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Metabolic Evaluation of the Combined Effect of Acute Cadmium Chloride and Restraint Stress Exposure in Female Wistar Rats

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Cadmium is a heavy metal that has been shown to induce metabolic changes while restraint stress is a model of psychological stress used to induce behavioural and physiological changes. This study investigated the combined effect of cadmium chloride administration and restraint stress exposure on metabolic profile of female Wistar rats. Twenty four female Wistar rats were randomly

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divided into four groups containing six rats per group; Control (CTL) was given only feed and water. Cadmium alone (CCC) and Restraint stress alone(RSS), respectively, were orally administered 100 mg/kg b.w of cadmium chloride and subjected to restraint stress using wire mesh for 30 minutes daily while Cadmium+Restraint stress (RSC) was administered 100 mg/kg b.w of cadmium chloride and restrained for 30 minutes daily. Body weights of the animals were recorded daily throughout the experiment. Twenty-four hours after the last cadmium administration and restraint stress exposure, all animal were anesthetized and sacrificed. Blood was collected via cardiac puncture for biochemical analysis. Results showed significant ($p<0.05$) increase in serum glucose and cortisol levels but not significant in insulin level of CCC group when compared to control. Serum glucose, insulin, cortisol showed significant ($p<0.05$) increase in RSS group when compared to control. In RSC group, glucose and insulin was significantly ($p<0.05$) increased when compared to CCC but not significant when compared with RSS. Cortisol was significantly ($p<0.05$) increased in RSC group when compared with other groups. Result showed significant ($p<0.05$) increase in CHO, LDL and TAG of CCC and RSS groups when compared with control. RSC showed significant ($p<0.05$) increase in CHO, LDL and TAG when compared with CCC and RSS groups. Serum HDL levels showed no significant difference across all groups. Conclusively, cadmium chloride and restraint stress exposure individually lead to metabolic dysfunction and dyslipidemia while the combined exposure exacerbated these effects in female rats.

Keywords: Cadmium chloride; restraint stress; biochemical parameters; female Wistar rats.

1. INTRODUCTION

Heavy metals contamination has emerged as a major global environmental concern owing to the growth in industrialization, urbanization and utilization of chemical compounds in various industries (Aziz et al., 2023). Heavy metals, due to their biotoxicity, bioaccumulation and environmental persistence have been shown to have significant effect on the quality of life (Shou et al., 2022). Cadmium (Cd), a highly toxic heavy metal, is widely dispersed in the environment. Primarily, Cd pollution stems from anthropogenic activities such as lead-zinc mining, non-ferrous metal smelting, plating, and sludge fertilization (Hong et al., 2019). Humans are continually exposed to cadmium through contaminated water, soil, and air. For example, smokers may absorb approximately 1 μg of Cd from 20 cigarettes (Genchi et al., 2020). Chronic, low-dose Cd exposure have been associated with a range of health issues, including circulatory toxicity, renal damage, central and peripheral neurotoxicity, pulmonary disease, and skin conditions like hyperkeratosis and acanthosis (Rahimzadeh et al., 2017). Additionally, studies have linked cadmium exposure to imbalanced glucose homeostasis, lipotoxicity and suppressed insulin expression (Hong et al., 2022).

Stress is any physiological and psychological stimuli that disrupt the body's internal environment (Tsigos et al., 2020). Restraint stress is one of the most widely used experimental methods to induce neuropsychiatric disorders such as depression and anxiety (Italia et al., 2020). This method involves the immobilization of animals, typically rodents in a confined space, which induces both physical and psychological stress responses (Santha et al., 2016). Research has shown a positive association between stress and lipid and glucose abnormalities, psychiatric disorders, inflammation and metabolic dysregulation.

Metabolic profile is a comprehensive analysis of an organism's metabolic state, which involves measuring a wide range of endogenous and exogenous molecules (Yu et al., 2012). Metabolic profile includes insulin resistance, pancreatic beta cell function, glycated hemoglobin and lipid profile (Olugbemidebe et al., 2022). Independently, exposure to stress and cadmium can impact metabolic health. However, studies involving the combined exposure to cadmium and restraint stress on metabolic profile of female Wistar rats is limited. Therefore, this study seeks to evaluate the effect of cadmium chloride administration and restraint stress exposure on the metabolic profile of female Wistar rats.

2. MATERIALS AND METHODS

2.1 Chemicals and Compounds

Cadmium chloride (Kermel, China), chloroform, normosaline and distilled water were purchased from Science laboratory, LAUTECH, Oyo state, Nigeria.

2.2 Experimental Animals

Female Wistar rats (24) weighing 180-220g were obtained from Animal laboratory of the Department of Physiology, Ladoke Akintola University of Technology (LAUTECH), Ogbomoso, Oyo State, Nigeria. They were kept under a standardized laboratory conditions (12/12 h light/dark cycle). The rats were acclimatized for a period of two weeks and were allowed free access to animal feed and water *ad libitum.* All animals received humane care in compliance with the guidelines of the International Standards for the Care and Use of Laboratory Animals.

2.3 Experimental Design

Twenty-four Wistar rats were randomly divided into four groups containing six (6) rats per group. Group I represent the control group while groups II, III, IV served as the experimental groups. The groups designate are: I = Control group (CTL), II = Cadmium chloride Alone (CCC), III= Restraint stress (RSS) and IV = Cadmium+Restraint stress (RSC). Group I was given only feed and water Group II and III, respectively, were administered 100 mg/kg body weight of cadmium chloride (Abd-El-Reheem, 2008) and subjected to restraint stress using wire mesh for 30 minutes (Yamada et al., 2003; Benini et al., 2019) daily while group IV was 100 mg/kg/b.w of cadmium chloride and restrained for 30 minutes daily.

2.4 Cadmium Preparation

A quantified powdered 50g of cadmium chloride was dissolved in 100mls of distilled water and administered orally (0.0025 x b.w) using a beaded oral cannula (Enebeli et al., 2022). Doses were prepared daily.

2.5 Sample Collection

Twenty-four hours after the last cadmium administration and restraint stress exposure, the animals were anesthetized by placing them each in a desiccator with a chloroform soaked cotton wool. Blood samples were collected via the cardiac puncture into sample bottles and the bloods were allowed to clot. Serum was obtained from the collected blood by centrifuging the clotted blood at 2500 revolutions per minute for 10 minutes. The obtained serums were stored at -80^{o}c until use.

2.6 Biochemical Assays

Commercial test kits were used for biochemical parameters. The following biochemical parameters were carried out in Serum: cholesterol (CHO), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triacylglycerol (TAG), cortisol and insulin. Glucose was measured using glucometer strip.

2.7 Statistical Analysis

All results obtained are expressed as Mean ± Standard Error of the Mean (S.E.M). Statistical analyses of result were performed using SPSS (version 16.0). Group comparisons were done using one way analysis of variance (ANOVA) and statistical differences between groups using Duncan's *posthoc test*. $p<0.05$ is considered significant.

3. RESULTS

Result showed significant decrease ($p<0.05$) in body weight of CCC and RSS groups when compared with the Control group. RSC showed significant decrease in body weight when compared with CCC and RSS groups.

Results showed significant ($p<0.05$) increase in serum glucose and cortisol levels but no significance insulin level of CCC group when compared with control. Serum glucose, insulin and cortisol showed significant ($p<0.05$) increase in RSS group when compared with control. In the RSC group, glucose and insulin was significantly ($p<0.05$) increased when compared with CCC but not significant when compared with RSS. Cortisol was significantly ($p<0.05$) increased when compared with CCC and RSS groups.

Table 1. Effect of cadmium chloride and restraint stress exposure on Body weight in female Wistar rats

Group	CTL	CCC	RSS	RSC
Mean±SEM	50.60±2.14^{a}	5.60±0.69 ^{b}	21.30±1.53^{c}	0.50±0.04 ^{d}

Values are expressed as Mean ± SEM (n=6). Mean group with superscript of different letters are significantly (p<0.05) different from one another

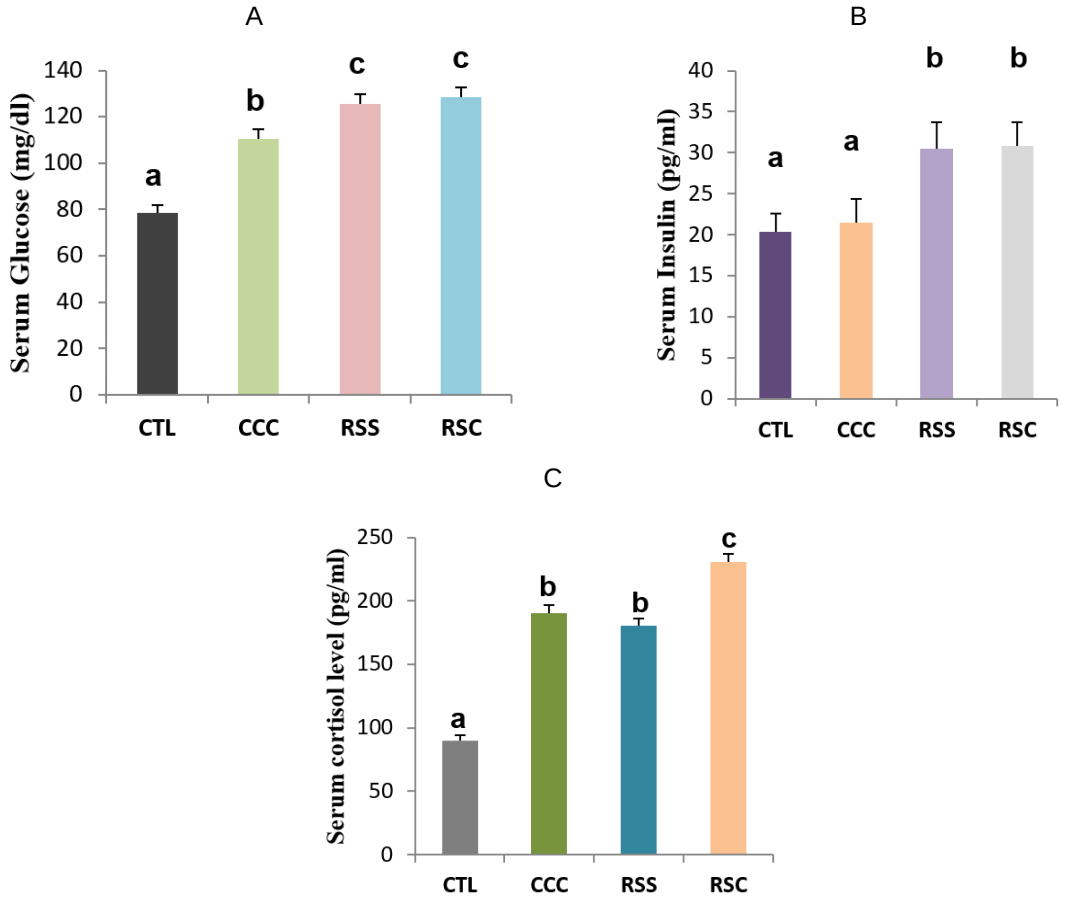

Fig. 1. Effect of cadmium chloride administration and restraint stress exposure on Serum (A) Glucose, (B) Insulin and (C) Cortisol Levels in female Wistar rats

Values are expressed as Mean ± SEM (n=6). Mean group with superscript of different letters are significantly (p<0.05) different from one another

Table 2. Effect of cadmium chloride and restraint stress exposure on Lipid profile in female Wistar rats

	Control	CCC	RSS	RSC
CHO	80.73±4.33^{a}	115.27±5.28^{b}	110.74±5.41^{b}	125.36±6.45^{c}
HDL	44.55±2.56^{a}	46.21±3.37^{a}	46.81±3.08^{a}	48.12±3.44^{a}
LDL	32.86±2.34^{a}	60.15±4.23^{b}	59.35±3.16^{b}	67.87±5.3^{c}
TAG	61.25±3.81^{a}	80.29±4.01^{b}	70.66±3.45^{c}	91.23±5.01^{d}

Values are expressed as Mean ± SEM (n=6). Mean group with superscript of different letters are significantly (p<0.05) different from one another

Result showed significant (p<0.05) increase in CHO, LDL and TAG of CCC and RSS groups when compared with control. RSC showed significant (p<0.05) increase in CHO, LDL and TAG when compared with CCC and RSS groups. Furthermore, HDL levels showed no significance across all groups.

4. DISCUSSION

Cadmium is an heavy metal that has been shown to induce strong metabolic changes while restraint stress is a model of subchronic psychological stress used to induce behavioural and physiological changes. This study investigated the combined effect of cadmium chloride administration and restraint stress exposure on metabolic profile of female Wistar rats.

Body weight provides a rough measure of total body energy stores, and a change in weight is proportional to dysregulation between food

consumption and energy expended by the body for basal functions. Result observed in Table 1 showed a significant ($p<0.05$) decrease in body weight of CCC groups when compared to control. This result correlates with Haeri et al. (2022) where Cd, which was added to the drinking water of mice reduced appetite and weight of mice. Cadmium have been shown to accumulate in the adipose tissue (AT) disrupting its capability to accommodate surplus energy and produce the required adipokine such as leptin and adiponectin for endocrine function (Attia et al., 2022). Adipose tissue is a key organ that regulate processes such as lipid metabolism and energy homeostasis. AT is responsible for releasing adipokines which regulate appetite, energy expenditure and fat distribution. Decrease in weight observed in this present study is suggestive of either loss of adipocytes or dysregulation of adipogenesis.

Result observed in the RSS group showed significant ($p<0.05$) decrease in body weight when compared with control (Table 1). This result correlates with a previous study where chronic restraint stress reduced body weight in day 1 to 4 of restraint (Jeong et al., 2013). Stress can induce anorexigenic effects through the release of corticotropin-releasing hormone which stimulates the sympathetic nervous system and cathecolamine release. Through their actions on white and brown adipose tissue, they can induce hypophagia and weight loss (Rabasa and Dickson, 2016). The significant ($p<0.05$) weight reduction observed in the RSC group is indicative of the combined mechanism of cadmium-induced dysregulation of adipogenesis and stress-induced dysregulation of brown adipose tissue.

The end product of carbohydrate digestion is predominantly glucose which undergoes series of biochemical reactions, releasing energy as adenosine triphosphate (ATP). Result observed in the CCC group showed significant ($p<0.05$) increase in glucose levels when compared with control (Fig. 1A). This result correlates with the study of Li et al. (2024) where blood glucose levels were increased in cadmium-exposed rats. Mechanisms by which CD potentially influence glucose homeostasis includes alteration in glucose transporter gene expression (GLUT2 and IGF-1) (Hong et al., 2022) and increased hepatic and renal gluconeogenesis (Lu and Agarwal, 2022). Cd disrupts insulin signaling pathways, reducing the sensitivity of target tissues to insulin, and thereby impairing glucose uptake. This leads to elevated blood glucose levels (Khalid et al., 2024).

Result observed in the RSS group showed increased glucose levels when compared with control (Fig. 1A). Counterregulatory hormones like catecholamines, cortisol, glucagon, and growth hormone disturb glucose hemostasis resulting to stress-induced hyperglycemia. Catecholamines additionally limit insulin binding, insulin activation by suppressing tyrosine kinase activity and glucose uptake in the periphery by GLUT-4. Similarly, Glucocorticoids also restrict glucose uptake in the peripheral tissue increasing circulating blood glucose (Vedantam et al., 2022). Result observed in the RSC group showed increased glucose levels when compared to control and CCC but not significant when compared with RSS group (Fig. 1A). This result is suggests that restraint-stress did not significantly contribute to cadmium-induced hyperglycemia.

Insulin is a peptide hormone secreted by the beta cells of the islets of Langerhans of the pancreas to regulate blood glucose levels (Mathieu *et al.,* 2017). Result observed in CCC group showed no significance insulin levels when compared with control (Fig. 1B). This result correlates with previous study of Barregarden et al., 2010 where no correlation between insulin and cadmium was observed in women and in contrast to Li et al., (2019) where exposure to cadmium decreased insulin levels in mice. The Liver is one of the targets for CD accumulation. Studies have reported that cadmium can disrupt hepatic IRS-1/PI3K/AKT insulin signaling cascade, which is characterized by inhibited expression of PI3K and phosphorylation of AKT and promoted phosphorylation of IRS-1 (Ser307), inducing hepatic insulin resistance (Li et al., 2024). However, in a study conducted by Lei et al., (2007), no significant change was observed in serum levels of insulin, but Insulin mRNA was decreased in pancreas after Cd exposure, suggesting that biosynthesis of insulin is inhibited by destabilizing insulin mRNA, while insulin release is not inhibited after exposure to cadmium. The metabolic alteration caused by exposure to cadmium may be not be related to serum insulin. Hence, the result of this study may be due to cadmium-induced destabilization of INS mRNA or the study might have been conducted over a short period in which significant changes might have been observed in this group.

The RSS group showed a significant ($p<0.05$) increase in insulin levels when compared with control (Fig. 1B). In correlation to Zhang et al. (2018) which chronic restraint stress induced insulin resistance in mice. Prolonged exposure to glucocorticoids which can impair insulin signaling cascade and inhibit insulin secretion from pancreatic beta cells which can result to insulin resistance and hyperglycemia. However, as a compensatory mechanism, hyperinsulinaemia occurs in response to glucocorticoid-induced hyperglycaemia and, when this condition is paired with increased hepatic glucose delivery (from glucocorticoid-induced peripheral insulin resistance), synergistic stimulation of de novo lipogenesis and subsequent hepatic steatosis occurs, which in turn exacerbates hepatic insulin resistance in a vicious feed-forward cycle in both humans and animal models (Beaupere et al., 2021; Li and Cummins, 2022).

Result observed in the RSC group showed increased Insulin levels when compared to control and RSS but not significant ($p<0.05$) when compared with CCC group (Fig. 1B). This result suggests that CCC did not significantly contribute to stress-induced hepatic insulin resistance. However, this study might have been conducted over a short duration for which significant change can be assessed in groups.

Cortisol is a steroid hormone realeased by the adrenal glands in response to stress and low blood glucose (Moscovitz *et al.,* 2017). Cortisol is negatively associated with insulin sensitivity. Cortisol acutely impairs insulin secretion and increases hepatic glucose output by inhibiting insulin secretion from pancreatic beta cells (Adam *et al.,* 2010). Result observed in CCC groups showed significant ($p<0.05$) increase in cortisol level when compared with control (Fig. 1C). In correlation with this result, previous studies have reported increased cortisol levels in Male Wistar rats exposed to cadmium (Osifo et al., 2018). Cadmium can activate the hypothalamic-pituitary-adrenal (HPA) axis resulting to elevated blood glucocorticoid levels, increased glucocorticoid receptor (GR) expression and activation (Zhang et al., 2023). Additionally, cadmium has been reported to downregulate the expression of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) placental trophoblast resulting to increased levels of active glucocorticoids (Shi et al., 2020).

In the RSS group, cortisol level was significantly increased when compared with control (Fig. 1C). Increased cortisol level observed in RSC group correlates with a previous study where concentrations of both cortisol and corticosterone went up to the highest level within 1 hour of restraint stress in female mice (Gong *et al.,* 2015). Corticotropin-releasing hormone plays a central role in response to restraint stress, activating the HPA axis, thereby increasing the circulating concentrations of glucocorticoids (Scanes *et al.,* 2024). The RSC showed significant increase in cortisol levels. The result suggests that combined exposure to cadmium and restraint stress could induce elevated levels of glucocorticoids.

Lipid profile consists of total cholesterol, triglyceride, LDL-cholesterol (LDL-C) and HDL-cholesterol (HDL-C). They are used to evaluate lipid abnormalities related to cardiovascular risks (Nigam, 2011). Serum CHO, LDL and TAG were significantly increased in CCC group when compared with control (Table 2). This result is in consonance to a previous study where exposure to cadmium chloride through drinking water for a duration of 3 months decreased CHO, TAG and LDL-C in rats (Samarghadian et al., 2015). Cadmium have been shown to deplete glutathione and protein-bound sulfhydryl groups, resulting in the enhanced production of reactive oxygen species, which induces increased lipid peroxidation (Zhou et al., 2016). Research reports found that Cd administration increases the activity of HMG-CoA reductase in the plasma and liver tissue (Prabu et al., 2010; Bashir et al., 2014). HMG-CoA reductase is a rate-limiting enzyme in cholesterol biosynthesis. An increase in the activity of HMG-CoA reductase increases the biosynthesis of cholesterol generally in hepatic cells and this may significantly contribute to alterations in lipid compounds levels in tissues and circulation (Famurewa and Ejezie, 2018). Furthermore, Cd has been linked to excess free fatty acid (FFA) in circulation which promotes conversion of FFA into phospholipids and cholesterol in the liver (Senthilkumar et al., 2012; Famurewa and Ejezie, 2018). The formation of phospholipids and cholesterol with excess TG in the liver is released into the circulation.

Result observed in the RSS group showed significant increase in CHO, TAG and LDL-C when compared with control (Table 2). Activation of the SNS and the consequent binding of norepinephrine to β-adrenergic receptors on white fat cells can trigger lipolysis and the

consequent release of FFAs (Matsuura et al., 2015). The RSC showed significant ($p<0.05$) increase in CHO, TAG and LDL-C levels. This result suggests that the combined mechanisms of cadmium-induced alteration in the liver, increased activity of HMG-CoA and stress-induced activation of SNS can trigger lipolysis which can result to alterations in lipid metabolism.

High density lipoprotein (HDL) levels showed no statistical significance across all groups (Table 2). The major function of HDL cholesterol is to enhance reverse cholesterol transport (RCT) by scavenging excess cholesterol from peripheral tissues followed by esterification through lecithin:cholesterol acyltransferase and delivering it to the liver and steroidogenic organs for subsequent synthesis of bile acids which is essential for elimination of cholesterol (Ademuyiwa *et al.,* 2005; Afolabi et al., 2012). A previous study by Afolabi et al., (2012) showed that cadmium exposed rats showed no significance in HDL levels despite increases in LDL, TG and TC. In this study, it was suggested that cadmium did not alter RCT hence, the no significant change in HDL levels. In another study by Silvennoinen et al., (2012) on acute psychological stress, HDL levels remain unchanged over 3-hour period of stress. This study indicated that during stress, serum cholesterol was redirected towards the liver without a net effect on HDL clearance. Additionally, acute stress period accelerates RCT to enable adaptive responses by the body. Hence, no change in HDL levels in this study suggests that cadmium and restraint stress exposure did not negatively impact reverse cholesterol transport.

5. CONCLUSION

In conclusion, combined exposure to heavy metals such as cadmium and psychosocial stress can result in the dysregulation of metabolic homeostasis promoting the risk for cardiovascular disease such as atherosclerosis and metabolic diseases.

6. RECOMMENDATION

These results highlight the need for more researches into the molecular mechanism via which the combined exposure to cadmium and stress impair metabolic balance, especially via pathways involving the HPA axis, insulin signalling, and lipid metabolism. These findings should foster public health measures to address the metabolic hazards linked to environmental pollutants and long-term stress.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Authors hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

ETHICAL APPROVAL

This study was conducted following the guidelines set by the Animal Handling and Experimental usage and the regulations were adhered to throughout the research process.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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