A Mechanistic Approach Elaborating the Association of Heavy Metals-Induced Oxidative Stress with Insulin Resistance Susceptibility

Hamza Tariq[1], Aamna Habib[2], Abdul Qader[3*], Amber Shafi[4], Sadia Rafique[5], Zunaira Afzal[6], Romana Riaz[7], Qudsia Rehman[2]

[1] College of Pharmacy, Lyallpur Institute of Advance Studies (LIAS) Faisalabad, Pakistan
[2] Medina College of Pharmacy, The University of Faisalabad, Faisalabad Pakistan
[3*]Department of Pharmaceutical Chemistry Government College University Faisalabad Pakistan/ Drugs Testing Laboratory Faisalabad Pakistan
[4] Department of Pharmacology and Physiology, University of Agriculture Faisalabad, Pakistan
[5] Department of Pharmacy, The University of Faisalabad, Faisalabad Pakistan
[6] Department of Pharmacy, University of Agriculture Faisalabad, Pakistan
[7] Department of Pharmaceutics, Bahauddin Zakariya University Multan, Pakistan

***Corresponding Author:** Abdul Qader
*Department of Pharmaceutical Chemistry Government College University Faisalabad Pakistan/ Drugs Testing Laboratory Faisalabad Pakistan: Pharmacistqader316@gmail.com

Abstract
Heavy metals are widely distributed in the environment and cause various life threatening diseases like metabolic syndrome (MS) or Diabetes Mellitus (DM). Various industrial, mining and pharmaceutical operations drain large quantities of toxic heavy metals in soil, air and water and rendering it contaminated and offer a store house for diseases. Investigations show that high blood serum levels of heavy metals cause insulin resistance in large number of population worldwide. Cd is known to cause mitochondrial malfunctioning, and increased level of proinflammatory mediators like IL-1β, IL-6, and TNF-α. Likewise, As is known to transduce various signaling factors such as NFκB, MPAK, TNFα, P13K, PKB/Akt and GLUT4 that ultimately disrupt the glucose levels and activity of insulin in the body leading to insulin resistance. While Ni exposure cause free radicals production which impair normal functioning of DNA repair enzymes casing hyperglycemia and insulin resistance in rats model indicating that Ni plays a major role as precipitating factor in insulin resistance. Studies revealed a large number of iNOS and cGMP levels in pancreatic islets that appear to cause dysregulation of glucose through ROS pathway leading to insulin resistance. Mercury (Hg) on the other hand is known to causes insulin resistance through the mechanism of oxidative stress which results in large expression of 8-hydroxy-2'-deoxyguanosine (8-OHdG), a biomarker of oxidative DNA damage. Glutathione (GSH), total protein thiols, and enzymes like glutathione peroxidase and superoxide dismutase levels are also markedly high. In the last, Lead (Pb) causes insulin resistance through the ROS which causes oxidative stress and ultimately causes insulin resistance in suspected individuals.

Key words: Diabetes Mellitus, Insulin resistance and heavy metals.

Introduction

Metabolic syndrome (MS) and Insulin Resistance are major public health concern because to its increasing global prevalence and relationship with catastrophic life-threatening illnesses such as diabetes mellitus, cardiovascular disease and all other mortality. [1, 2] Heavy metals like mercury (Hg), cadmium (Cd), nickel (Ni), arsenic (As), thallium (Tl), cobalt (Co) and lead (Pb) are environmental pollutants that are proved to cause metabolic syndrome along with insulin resistance in diabetic and non-diabetic patients. [4, 6] Numerous epidemiological studies have found that ambient air pollution causes an increase in morbidity and mortality.

Toxics in ambient air include particulate matter (PM), irritating gases, and benzene. PM is the component of air pollution thought to be responsible for many of these harmful health impacts, and multiple studies have found a link between overall daily mortality and ambient particle concentrations. Long-term exposure to high particle levels increases the risk of cancer, respiratory disorders, and arteriosclerosis, whereas short-term exposure peaks induce exacerbation of bronchitis, asthma, and other respiratory ailments, as well as alterations in heart rate variability. Heavy metals are naturally occurring metallic elements with high atomic weights and densities relative to water.

They are employed in several industrial operations, including mining, medicine, technology, and agriculture. Once released into the environment, they cannot be destroyed or degraded. Thus, heavy metals are long-term environmental pollutants. Heavy metal exposure can occur through contaminated water and food consumption, industrial operations, occupational, cigarette smoke, fossil fuel, waste, and cosmetic preparations. The utilization of heavy metals is increasing in fulfilling our daily basis requirements that may bring up a major threat to human health. [3,4].

Figure 1: Illustrating the different sources of heavy metals exposure.

The main objective of our study is to describe the insulin resistance susceptibility associated with heavy metals exposure accompanying its potential threat towards diabetes mellitus.

Cadmium

Cadmium (Cd) is an environmental pollutant that is discharged into the environment through both natural and manmade activities. It is used for corrosion protection of steel (cadmium plating), as solder and weld metal in alloys, polyvinyl chloride plastics, as pigments in paint colors, various forms of paint and glazes, fertilizers. Hong et al. (2022) established that Cd inhibited insulin synthesis and pancreatic β-cell survival by causing mitochondrial malfunction, mitoROS overproduction, and increased proinflammatory IL-1β, IL-6, and TNF-α levels. The mitochondrion is not only an essential target for Cd toxicity, but it also produces the majority of intracellular ROS. Cd can accumulate in mitochondria and alter oxidative phosphorylation pathways, causing mitochondrial ROS generation and malfunction. Further research is needed to determine the impact of oxidative stress, mitochondrial dysfunction, and the inflammatory response on pancreatic β-cell damage caused by Cd. [5, 6, 12]

Arsenic

Arsenic (As) is a naturally occurring, poisonous metalloid. It can be found in both inorganic and organic forms in the environment. Arsenic can be easily dissolved in ground water. Groundwater with arsenic contents higher than the drinking water standard of 10 mg/liter was not unusual. Man-made sources of arsenic, including mineral extraction and processing wastes, poultry and swine feed additives, pesticides, and highly soluble arsenic trioxide stocks, have contaminated soil and groundwater. There is a possibility that arsenic affects glucose metabolism; nevertheless, limited research has assessed how arsenic exposure in the environment affects β-cell insulin secretion in mammals. Nevertheless, a number of studies have suggested that arsenic may modify signaling transduction factors, such as NFκB, p38 mitogen-activated protein kinase (MAPK), tumor necrosis factor-α (TNFα), phosphatidylinositol-3-kinase (PI3K), and PI3K-dependent phosphorylation of protein kinase B (PKB/Akt). Arsenic may also have an impact on insulin-stimulated glucose uptake (ISGU) in adipocytes or skeletal muscle cells, which may be linked to insulin resistance. Insulin's metabolic effects depend heavily on PI3K signaling, which controls a variety of signal transduction pathways when it is activated. β-cells exposed to high doses of arsenic showed increased PI3K-mediated PKB/Akt phosphorylation. Insulin activates glucose transporter 4 (GLUT4) through phosphorylation of the PKB/Akt signaling pathway. High doses of arsenic may imitate insulin's activity by phosphorylating PKB/Akt and GLUT4 expression in vitro. [13, 14, 15]

Nickel

Nickel is also an environmental pollutant that is widely distributed in the environment and can be released into the atmosphere and soil when coal, fuel oil, and trash are burned, or when sewage is discharged. Nickel and its compounds are also widely employed in a variety of industries, including electroplating, alloy manufacturing, and nickel-cadmium battery production. As a result, the whole public is exposed to nickel through the air, food, and drinking water. Other forms of nickel exposure include tobacco use, dental or orthopedic implants, stainless steel kitchen utensils, low-cost jewelry, and nickel-releasing coins. Nickel exposure caused the formation of free radicals. Nickel impairs DNA repair enzymes by producing ROS. [7] Nickel treatment has been linked to decreased islet function and higher plasma glucose levels, according to studies. A-tocopherol, an antioxidant, appears to reduce nickel-induced hyperglycemia in rats. Nickel appears to cause glucose dysregulation through the ROS pathway. Nickel-induced hyperglycemia is associated with higher

iNOS and cGMP levels. The study identified a large rise in iNOS protein expression in the pancreas, which led to an increase in cGMP levels in the adrenals, brain, and pancreas. This could be due to cytosolic guanylate cyclase activation that ultimately causes insulin resistance. [16, 17]

Mercury

Mercury (Hg) is a heavy metal that is widely distributed and persistent in the environment. Mercury has been a major public health concern in recent years, with mounting evidence of its presence in some components of the human food chain. Fish diet, for example, is advantageous in the prevention of cardiovascular disorders and Alzheimer's disease; yet, multiple studies have found that fish consumption is the primary source of mercury exposure. [18, 19, 20] Mercury exists in three forms in the environment: elemental or metallic mercury, inorganic mercury, and organic mercury. Mercury compounds are commonly employed in dry-cell batteries, fluorescent bulbs, arc lights, mirrors, the extraction of gold and silver from ores, thermometers, dental amalgam fillings, and vaccine preservatives. [21, 22, 23, 24] The toxicity of mercury in islets is strongly associated with oxidative stress. It has been demonstrated that 8-hydroxy-2'-deoxyguanosine (8-OHdG), a biomarker of oxidative DNA damage, is dramatically higher in urine samples from people living in mercury-contaminated environments. [25] The group exposed to mercury had greater levels of glutathione (GSH), total protein thiols, and the activities of glutathione peroxidase and superoxide dismutase compared to the control group. [26] Mercury has the ability to impact islet β-cell survival and function both in vivo and in vitro via an oxidative stress route, according to a new study. In both cell culture and animal models, low-dose mercury produced malfunction of the mouse pancreatic islet β-cells via an Akt pathway triggered by oxidative stress or PI3K. [27] Thus these considerations give strong evidence that mercury exposure led to insulin resistance and is aa major risk factor for diabetic population.

Lead

Lead is a hazardous environmental pollutant that is extremely damaging to numerous body organs. Although Pb can be absorbed through the skin, it is primarily absorbed by the respiratory and digestive systems. Pb exposure can cause neurological, pulmonary, urinary, and cardiovascular problems due to immune-modulation, oxidative, and inflammatory pathways. Furthermore, Pb can disrupt the oxidant-antioxidant system balance and cause inflammatory reactions in a variety of organs. Exposure to Pb can cause changes in physiological functions in the body and is connected with various disorders. [28, 35, 36, 37] Possible lead sources are paints, air, soil, tableware, folk medicines and cosmetics, occupational sources, toys and cosmetic jewelry. [29, 33, 34] Reactive oxygen species (ROS) have been shown to disrupt multiple important components of the insulin signaling pathway, encouraging the development of insulin resistance and diabetes. Existing research indicates that metal-induced toxicity might disrupt antioxidant processes in living tissues, resulting in the generation of highly reactive oxygen species (ROS). Proteins, nucleic acids, and lipids may be degraded as a result of an antioxidant imbalance. ROS's oxidative attack on cellular components has been linked to the etiology of various human illnesses, including diabetes and insulin resistance. [30, 31, 32].

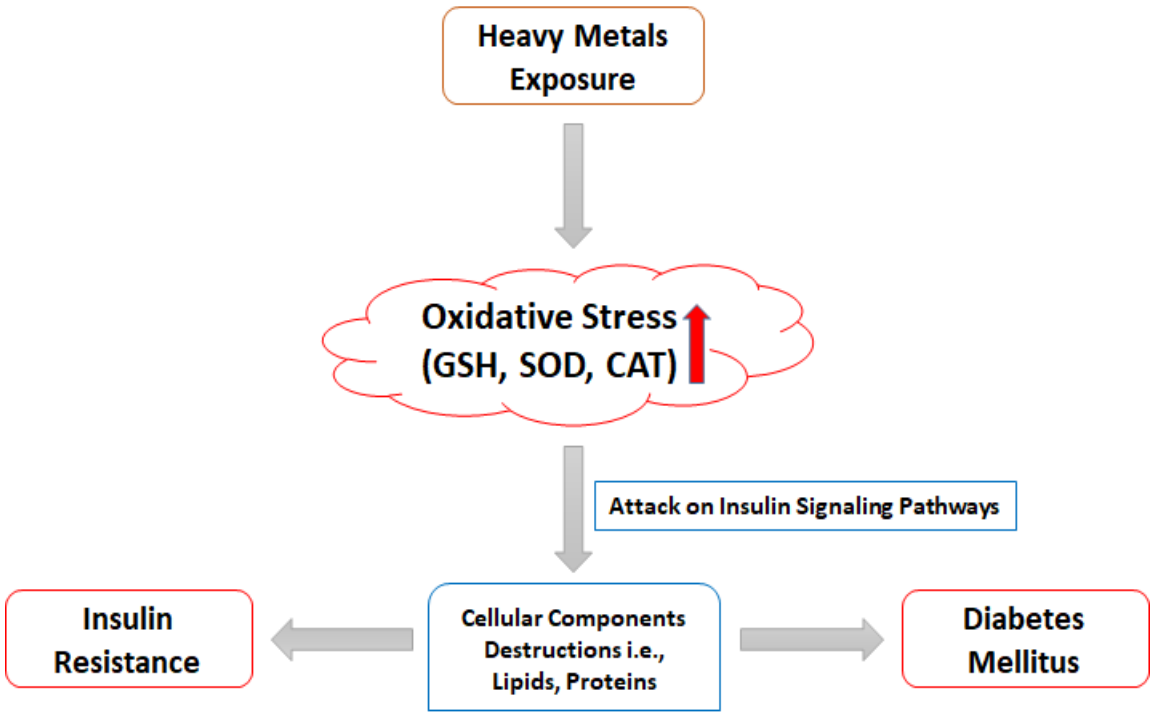

Figure 2: Elaborating the general mechanism of action of heavy metals-induced cellular components destruction that may lead to impaired insulin secretion and diabetes mellitus.

Conclusion

It is investigated that various sources of heavy metals like industries, paints and glazes, fertilizers, plastics, pesticides, mining waste, fuel oil and sewage waste may drastically alter the functioning of islets of Langerhans and development of resistance against insulin. Toxic metals can affect glucose absorption and change the molecular mechanism for glucose control. This study indicates that exposure of heavy metals like Cd, Ni, As, Hg and Pb from different sources associated with diabetes mellitus and insulin resistance causing complications in insulin therapy. Cd is associated with overproduction of mitoROS and pro-inflammatory mediators while As disrupt various signal transduction pathways. Whereas Ni not only causes the production of free radicals but also increases iNOS and cGMP levels which plays key role in insulin resistance. Hg and Pb induce insulin resistance through oxidative stress disrupting various signaling pathways and enzymes. This study revealed that environmental pollutants are highly contagious to human health, and it is confirmed through various studies that these pollutants are evident to cause insulin resistance worldwide.

Funding source

Not available.

Conflict of Interest

The authors have not mentioned any conflict of interest.

References

1. Akash, M. S. H., M. E. U. Haq, A. Qader, and K. Rehman. "Biochemical Investigation of Human Exposure to Aflatoxin M1 and Its Association with Risk Factors of Diabetes Mellitus." [In eng]. *Environ Sci Pollut Res Int* 28, no. 44 (Nov 2021): 62907-18. https://doi.org/10.1007/s11356-021-14871-w.
2. Balali-Mood, M., K. Naseri, Z. Tahergorabi, M. R. Khazdair, and M. Sadeghi. "Toxic Mechanisms of Five Heavy Metals: Mercury, Lead, Chromium, Cadmium, and Arsenic." [In eng]. *Front Pharmacol* 12 (2021): 643972. https://doi.org/10.3389/fphar.2021.643972.
3. Beyersmann, D., and A. Hartwig. "Carcinogenic Metal Compounds: Recent Insight into Molecular and Cellular Mechanisms." [In eng]. *Arch Toxicol* 82, no. 8 (Aug 2008): 493-512. https://doi.org/10.1007/s00204-008-0313-y.
4. Bwititi, P. T., and R. B. Ashorobi. "Effects of Chronic Oral Nickel Chloride Administration on Glycaemia and Renal Function in Normal and Diabetic Rats." [In eng]. *Afr J Health Sci* 5, no. 3-4 (Jul-Dec 1998): 198-201.
5. Chen, C., L. Qu, B. Li, L. Xing, G. Jia, T. Wang, Y. Gao, *et al.* "Increased Oxidative DNA Damage, as Assessed by Urinary 8-Hydroxy-2'-Deoxyguanosine Concentrations, and Serum Redox Status in Persons Exposed to Mercury." [In eng]. *Clin Chem* 51, no. 4 (Apr 2005): 759-67. https://doi.org/10.1373/clinchem.2004.042093.
6. Chen, Y. W., C. F. Huang, K. S. Tsai, R. S. Yang, C. C. Yen, C. Y. Yang, S. Y. Lin-Shiau, and S. H. Liu. "The Role of Phosphoinositide 3-Kinase/Akt Signaling in Low-Dose Mercury-Induced Mouse Pancreatic Beta-Cell Dysfunction in Vitro and in Vivo." [In eng]. *Diabetes* 55, no. 6 (Jun 2006): 1614-24. https://doi.org/10.2337/db06-0029.
7. Chen, Y. W., C. Y. Yang, C. F. Huang, D. Z. Hung, Y. M. Leung, and S. H. Liu. "Heavy Metals, Islet Function and Diabetes Development." [In eng]. *Islets* 1, no. 3 (Nov-Dec 2009): 169-76. https://doi.org/10.4161/isl.1.3.9262.
8. Clarkson, Thomas, Laszlo Magos, and Gary Myers. "The Toxicology of Mercury — Current Exposures and Clinical Manifestations." *The New England journal of medicine* 349 (11/01 2003): 1731-7. https://doi.org/10.1056/NEJMra022471.
9. Debnath, Bikash, Somraj Singh, and Kuntal Manna. "Sources and Toxicological Effects of Lead on Human Health." *Indian Journal of Medical Specialities* 10 (01/01 2019): 66. https://doi.org/10.4103/INJMS.INJMS_30_18.
10. Hayat, Abdul Qader. "Impact of Thyroid Hormones Disrupting Potential of Environmental Polychlorinated Biphenyls and Heavy Metals on Brain Functions: A Review Article." *Life Science Journal of Pakistan* 2, no. 1 (2020): 20-28.
11. Hong, Huihui, Haotian He, Xiqin Lin, Tali Hayuehashi, Jia Xu, Jingjing Zhang, Yudong Xu, *et al.* "Cadmium Exposure Suppresses Insulin Secretion through Mtros-Mediated Mitochondrial Dysfunction and Inflammatory Response in Pancreatic Beta Cells." *Journal of Trace Elements in Medicine and Biology* 71 (2022/05/01/ 2022): 126952. https://doi.org/https://doi.org/10.1016/j.jtemb.2022.126952. https://www.sciencedirect.com/science/article/pii/S0946672X22000323.
12. Kaur, J. "A Comprehensive Review on Metabolic Syndrome." [In eng]. *Cardiol Res Pract* 2014 (2014): 943162. https://doi.org/10.1155/2014/943162.
13. Kazi, T. G., N. Jalbani, N. Kazi, M. B. Arain, M. K. Jamali, H. I. Afridi, G. A. Kandhro, *et al.* "Estimation of Toxic Metals in Scalp Hair Samples of Chronic Kidney Patients." [In eng]. *Biol Trace Elem Res* 127, no. 1 (Jan 2009): 16-27. https://doi.org/10.1007/s12011-008-8222-8.
14. Krantz, Anne, and Samuel Dorevitch. "Metal Exposure and Common Chronic Diseases: A Guide for the Clinician." *Disease-a-Month* 50, no. 5 (2004/05/01/ 2004): 220-62. https://doi.org/https://doi.org/10.1016/j.disamonth.2004.04.001. https://www.sciencedirect.com/science/article/pii/S0011502904000616.
15. Latshaw, M. W., T. Glass, P. Parsons, J. Hidalgo, and B. Schwartz. "Predictors of Blood Mercury Levels in Older Urban Residents." [In eng]. *J Occup Environ Med* 48, no. 7 (Jul 2006): 715-22. https://doi.org/10.1097/01.jom.0000205208.85800.70.

16. Liu, Gang, Liang Sun, An Pan, Mingjiang Zhu, Zi Li, Zhenzhen Wang, Xin Liu, *et al.* "Nickel Exposure Is Associated with the Prevalence of Type 2 Diabetes in Chinese Adults." *International Journal of Epidemiology* 44, no. 1 (2014): 240-48. https://doi.org/10.1093/ije/dyu200. https://doi.org/10.1093/ije/dyu200.
17. Morris, M. C., D. A. Evans, J. L. Bienias, C. C. Tangney, D. A. Bennett, R. S. Wilson, N. Aggarwal, and J. Schneider. "Consumption of Fish and N-3 Fatty Acids and Risk of Incident Alzheimer Disease." [In eng]. *Arch Neurol* 60, no. 7 (Jul 2003): 940-6. https://doi.org/10.1001/archneur.60.7.940.
18. Planchart, A., A. Green, C. Hoyo, and C. J. Mattingly. "Heavy Metal Exposure and Metabolic Syndrome: Evidence from Human and Model System Studies." [In eng]. *Curr Environ Health Rep* 5, no. 1 (Mar 2018): 110-24. https://doi.org/10.1007/s40572-018-0182-3.
19. Qader, A., K. Rehman, and M. S. H. Akash. "Biochemical Profiling of Lead-Intoxicated Impaired Lipid Metabolism and Its Amelioration Using Plant-Based Bioactive Compound." [In eng]. *Environ Sci Pollut Res Int* 29, no. 40 (Aug 2022): 60414-25. https://doi.org/10.1007/s11356-022-20069-5.
20. Qader, Abdul, Kanwal Rehman, and Muhammad Sajid Hamid Akash. "Genetic Susceptibility of Δ-Alad Associated with Lead (Pb) Intoxication: Sources of Exposure, Preventive Measures, and Treatment Interventions." *Environmental Science and Pollution Research* 28, no. 33 (2021/09/01 2021): 44818-32. https://doi.org/10.1007/s11356-021-15323-1. https://doi.org/10.1007/s11356-021-15323-1.
21. Ratcliffe, Hope E., G. Marie Swanson, and Lawrence J. Fischer. "Human Exposure to Mercury: A Critical Assessment of the Evidence of Adverse Health Effects." *Journal of Toxicology and Environmental Health* 49, no. 3 (1996/10/25 1996): 221-70. https://doi.org/10.1080/00984108.1996.11667600. https://doi.org/10.1080/00984108.1996.11667600.
22. Rehman, K., F. Fatima, I. Waheed, and M. S. H. Akash. "Prevalence of Exposure of Heavy Metals and Their Impact on Health Consequences." [In eng]. *J Cell Biochem* 119, no. 1 (Jan 2018): 157-84. https://doi.org/10.1002/jcb.26234.
23. Sørensen, M., H. Autrup, P. Møller, O. Hertel, S. S. Jensen, P. Vinzents, L. E. Knudsen, and S. Loft. "Linking Exposure to Environmental Pollutants with Biological Effects." [In eng]. *Mutat Res* 544, no. 2-3 (Nov 2003): 255-71. https://doi.org/10.1016/j.mrrev.2003.06.010.
24. Sriwijitkamol, Apiradee, Christine Y. Christ-Roberts, Rachele Berria, Phyllis A. Eagan, Thongchai Pratipanawatr, Ralph A. DeFronzo, Lawrence J. Mandarino, and Nicolas Musi. "Reduced Skeletal Muscle Inhibitor of Kappab Beta Content Is Associated with Insulin Resistance in Subjects with Type 2 Diabetes: Reversal by Exercise Training." *Diabetes* 55 3 (2006): 760-7.
25. Sweet, Leonard, and Judith Zelikoff. "Toxicology and Immunotoxicology of Mercury: A Comparative Review in Fish and Humans." *Journal of toxicology and environmental health. Part B, Critical reviews* 4 (04/01 2001): 161-205. https://doi.org/10.1080/10937400117236.
26. Tikare, S. N., A. Das Gupta, S. A. Dhundasi, and K. K. Das. "Effect of Antioxidants L-Ascorbic Acid and Alpha-Tocopherol Supplementation in Nickel Exposed Hyperglycemic Rats." [In eng]. *J Basic Clin Physiol Pharmacol* 19, no. 2 (2008): 89-101. https://doi.org/10.1515/jbcpp.2008.19.2.89.
27. Tinkov, A. A., T. Filippini, O. P. Ajsuvakova, J. Aaseth, Y. G. Gluhcheva, J. M. Ivanova, G. Bjørklund, *et al.* "The Role of Cadmium in Obesity and Diabetes." [In eng]. *Sci Total Environ* 601-602 (Dec 1 2017): 741-55. https://doi.org/10.1016/j.scitotenv.2017.05.224.
28. Virtanen, Jyrki K., Tiina H. Rissanen, Sari Voutilainen, and Tomi-Pekka Tuomainen. "Mercury as a Risk Factor for Cardiovascular Diseases." *The Journal of Nutritional Biochemistry* 18, no. 2 (2007/02/01/ 2007): 75-85. https://doi.org/https://doi.org/10.1016/j.jnutbio.2006.05.001. https://www.sciencedirect.com/science/article/pii/S0955286306001008.
29. Walton, F. S., A. W. Harmon, D. S. Paul, Z. Drobná, Y. M. Patel, and M. Styblo. "Inhibition of Insulin-Dependent Glucose Uptake by Trivalent Arsenicals: Possible Mechanism of Arsenic-Induced Diabetes." [In eng]. *Toxicol Appl Pharmacol* 198, no. 3 (Aug 1 2004): 424-33. https://doi.org/10.1016/j.taap.2003.10.026.
30. Zawalich, W. S., and K. C. Zawalich. "A Link between Insulin Resistance and Hyperinsulinemia: Inhibitors of Phosphatidylinositol 3-Kinase Augment Glucose-Induced Insulin Secretion from Islets of Lean, but Not Obese, Rats." [In eng]. *Endocrinology* 141, no. 9 (Sep 2000): 3287-95. https://doi.org/10.1210/endo.141.9.7636.
31. Akash, M. S. H., Qader, A., & Rehman, K. (2022). Insulin resistance susceptibility is associated with BPA exposure. *Metabolism-Clinical and Experimental*, *128*.
32. Rehman, K., Qader, A., ul Haq, M. E., & Akash, M. S. H. (2022). Long-term exposure of Bisphenol A impairs metabolism and develop insulin resistance. *Metabolism-Clinical and Experimental*, *128*.
33. Qader, A., Rehman, K., & Akash, M. S. H. (2021). Genetic susceptibility of δ-ALAD associated with lead (Pb) intoxication: sources of exposure, preventive measures, and treatment interventions. *Environmental Science and Pollution Research*, *28*, 44818-44832.
34. Akash, M. S. H., Haq, M. E. U., Qader, A., & Rehman, K. (2021). Biochemical investigation of human exposure to aflatoxin M1 and its association with risk factors of diabetes mellitus. *Environmental Science and Pollution Research*, *28*(44), 62907-62918.
35. Qader, A., Rehman, K., & Akash, M. S. H. (2022). Biochemical profiling of lead-intoxicated impaired lipid metabolism and its amelioration using plant-based bioactive compound. *Environmental Science and Pollution Research*, *29*(40), 60414-60425.
36. Hayat, A. Q. (2020). Impact of Thyroid Hormones Disrupting Potential of Environmental Polychlorinated Biphenyls and Heavy Metals on Brain Functions: A Review Article. *Life Science Journal of Pakistan*, *2*(1), 20-28.

37. Qader, A. (2024). LEAD INTOXICATION AND ITS SOURCES OF EXPOSURE: A PERSPECTIVE STUDY. *Health Notions*, *8*(1), 22.