grade)	
	Red bulb	White bulb	Red bulb	White bulb
GI	-/none.	-/none.	-/none.	-/none.
GII	-/none.	-/none.	-/none.	-/none.
GIII	++	++	+++	+++
GIV	+	+	++	+

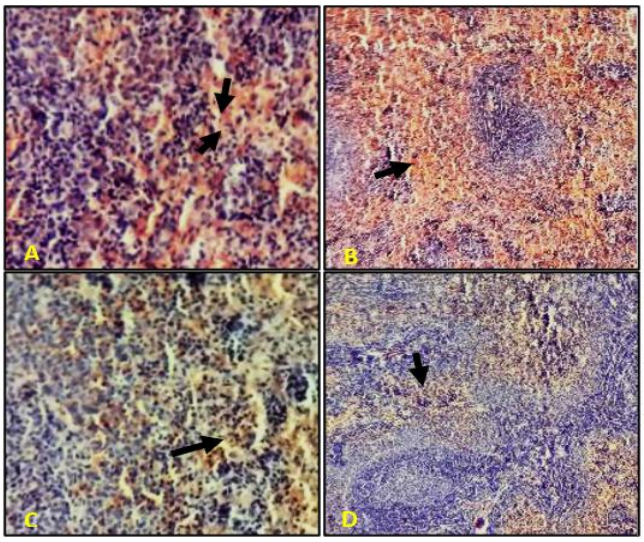

Figure 12: A: Histological section of rat spleen treated with 3 ml 8% sodium caseinate for 25 days, showing moderate amyloid deposition (++) black arrow (400X). B: Histological section of rat spleen was treated with 3 ml 8% sodium caseinate for 60 days, and sever amyloid deposition (+++) black arrow (100X). C: The histological section of the rat spleen was treated with sodium caseinate and zinc oxide nanoparticles for 25 days, and mild amyloid deposition (+) black arrow (400X). D: The histological section of the rat kidney was treated with sodium caseinate and zinc oxide nanoparticles for 60 days, and moderate amyloid deposition (++) black arrow (100X). Gongo red.

Immunohistochemistry

The immunohistochemical stain of kidney and spleen section revealed strong reaction (extracellular of renal tissues) for beta amyloid A in group treated with sodium caseinate for 60 days while the reaction became weak in group treated with sodium caseinate and nano zinc oxide (Figures 13 and 14).

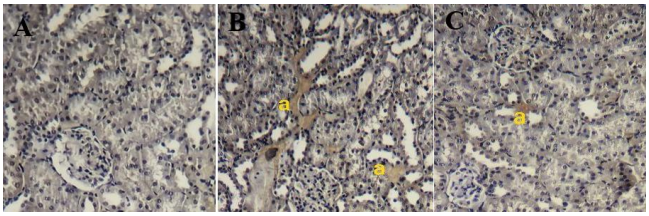

Figure 13: A: Histological section of a rat kidney control group showing negative reaction to beta-amyloid A immunostaining: Histological section of a rat kidney treated with sodium caseinate for 60 days showing strong reaction to beta-amyloid A immunostaining (a). C: Histological section of a rat kidney treated with sodium caseinate and zinc oxide nanoparticles for 60 days showing weak reaction to beta-amyloid A immunostaining (a). 100X.

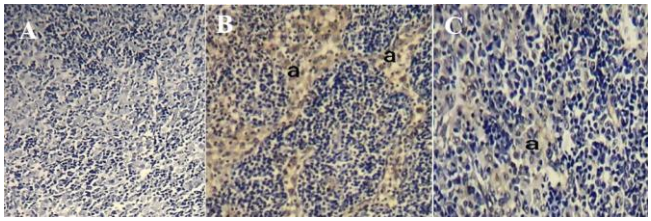

Figure 14: A: Histological section of a rat spleen control group showing negative reaction to beta-amyloid. (A): immunostaining. (B): Histological section of a rat spleen treated with sodium caseinate for 60 days showing strong reaction to beta-amyloid A immunostaining (a). (C): Histological section of a rat spleen treated with sodium caseinate and zinc oxide nanoparticles for 60 days showing weak reaction to beta-amyloid A immunostaining (a). 100X.

Discussion

Amyloidosis is a group of illnesses described by abnormal protein (known as amyloid) accumulation in tissues and organs, causing progressive injury, which may lead to death. Amyloidosis may occur in different organs such as kidneys, heart, liver, spleen, nervous system, GIT, glands, musculoskeletal system, eyes, and oral cavity (21). If the amyloidosis affects the kidneys, their capacity to filter the blood reduced. Protein escapes from the blood into the urine. The loss of protein from the blood can cause fluid to leak out of the blood vessels, the kidneys finally sustain so much damage that they are unable to eliminate waste from the body and eventually fail (22).The present study showed that treating rats with sodium caseinate at a dose of 3 ml 8% led to kidney and spleen damage represented by cogaulative necrosis in epithelial cells of renal tubules and dense infiltration of mononuclear inflammatory cells and the deposition of a homogeneous protein substance in the interstitial tissue of the kidney, basement membrane of the epithelial cells, in the glomerulus and in the wall of blood vessels, in the spleen, there were pathological changes represented by atrophy in the white pulp and severe necrosis of the white and red pulp, with severe deposition of proteinaceous material in the spleen tissue. This is consistent with what the researcher mentioned, as he found that injecting mice with sodium caseinate led to the infiltration of inflammatory cells Sodium caseinate has the ability to stimulate many inflammatory factors including macrophage-colony stimulating factor (M-CSF), granulocyte-CSF (G-CSF), and granulocyte–macrophage-CSF (GM-CSF) (23). Researchers have reported that the accumulation of protein deposits, including amyloid deposits, leads to local oxygen deficiency, which in turn causes necrosis of the affected tissue and an increase in inflammatory mechanisms represented by the secretion of many chemical mediators at the site of injury and the infiltration of inflammatory cells (24). In addition, it well recognized cellular exposure to beta

amyloid (Aβ) generates an increment in the intracellular Ca, which closely linked to several processes of damage also necrosis of cells. How ever, the mechanism in which increase in intracellular Ca is induced is not well understood. A great variety of Aβ-triggered receptors and channels have been involved, but it is also known that Aβ can directly interaction with the lipid components of the cell membrane, forming pores or ionic channels that help with Ca^{2+} entering into the cell (25). This is consistent with what the researcher mentioned (26), as he found that feeding male rats a high percentage of casein, even for a short period, led to degenerative changes and necrosis in the epithelial cells of the kidney. the mechanical replacement of parenchymal tissue by amyloid deposits lead to pressure atrophy in white pulp.

The researcher stated that intraperitoneal injection of sodium caseinate into mice leads to damage to the spleen tissue, which may be due to the cytotoxicity of the substance (27,28). The groups treated with sodium caseinate and nano zinc oxide for 25 and 60 days showed a noticeable improvement in disease lesions. Recently, ZnONPs usage been controversial as it permits easily through cell membrane to interact with cellular macromolecules leading to therapeutic effect on some organs. Also, ZnO-NPs can block pro-inflammatory cytokines like interleukin 1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) (29-31).

Studies have shown that nano zinc oxide has the ability to directly interact and combine with beta-amyloid, which forms amyloid plaques, leading to a change in their shape or a reduction in their formation rate. Thus, it plays an important role in the decomposition of beta-amyloid and preventing its deposition within various tissues (32). While the researcher found that mature amyloid fibers can disintegrate into an amorphous form in the presence of nano zinc oxide (33). Congo red staining of the protein produced a favorable reaction. Depending on the kind and length of treatment, the reaction's severity varied from mild to moderate to severe. This supports the findings of the researcher, who discovered that giving mice an amyloid-promoting agent caused amyloid to accumulate in a number of body organs, including the spleen, liver, intestines, kidneys, and heart, with the degree of the deposition changing with the duration of the treatment (34).

In this study, the gene expression of the protein beta-amyloid was evaluated in the kidney and spleen of rats according to the groups. The results of microscopic examination of the sections stained with immunohistochemistry showed the presence of an immune reaction to this protein extracellular of the two aforementioned organs, but at varying degrees and intensity depending on the nature of the treatment. The high level of pigment intensity in group that treated with sodium caseinate may be due to the fact that this substance is considered an amyloid promoting agent, as it stimulates the production of large amounts of beta-amyloid from amyloid precursor protein (APP) and then deposition outside the cells in various organs (35). Under pathological circumstances, metabolic dysregulation seems to cause accumulation of Aβpeptides in extracellular space, which oligomerize and aggregate, forming insoluble Aβ plaques (36). The kidney controls levels of many blood metabolites via its filtering and excretory functions Several studies have suggested a role for the kidneys in clearance of plasma amyloid-β (37). However, through what was diagnosed from the pathological lesions of the kidney such as inflammation, necrosis and atrophy, which in turn negatively affected the glomerular filtration process of plasma amyloid beta, which caused its level to rise in the plasma and consequently its deposition in various organs such as the spleen and kidney.

The intensity of the immunostaining of beta-amyloid protein decreased in both the kidney and spleen of the rats treated with sodium caseinate and nano zinc oxide. The researchers (38) stated that the nanomaterials prevent the formation of amyloid plaques by destruction of protein aggregates through interaction with specific amino-acid sequences, thus inhibiting aggregation. This is consistent with what the researcher stated, where he found that mature amyloid fibers can disintegrate into an amorphous form in the presence of nano zinc oxide (39).

Conclusion

We conclude from this study that zinc oxide has the ability to reduce the development of amyloidosis lesions in kidney and spleen, which was demonstrated through, histopathological examination, histochemistry and immunohistochemical of kidney and spleen samples.

Acknowledgment

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Conflict of interest

None.

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تقييم كيميائي ومناعي نسجي لأوكسيد الزنك النانوية ضد داء النشوانية الجهازي التجريبي في ذكور الجرذان

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الخلاصة

استخدم في هذه التجربة أربعين من ذكور الجرذان بعمر شهرين، وقسمت إلى أربع مجموعات، بواقع عشرة حيوانات لكل مجموعة. اعتبرت المجموعة الأولى سيطرة. تم حقن المجموعة الثانية داخل الصفاق باستخدام أكسيد الزنك النانوي بجرعة ٥ ملغم/كجم من وزن الجسم. تم حقن المجموعة الثالثة بـ ٣ مل من كازينات الصوديوم بنسبة ٨%حقنت المجموعة الرابعة بكازينات الصوديوم وأوكسيد الزنك النانوي. أظهرت نتائج الفحص النسيجي لكلى المجموعة المعاملة بكازينات الصوديوم نخرا تجلطي في الخلايا الظهارية للأنابيب الكلوية وترسب الياف النشوانية في الأنسجة الخلالية والغشاء القاعدي للخلايا الظهارية وجدار الأوعية الدموية. كانت الآفات أكثر شدة بعد ٦٠ يوما من العلاج أظهر الرابعة تحسنا واضحا، خاصة بعد ٦٠ يوما من العلاج. في الطحال، أظهرت المقاطع النسيجية ضمورا وترسبا للأميلويد في اللب الأحمر والأبيض بعد ٢٥ يوما من العلاج، وازدادت حدة التغيرات في نهاية التجربة (٦٠ يوما)، والتي تمثلت في نخر في اللب الأبيض والأحمر. أظهر الفحص المجهري لعينات الطحال في النخاع العظمي الرابع انخفاضا في الآفات المرضية. أظهرت نتائج الفحص النسيجي الكيميائي لعينات الكلى والطحال رد فعل إيجابي لترسب الأميلويد في الفحص المناعي الكيميائي، وكان هناك تفاعل قوي تجاه بروتين بيتا أميلويد في الكلى والطحال في المجموعة الثالثة وتفاعل ضعيف في المجموعة الرابعة بعد ٦٠ يوما من المعاملة.