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ORIGINAL ARTICLE

Cadmium and Arsenic: A Deadly Duo for Diabetic Rats

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KEYWORDS

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Diabetes;
Heavy metals;
Toxicity;
Co administration

ABSTRACT: This study investigates the synergistic impact of cadmium and arsenic co-exposure on diabetic rats, highlighting their intricate interplay within the context of diabetes. Male and female rats, induced with diabetes via streptozotocin, were exposed to cadmium chloride and arsenic trioxide. Blood glucose dynamics, organ histopathology, and vital functions were scrutinized to elucidate the toxicological consequences. Results revealed significant deviations in blood glucose levels, amylase concentrations, and kidney and liver functions, coupled with discernible impairments in vital organs. These findings underscore the formidable health risks posed by concurrent cadmium and arsenic exposure in diabetic individuals, emphasizing the urgent need for further research to unravel the underlying mechanisms and devise preventive measures. This study accentuates the necessity for continued exploration in this domain to mitigate the perilous consequences of such co-exposure, emphasizing the critical intersection of diabetes and heavy metal toxicity.

INTRODUCTION

Diabetes mellitus (DM) is broadly classified as insulin-dependent (Type 1) and non-insulin dependent (Type 2), representing a chronic metabolic disorder that disrupts the digestion of carbohydrates, proteins, and lipids. Currently, DM is recognized as an epidemic, with a staggering increase in global prevalence [1]. In the year 2000, India recorded the highest number of diabetic patients, and projections suggest that the global number of individuals with diabetes will double within a decade [2, 3]. DM compromises the function and integrity of the endothelial layer, leading to a swollen and eroded endothelial lining, which elevates the risk of cardiovascular disease and arthrosis [4, 5]. Hyperglycemia, a hallmark of diabetes, has been shown to cause intestinal disruptions in rats, facilitating the transition of local intestinal infections to systemic infections [6, 7]. While the well-documented complications of diabetes include nephropathy, retinopathy, peripheral neuropathy, and stroke, emerging evidence highlights additional complications such as cancer, infections, liver disease, and functional disabilities [8].The World Health Organization lists six major air pollutants: particle pollution, ground-level ozone, carbon monoxide, sulfur oxides, nitrogen oxides, and lead. Exposure to these pollutants, both short-term and long-term, can lead to various health issues such as respiratory and cardiovascular diseases, neuropsychiatric disorders, eye and skin diseases, and chronic conditions like cancer [9]. Concurrently, the pervasive presence of heavy metals in our environment—contaminating air, water, soil, and food—poses significant health risks. Industrial activities and the use of fossil fuels have

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intensified exposure to these toxic metals, which are also used in traditional Ayurvedic and Unani medicine [10]. Metals like arsenic, lead, chromium, cadmium, and mercury are particularly harmful due to their ability to remain intact and reactive within organ systems, disrupting cellular functions by electron donation [11]. Arsenic, for instance, is known for its carcinogenic potential and multi-organ toxicity. It exists in various forms in the earth's crust and is notably absorbed through the small intestine, often sourced from contaminated drinking water. This is a pressing issue in many regions, including India, where groundwater contamination with arsenic is prevalent [12, 13]. In animal studies, arsenic exposure has led to neurodegeneration, hepatotoxicity, increased oxidative stress, and reduced serum cholinesterase levels [14]. Inhalation of arsenic can cause lung cancer, while dietary intake is linked to cancers of the kidney, bladder, liver, and skin [15]. Cadmium, another hazardous heavy metal, poses severe health risks to both humans and animals. It is used extensively in industries, particularly in the production of polyvinyl chloride (PVC), batteries, and metal electroplating for the automotive sector [16, 17]. Cadmium exposure weakens bones through demineralization, leading to pain, fractures, and decreased bone density, as well as releasing calcium from bones and reducing parathyroid hormone levels [18, 19]. In severe cases, cadmium poisoning can result in Itai-itai disease. Additionally, cadmium induces kidney dysfunction, damaging renal cells and reducing glomerular filtration rates [20]. It is also carcinogenic, associated with cancers of the liver, bladder, stomach, and blood. Given the extensive use and environmental presence of these metals, the primary focus of this study is to assess and document biochemical and histopathological alterations in animals already affected by diabetes. By exploring the potential risks associated with heavy metal exposure in individuals with pre-existing conditions, this study aims to provide a deeper understanding of the compounded health threats posed by such exposures.

MATERIALS AND METHODS

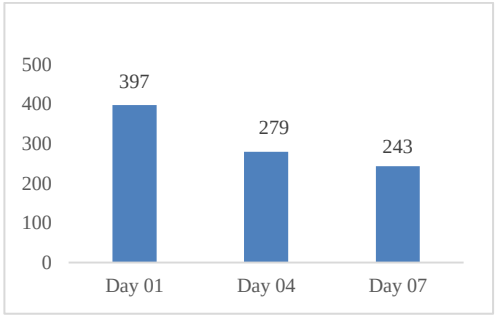
Streptozotocin and nicotinamide-induced diabetes rat model was employed for this study [21, 22]. To induce diabetes, streptozotocin was administered intraperitoneally at a dose of 40 mg kg^{-1}, following an intraperitoneal injection of nicotinamide at a dose of 80 mg kg^{-1}. Streptozotocin was procured from HIMedia, Thane, Maharashtra. The study utilized 20 rats of both sexes, with an average weight ranging from 160 g to 210 g, sourced from the animal facility of Shri Pharmaceutical Institute Rawatpura, Kumhari, Durg, and Chhattisgarh, India. Cadmium chloride and nicotinamide were purchased from Molychem, Mumbai, and arsenic trioxide was obtained from Loba Chemie PVT LTD, Mumbai. A 10% formalin solution was used for organ preservation.Periodic blood glucose measurements were conducted using the GLUCOOne BG-03 Blood Glucose Meter by Dr. Morepen, New Delhi. The rats were categorized into four groups: Group 1 received only streptozotocin and nicotinamide; Group 2 received streptozotocin, nicotinamide, and arsenic trioxide; Group 3 received streptozotocin, nicotinamide, and cadmium chloride; and Group 4 received streptozotocin, nicotinamide, arsenic trioxide, and cadmium chloride. Groups 2, 3, and 4 were compared to Group 1 to provide evidence of disease deterioration and organ damage. Arsenic trioxide and cadmium chloride were administered intraperitoneally on the second day after blood glucose measurement [23], at a dosage of 8 mg kg^{-1}, prepared in a saline solution [24]. On day 0, all groups received streptozotocin and nicotinamide. From day 1 to day 7, arsenic and cadmium were injected once daily. Blood glucose levels were measured on days 1, 4, and 7. On day 7, the rats were sacrificed for organ isolation and blood sampling. Kidneys and livers were immediately preserved in a 10% formalin solution for subsequent histopathological evaluation. Blood samples were analyzed for liver function tests, renal function tests, and amylase levels [25, 26].

RESULTS

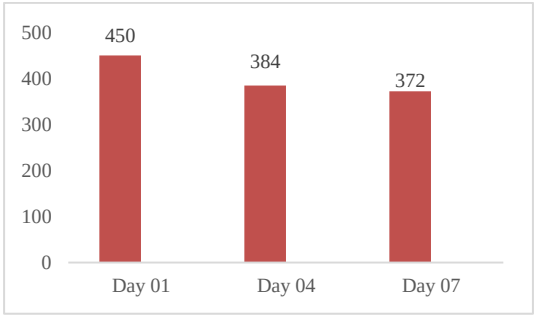
Blood glucose level

Figure 1 (a) show the blood glucose levels of group 1, which was administered with streptozotocin and nicotinamide. The day of administration was designated

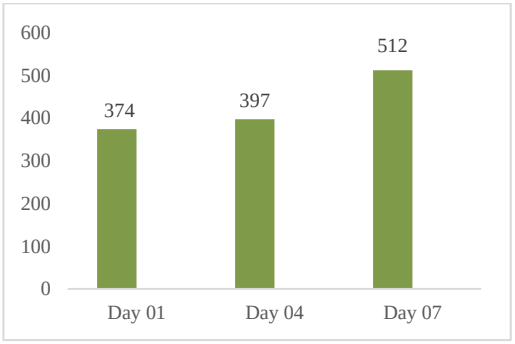
as day 0, and blood glucose levels were measured on days 1, 4, and 7. As can be seen, the blood glucose levels of group 1 remained relatively stable throughout the study period. Figure 1 (b) shows the blood glucose levels of group 2, which was administered with streptozotocin, nicotinamide, and arsenic. As can be seen, the blood glucose levels of group 2 increased significantly on days 4 and 7. This suggests that arsenic exposure can lead to an elevation in blood glucose levels in diabetic rats. Figure 1 (c) shows the blood glucose levels of group 3, which was administered with streptozotocin, nicotinamide, and cadmium chloride. As can be seen, the blood glucose levels of group 3 also increased significantly on days 4 and 7. This suggests that cadmium exposure can also lead to an elevation in blood glucose levels in diabetic rats. Figure 1 (d) shows the blood glucose levels of group 4, which was administered with streptozotocin, nicotinamide, arsenic, and cadmium chloride. As can be seen, the blood glucose levels of group 4 were the highest of all four groups. This suggests that co-exposure to arsenic and cadmium can lead to the greatest elevation in blood glucose levels in diabetic rats.



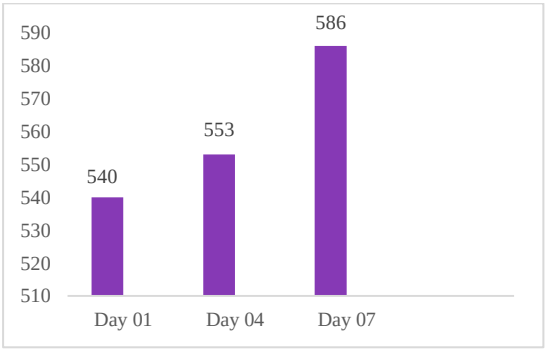
(a) Group 01. Streptozotocin and nicotinamide



(b) Group 02. Streptozotocin, nicotinamide and arsenic trioxide



(c) Group 3. Streptozotocin, nicotinamide and cadmium chloride



(d) Group 04. Streptozotocin, nicotinamide, arsenic and cadmium chloride

Figure 1. Blood Glucose Levels in Different groups of Induced Diabetic Rats.

Figure 2 shows a comparison of the blood glucose levels of all four groups. As can be seen, group 4, which was exposed to arsenic and cadmium, had significantly higher blood glucose levels than the other three groups. This suggests that co-exposure to arsenic and cadmium can have a more pronounced effect on blood glucose levels than exposure to either metal alone. However, when we observe the data from group 1 and 2, where streptozotocin, nicotinamide alone, and arsenic was administered, the data shows both elevation and reduction. Summarizing the effects in the presence of either one or both arsenic and cadmium, blood glucose levels in prediabetics will get elevated further, indicating a serious health hazard.

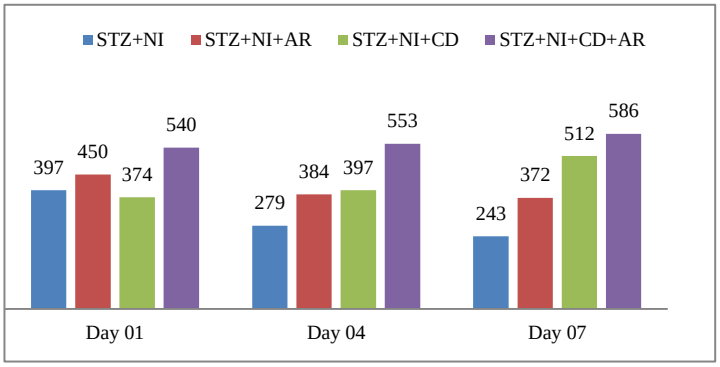


Figure 2. Blood Glucose level Comparisons between above 4 experimental groups.

Results of liver and kidney function tests

On the 7th day, the animals were sacrificed and blood was extracted using a cardiac puncher. This method was used because serum is required for liver function tests, kidney function tests, and amylase tests, and more than 3 mL of blood is required. Amylase was measured using an enzymatic colorimetric assay. Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvic Transaminase(SGPT) were measured using International Federation of Clinical Chemistry(IFCC) without pyridoxal phosphate assay.

Alkaline phosphatase was determined using a 4-nitrophenyl phosphate buffer and urea was estimated using urease and glutamate dehydrogenase.In all groups, amylase levels were elevated above normal. SGOT, SGPT, alkaline phosphatase, and urea levels were also elevated. Elevation of amylase indicates acute and chronic pancreatitis, renal failure, liver failure, and obstruction in the salivary duct (25). Elevation in levels of SGOT and SGPT indicates damage to the liver, cirrhosis, and hepatitis (Table 1). Elevated levels of alkaline phosphatase indicate hepatic dysfunction. Increased urea indicates kidney dysfunction. The above biochemical results indicate that if arsenic and cadmium, either one or both, enter a living organism with a pre-existing diabetic condition, the symptoms will worsen.

Table 1. Blood biochemical test results.

	Biochemical Test Result				
	Amylase	**SGOT**	**SGPT**	**Alkaline phosphate**	**Urea**
Group 01	296.74	48	59	374.37	31.9
Group 02	448.01	132.07	90	385.9	40.06
Group 03	464.61	230.03	133.95	410.15	44.46
Group 04	636.6	367.66	229.91	526.1	55.2

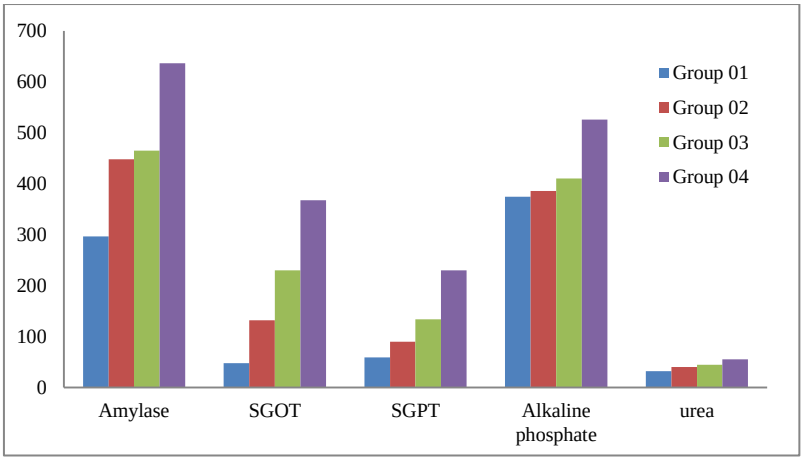
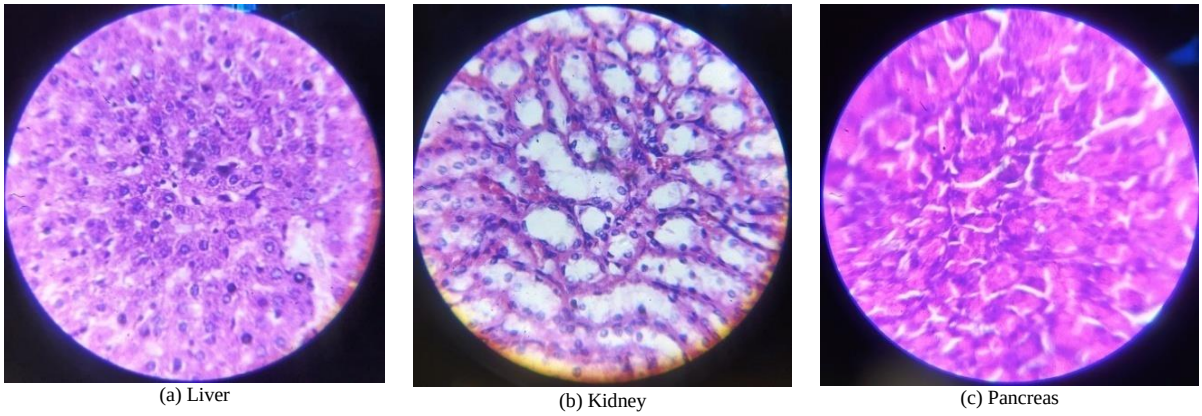


Figure 3. Summary of Biochemical test in the four groups.

Result of pathological evaluation

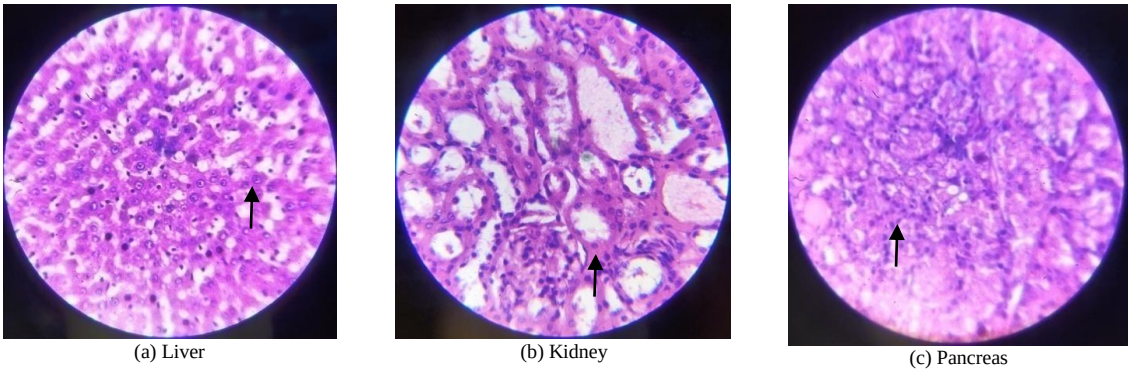
Figure 4 (a) shows the normal liver of Streptozotocin induced rat; figure 4 (b) shows the normal kidney of Streptozotocin induced rat whereas Figure 4 (c) shows irreversible degeneration of beta cells of Islets of Langerhans due to administration of Streptozotocin.



(a) Liver (b) Kidney (c) Pancreas

Figure 4. Pathological Evaluation of Group 1 rats.

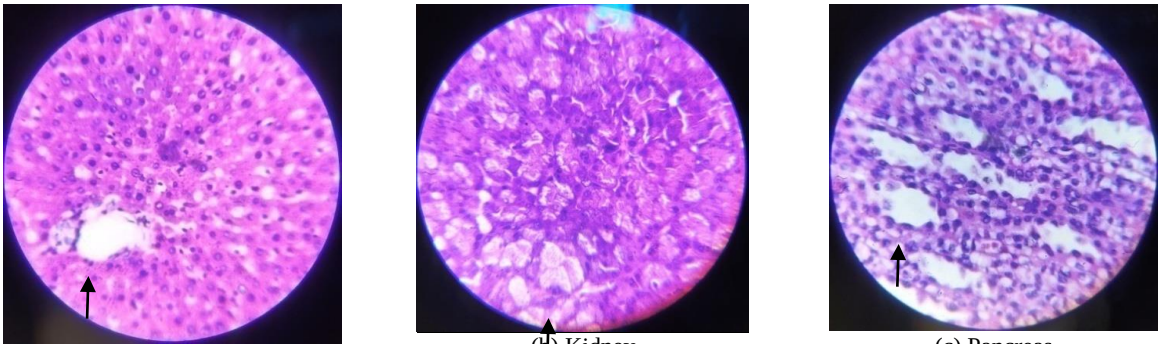
The histopathology slides presented in Figures 5 (a), (b), and (c) depict liver, kidney, and pancreas samples of rats that were induced with streptozotocin and arsenic. These experimental conditions have led to significant alterations in the pathology of the respective organs. In Figure 5 (a), the liver histopathology slide reveals notable changes characterized by inflammation, degeneration, and necrosis. These pathological alterations indicate the impact of streptozotocin and arsenic exposure on the liver tissue. Similarly, Figure 5 (b) showcases the histopathology of the kidney affected by streptozotocin and arsenic. The slide exhibits disrupted architectural features, including inflammation, necrosis, and cellular detachment. These observations suggest the deleterious effects of the experimental conditions on kidney tissue. In Figure 5 (c), the pancreas histopathology slide reveals prominent changes induced by streptozotocin and arsenic exposure. The observed alterations include diffused atrophy of acinar cells, shrinkage of Islets of Langerhans, and increased degranulation and degeneration. These findings point to the adverse impact on pancreas tissue integrity due to the experimental conditions.



(a) Liver (b) Kidney (c) Pancreas

Figure 5. Pathological Evaluation of Group 2 rats.

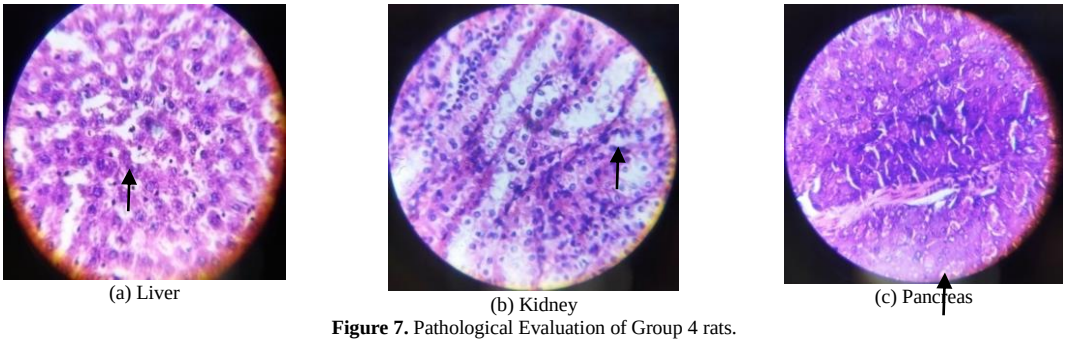
The histopathology slide in Figure 6 (a) displays a liver sample from rats induced with streptozotocin and cadmium, showcasing severe histopathological alterations characterized by cellular necrosis, degeneration, and congested red blood cell vessels. In Figure 6 (b), the kidney histopathology slide, also induced by streptozotocin and cadmium, demonstrates significant damage to the kidney tissues, including inflammation and necrosis affecting all types of kidney cells. Additionally, the damage extends to the cortex, brush border membrane, and both proximal and distal tubules.Figure6 (c) presents the pancreas histopathology slide of rats subjected to streptozotocin and cadmium, revealing severe alterations in pancreatic tissues. The observed changes include marked atrophy in acinar cells, nuclear vascularization, and shrinkage of Islets of Langerhans.



(a) Liver (b) Kidney (c) Pancreas

Figure 6. Pathological Evaluation of Group 3 rats.

In the liver (Figure 7 (a)), the histopathological examination reveals a complete disruption of the normal tissue structure, characterized by inflammation, necrosis, and significant areas of cellular loss. Similarly, the kidney (Figure 7 (b)) displays substantial damage, exhibiting a disrupted pathological architecture with widespread inflammation, necrosis, and noticeable blank regions within the tissue. The pancreas (Figure 7 (c)) exhibits severely altered pancreatic tissues with marked inflammation, areas of necrosis, and patches of tissue loss, indicating a severe impact on the organ's integrity.



(a) Liver (b) Kidney (c) Pancreas

Figure 7. Pathological Evaluation of Group 4 rats.

DISCUSSION

The blood glucose level data presented in Figure 1 and 2 provide crucial insights into the impact of various exposures on diabetic rats. Group 1, administered with streptozotocin and nicotinamide, exhibited relatively stable blood glucose levels throughout the study period, confirming the successful induction of diabetes. This baseline stability underscores the reliability of the diabetic model used in this study. In contrast, Figure1 (b) and 1 (c), depicting groups exposed to arsenic and cadmium chloride respectively, showed significant increases in blood glucose levels on days 4 and 7, suggesting that both arsenic and cadmium independently contribute to elevated blood glucose levels in diabetic rats. The pronounced elevation observed in Figure 1 (d), illustrating co-exposure to both arsenic and cadmium emphasizes a synergistic effect, resulting in the highest blood glucose levels among all groups. This synergistic impact was further reinforced by the comparative analysis in Figure 2, which highlighted significantly higher blood glucose levels in the co-exposure group compared to the individual exposure groups.

Notably, the data from Group 1 and 2, where arsenic was administered alongside streptozotocin and nicotinamide, exhibited both elevation and reduction in blood glucose levels, suggesting complex interactions between these substances. This indicates that arsenic's impact on glucose metabolism might involve multifaceted pathways that warrant further investigation.

The subsequent sacrifice of animals on the 7th day enabled comprehensive biochemical assessments. Elevated levels of amylase, SGOT, SGPT, alkaline phosphatase, and urea across all exposed groups indicated potential pancreatic dysfunction, liver damage, and kidney dysfunction. These biochemical markers corroborate the findings of other recent studies, such as those by Kumar et al., the study reviled similar disruptions in pancreatic and hepatic function in their investigation of heavy metal exposure in diabetic models. The concurrence of these results highlights the consistency and reliability of the observed toxicological effects of arsenic and cadmium co-exposure.

Histopathological assessments of liver, kidney, and pancreas tissues provided visual evidence of the detrimental effects of streptozotocin, arsenic, and cadmium exposure. Notable changes in liver tissue, including inflammation, degeneration, and necrosis (Figure 5(a)), mirrored the biochemical results, highlighting the adverse impact on liver integrity. This is consistent with findings by Zhang et al., (20), the study reported extensive hepatic damage upon combined heavy metal exposure in rodent models. Kidney histopathology (Figure 5(b)) displayed disrupted architecture with inflammation, necrosis, and cellular detachment, underlining the deleterious effects on kidney tissue. These findings align with the renal impairments documented in the work of Singh et al, reinforcing the nephrotoxic potential of such co-exposure. Pancreas histopathology (Figure 5 (c)) indicated alterations such as atrophy of acinar cells and shrinkage of Islets of Langerhans, aligning with the biochemical findings of pancreatic dysfunction. Such pathological changes echo the observations of Wang et al., the research reported significant pancreatic damage and dysregulation of insulin secretion mechanisms under similar exposure conditions.

Overall, the findings of this study suggest that arsenic and cadmium exacerbate pre-existing diabetic conditions, leading to worsened symptoms. This is particularly concerning given the prevalent exposure to these metals in various environments. The study underscores the urgent need for further research to unravel the intricate mechanisms underpinning these deleterious effects and to develop effective preventive strategies. Moreover, these insights advocate for a holistic approach to disease management that includes environmental considerations, calling for increased awareness among healthcare professionals, policymakers, and the public about the implications of heavy metal pollution in diabetes. By addressing these challenges, we can work towards a healthier and more sustainable future, minimizing the threat of cadmium and arsenic in individuals with diabetes.

Impact on Blood Glucose Levels

The research demonstrates that co-exposure to cadmium and arsenic in diabetic rats leads to a significant increase in blood glucose levels compared to rats exposed to either metal alone or the control group. This finding highlights the potential role of heavy metal pollution in exacerbating hyperglycemia, which is a key characteristic of diabetes mellitus. The observed elevation in blood glucose levels may result from the disruption of glucose metabolism pathways or impaired insulin function induced by the toxic effects of these heavy metals. These results corroborate previous studies indicating that heavy metal exposure can lead to insulin resistance and worsen glycemic control in diabetic individuals [26, 27].

Impact on Organ Function

The biochemical analysis reveals that co-exposure to cadmium and arsenic causes significant alterations in liver and kidney function, as evidenced by elevated levels of amylase, SGOT, SGPT, alkaline phosphatase, and urea. The increased levels of amylase suggest the possibility of pancreatitis and potential pancreatic damage due to heavy metal exposure [28]. Elevated SGOT and SGPT levels indicate liver damage, which is consistent with previous research linking heavy metal toxicity to hepatotoxic effects [29, 30]. Moreover, elevated alkaline phosphatase and urea levels suggest impaired liver and kidney function, respectively [31]. These findings emphasize the multi-organ toxicity of heavy metal exposure and underscore the need for vigilant monitoring of liver and kidney function in diabetic patients exposed to environmental pollutants.

Histopathological Evaluation

The histopathological evaluation further supports the biochemical findings, revealing severe damage to the kidneys, pancreas, and livers of rats exposed to co-administration of cadmium and arsenic. The observed inflammation, necrosis, and cellular degeneration in these vital organs indicate the adverse impact of heavy metal pollution on tissue integrity and function. Notably, the histopathological changes were more pronounced in rats exposed to both cadmium and arsenic, suggesting a potential synergistic effect of co-exposure. These histological alterations resonate with earlier studies, which have reported heavy metal-induced tissue damage in various organs [32].

Implications for Diabetic Patients

The results of this research have significant implications for diabetic patients, especially those living in regions with high heavy metal pollution. Diabetic individuals are already vulnerable to various health complications, and co-exposure to cadmium and arsenic can exacerbate these risks. The study highlights the urgent need for awareness and action to minimize heavy metal exposure in diabetic populations. Implementing measures to reduce heavy metal contamination in the environment, such as stricter industrial regulations and improved waste disposal practices, becomes crucial to protect the health of vulnerable individuals.

Future Directions

Further research involving human subjects and epidemiological studies would be necessary to validate the findings. Secondly, the specific mechanisms underlying the observed effects remain unclear. Future investigations should delve into the molecular and cellular pathways involved in heavy metal-induced toxicity in diabetic individuals. Additionally, this study focused on the impact of cadmium and arsenic; however, other heavy metals and environmental pollutants may also play a role in diabetic health. A comprehensive assessment of multiple environmental heavy metals like arsenic and cadmium on diabetes progression would provide a more holistic understanding of the disease.

CONCLUSIONS

The study underscores the heightened health risks posed by simultaneous exposure to cadmium and arsenic in diabetic rats, significantly worsening key health indicators. This highlights the urgent need to address heavy metal pollution, especially in diabetic individuals. Proactive measures are essential to mitigate exposure,

and further research is warranted to understand underlying mechanisms and develop preventive strategies. This study contributes valuable insights, advocating for a holistic approach to disease management that includes environmental considerations. It calls for increased awareness among healthcare professionals, policymakers, and the public about the implications of heavy metal pollution in diabetes. Addressing these challenges can lead to a healthier and more sustainable future, minimizing the threat of cadmium and arsenic in individuals with diabetes.

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Conflict of interests

The authors declare no conflict of interest.

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