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Contraceptive Effect on Serum Glucose and Lipid Profile in Alloxan-Induced Diabetic Female Wistar Rat

Suday O.D.[1*], Toryila J. E.[2], Ango A. A.[3] & Adelaiye A.B.[4],
[1,2,4]Physiology Department, Faculty of Basic Medical Sciences, Bingham University, Karu
[3]Physiology Department, Faculty of Basic Medical Sciences, Federal University, Wukari
[*]Corresponding Author Email: toryila.joseph@binghamuni.edu.ng

ABSTRACT
Diabetes mellitus is a metabolic disorder that affects many women of reproductive age. Oral contraceptive pills are now commonly used in millions of women worldwide. The study aim to evaluate the effect of a combined oral contraceptive on the glucose levels and lipid profile in alloxan-induced hyperglycemic rats. Twenty-five female albino Wistar rats weighing 150-200g were divided into five groups(A-E) of five rats each. Animals in group A (control) received distilled water, and Groups B-E were induced into hyperglycemia by intraperitoneal injection of alloxan monohydrate (150mg/kg body weight). Groups (B-D) received distilled water, COCs 0.6mg/kg BW, glibenclamide reference antidiabetic drug) 25mg/kg body weight, for 14 days, 18days, and 22 days, respectively, while those in group E received glibenclamide 25mg/kg BW for 22 days. At the end of the study, all rats were sacrificed, blood sample was collected via cardiac puncture and placed in plane bottles for biochemical analysis, Administration of a COCS significantly ($P<0.05$) increased blood glucose, a well as lipid profile. This result suggests that diabetic rats administered oral contraceptive pills may be more susceptible to oxidative stress by enhanced depletion of antioxidant and increased lipid peroxidation.

Keywords:
Diabetes,
Hyperglycemia,
Lipid profile

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent rise in blood glucose level resulting from defects in insulin secretion, insulin action or both (Saeedi *et al,* 2019). Diabetes mellitus (DM) is a major global health issue, with prevalence estimated to be about 463 million people affected worldwide as of 2025, and this number is projected to rise to 700 million by 2045 (WHO, 2015)

Combined Oral contraceptives (COCs) are widely used by millions of women globally for birth control and reproductive health management (Bahamondes *et al,* 2015). These contraceptives commonly contain synthetic versions of the hormones estrogen and progestin, which work synergistically to prevent ovulation, alter the endometrial lining, and thicken cervical mucus, thereby preventing pregnancy (Yu *et al,* 2014). The hormonal composition of COCs plays a significant role in modulating various physiological processes beyond reproduction, including glucose metabolism, lipid regulation, and cardiovascular function (Toryila *et al,* 2014).

Over 100 million women worldwide use combined oral contraceptives, sometimes it is used to treat heavy or irregular menstruation and endometriosis (Cooper *et al,* 2022). Combined oral contraceptives are readily acceptable in different countries to aid in the reduction of population and prevent mortality from unwanted pregnancy (Giacco *et al,* 2010). Around 2020, it was recorded that the prevalence of oral contraceptive use in Africa varies across countries and regions. Available information indicates that the use of oral contraceptives in Africa is still region-specific, though current data show an increase in usage. The overall percentage of modern contraceptive use in Africa was estimated at 30% in 2019, with oral contraceptive pills being one of the widely used methods, as adopted from the World Health Organization (Bandeira*et al,* 2023). Studies have shown that combined oral contraceptives can lead to an increase in oxidative stress. Mainly due to high levels of estrogen and progestin, which can increase the production of reactive oxygen species (ROS) (Nadir *et al,* 2013). Combined oral contraceptives have been known to influence glucose metabolism through oxidative stress,

a condition characterized by an imbalance between the production of free radicals and the body's antioxidant defenses(Gamde *et al*, 2023) . It is said to affect oxidative parameters such as increased oxidative stress, cause an impact on antioxidant levels, liquid peroxidase and inflammatory markers, thereby predisposing individuals to chronic health conditions such as diabetes mellitus (Taneepanichskul *et al* 2022) .

In women with diabetes, the use of COCs presents additional clinical challenges as hormonal fluctuations induced by estrogen and progestin can influence insulin sensitivity and glucose metabolism, potentially exacerbating diabetic conditions. Previous research has shown that COCs may also impact lipid metabolism and inflammatory markers, both of which are already dysregulated in patients with diabetes(.Yadav *et al* 2022). Given the potential risks of using COCs in women with diabetes, there is an urgent need to investigate the metabolic, hormonal, and physiological effects of COCs in diabetic models, which is critical for developing guidelines that ensure the safety and efficacy of contraceptive practices in this vulnerable population.

The objective of this research is to examine the impact of a COC on glucose levels and lipid profiles in female diabetic Wistar rats produced by alloxan.

MATERIALS AND METHODS

Chemical and reagents

Alloxan monohydrate was obtained from the Department of Pharmacology, Bingham University Karu. Glucose oxidase kit was used to measure the blood glucose levels. Others include; Alloxan, Glibenclamide, methylated spirit, chloroform, formalin, methanol.

Experimental animals

Twenty-five (25) Wistar rats were obtained from the Department of Pharmacology, Bingham University Karu. The rats were kept in the Animal Care Unit of Bingham University, Nasarawa state, Nigeria. They were given a period of two weeks before the commencement of the experimental procedures to acclimatize to the new environment. Animals received standard rat diet and distilled water ad libitum on a daily basis under hygienic conditions.

The Animal Care Unit was well ventilated and swept every day, and the rats were housed in properly aerated plastic cages (4 per cage) alongside with wood dust as beddings. The beddings of the animals were changed every three days. They were kept under the temperature of 27˚c under 12 hours of light and of darkness periodically.

All experimental investigations, rat handling and treatment conforms to the guidelines of the National Institute of Health (De Leo,*et al* 2016). The study protocol was approved by the Animal Ethics Committee of Bingham University, Karu, Nasarawa State.

Experimental design

In this study, twenty-five Wistar rats (5 rats per group) weighing 150±50 were used. The Wistar rats were left to acclimatize for two weeks and were fed with vital feed and water. Administration began and lasted for 14 days (2 weeks). The blood glucose level of the rats was measured before the commencement of the experiment and 72 hours after alloxan administration using a glucometer. The rats whose blood glucose levels were greater than 200mg/dL were included in test groups II-V. The rats were then grouped as follows:

Group I: Normal control group that was fed with normal feed and distilled water for 22 days (no induction of diabetes).

Group II: Alloxan-induced diabetic group that was treated with COC 0.6mg/kg body weight and glibenclamide 25mg/kg body weight for 14 days.

Group III: Alloxan-induced diabetic group that was treated with COC 0.6mg/kg body weight and glibenclamide 25mg/kg body weight for 18 days.

Group IV: Alloxan-induced diabetic group that was treated with COC 0.6mg/kg body weight and glibenclamide 25mg/kg body weight for 22 days.

Group V: Alloxan-induced diabetic group that was treated with glibenclamide 25mg/kg body weight for 22 days(Toryila *et al*, 2014)

After the last dose, the animal's body weights were recorded using a weighing balance. The animals were humanely euthanized and blood samples were individually collected via cardiac puncture into plain bottles. The serum was removed from the blood; samples were labeled and stored for future analysis at 4 °C. Blood serum glucose was estimated from the serum by using a standard kit. For the determination of glucose, samples were prepared by taking 20µl of serum in small glass bottle added 1200µl of reagent present in kit mixed samples and incubated it for 10 minutes at 25°C and absorbance was read at 500 nm of the standard and samples against reagent blanks within 60 minutes (Haverinen *et al* 2021). The blood samples were spun at 2500 rpm for 10min using a centrifuge. Serum samples were assayed for levels of lipid profile using the Microwell enzyme linked immunoassay (ELISA) technique(Das *et al* 2012) . The liver and pancreas were excised via abdominal incision and processed using the paraffin wax method. The tissues were fixed in 10% buffered formalin for 24 hours. After dehydration by three changes of ethanol, clearing in xylene, and embedding in molten paraffin, 3µm of the paraffin mass was cut into a section using a microtome (Surgcare Microtome, Model 335A USA). Cut sections were deparaffined and stained with hematoxylin and eosin

(H&E) for the observation of histopathological changes (Szatmary *et al* 2022)

Ethical approval

Appropriate ethical approval was obtained in writing from the university's ethical committee for scientific research and was assigned batched number HUEC 334

Statistical analysis

Data obtained were expressed as Mean ± SEM. One-way analysis of variance (ANOVA) was used to evaluate the significant difference between the groups a p-value of $p<0.05$ was considered statistically significant. A post hoc Turkey's test was applied for inter and intra group comparisons (to evaluate the significant difference between the groups). All analyses were performed using the statistical package for the social sciences (SPSS) version 25.

RESULTS AND DISCUSSION

Table 1: Effect of combined oral contraceptive on liver enzyme levels of alloxan-induced diabetic female Wistar rats.

Treatment Group	AST (IU/L)	ALT (IU/L)	ALP(IU/L)
1	9.50± 3.75^{c}	78.33±3.18^{b}	192.00±52.35^{a}
2	14.75±5.41^{c}	112.25±11.06^{b}	182.25 ±75.51^{bc}
3	39.00±13.73^{a}	81.25±75.50^{b}	163.50±37.70^{bc}
4	8.03±3.39^{d}	83.00 ±10.12^{bc}	226.25±20.28^{a}
5	18.03±10.13^{b}	127.50±17.50^{a}	116.25±13.92^{bc}

Table 2: Serum lipids of alloxan-induced hyperglycemic rats following oral administration of COCs and Glibenclamide.

Treatment Group	Total chol(mmol/L)	Trigglyceride mmol/L	HDLC	LDLC
1	2.59± 0.01^{ab}	2.57±0.41^{a}	1.67±0.03^{ab}	0.37±0.18^{b}
2	1.86±0.06^{a}	1.57±0.41^{a}	1.99±0.09^{ab}	0.83±0.43^{a}
3	1.49±0.17^{a}	1.76±0.17^{c}	0.59±0.05^{a}	0.74±0.12^{ac}
4	2.49± 2.36^{ab}	1.34±0.24^{ab}	1.26±0.19^{ab}	0.73±0.12^{c}
5	2.61±0.02^{ab}	2.83±0.43^{ac}	1.53±0.08^{ab}	0.37±0.13^{b}

A = Control (1ml distilled water for 21 days);
B=Diabetic rats + COCs + Glibenclamide (for 14 days);
C=Diabetic rats + COCs + Glibenclamide (for 18 days);
D=Diabetic rats + COCs + Glibenclamide (for 22 days);
E=Diabetic rats + Glibenclamide (22 days).
Data are mean +- SEM of five determinations. Test values with superscript different from their respective control down the column for each day are significantly different ($p< 0.05$).

Presents the effects of combined oral contraceptive on lipid profile in alloxan-induced diabetic Wistar rats. The control group (Group I) had a mean TC level of 2.59±0.01, TG (2.57±0.41), HDLc (1.67±0.03), and LDLc (0.37±0.18) while the diabetic group (Group II) treated with COCs and glibenclamide for 14 days showed a slight increase in the lipid profile levels HDLc1.99±0.09, LDLc 2.83±0.43. This suggests that alloxan-induced diabetes did not drastically lower some lipid profile levels in the treated diabetic. The group treated with COC and glibenclamide for 22 days (Group III) demonstrated a significant increase in TC levels (2.90±0.20), and LDLc (0.73±0.12) while significantly ($p<0.05$) decreasing HDLc (0.73±0.12) which could be indicative of metformin's positive role in maintaining or even boosting testosterone levels in diabetic conditions. glibenclamide is known for improving insulin sensitivity and reducing oxidative stress, factors that may positively affect levels in diabetic rats.

Group IV, which was treated with COC and glibenclamide for 28 days, showed varied results. This intermediate treatment caused a reduction in TC levels (1.49±0.17), TG (1.76±0.17), and HDLc (0.59±0.05) while causing an increase in LDLc (0.74±0.12) suggesting that at this duration of administration, COC may have an inhibitory effect on TC, TG, and HDLc levels while enhancing the production of LDL. However, group V which was treated with glibenclamide without COC for 22 days, the TC, and TG, levels increased significantly to 2.62±0.17, and 2.83±0.43 respectively surpassing even the COC treated group. This indicates a conflicting effect of COC on lipid profile in diabetic rats. Although there was no Statistical significant differences

between the groups, the trend of increasing lipid profile with longer duration of administration COC points toward its potential risk in the management of diabetes, though further research is needed to validate these findings.

The diabetic group administered COCs for 14 days showed significantly improved glucose control ($p<0.05$) compared to the diabetic rats administered COCs for 22 days. This agrees with some research that links long-term pill use to prediabetes and type 2 diabetes. In women with normal glucose tolerance, short-term COC use has minimal effect on insulin action, but chronic exposure may lead to subtle β-cell stress due to compensatory hyperinsulinemia (Cheekati *et al* 2017). This hyperinsulinemia represents a physiological adaptation to maintain euglycemia despite decreased insulin sensitivity, but it may precipitate glucose intolerance over time in genetically predisposed individuals.

Recent studies reveal a nuanced relationship between COCs and glucose regulation. In a randomized study by Yadav *et a*l(2022), women using COCs containing ethinylestradiol and levonorgestrel exhibited mild increases in fasting glucose and insulin levels after six months of use. This effect was attributed to decreased insulin sensitivity secondary to progestin-induced hepatic insulin resistance. However, it is important to note that findings are mixed. Other studies haven't found a significant impact on blood sugar control in healthy women of normal weight(Deleskog*et a*l, 2011) .

Results from the lipid profiles revealed that the COC significantly increases ($p<0.05$) total cholesterol levels (1.86±0.06 and 2.90±0.20) of animals treated for 14 days and 22 days respectively as compared to control (1.59±0.01) as well as triglyceride levels in some of the diabetic groups (1.76±0.17), and (2.83±0.43) as compared to the control group (1.57±0.41), estrogen raises serum triglyceride levels by lowering hepatic triglyceride lipase, and promoting hepatic production of triglycerides which are released into the circulation through VLDLs . This result also agrees with the findings of (Eze *et a*l, 2016) . Elevated serum levels of lipids are probably the most important biochemical risk factors for atherosclerosis(Chane *et a*l, 2023) . The HDL however is refered to as the good cholesterol because it carries fat from the peripheral tissues to the liver for it to be broken down. A reduction in the HDL could lead to a conditions such as obesity and hyperlipidemia which is a risk factor for women taking oral contraceptives.

Our results indicate that diabetic animals administered COCs for 18 days had significantly ($p<0.05$) higher levels of TG (1.76±0.17) and LDL (0.74±0.12) cholesterol when compared to control (1.57±0.41) and (0.37±0.18) respectively. The HDLc is slightly lower in all diabetic groups treated with COCs (0.59±0.05, 1.26±0.19), as well as diabetic untreated group (1.53 ± 0.08) but reduced in the intermediate treated group (0.59±0.05) as compared with control group (1.67±0.03).

findings are consistent with previous research, which has shown that COCs can adversely affect lipid metabolism, leading to elevated TG and LDL levels, suggesting meaningful alterations in lipid metabolism that could elevate cardiovascular risk over time. This agrees with Clinical studies of combined oral contraceptives showing variable changes in LDL, HDL(Bolajoko *et a*l, 20008). This is also in line with the study that showed that combined oral contraceptives have been associated with elevated triglyceride levels due to their estrogen componen[t32]

This occurred due to an increase in the cholesterogenesis in the alloxan-induced diabetic rats. High cholesterol level in the blood is associated with atherosclerosis, which leads to clogging of the blood vessels and an increased risk of diabetes, stroke, and other cardiovascular diseases(Ceriello,20003). During diabetic conditions, the HDL is reduced while that of triglycerides, VLDL, and LDL is increased . (Bolajoko *et a*l, 20008). This is very bad for the body because the latter carries cholesterol from the liver to other cells, which leads to an increase in the cholesterol levels in the body, while the former reduces the level of cholesterol by collecting cholesterol from the body and taking it to the liver for synthesis(Bandeira *et a*l, 2023) .

Diabetic women taking combined oral contraceptives are at greater risk of developing cardiovascular disease due to the interaction of COCs with lipid metabolism. Insulin resistance reduces lipoprotein lipase (LPL) activity, leading to decreased TG clearance. Thus, when COCs increase hepatic TG synthesis, the imbalance between production and clearance exacerbates hypertriglyceridemia (Bandeira *et a*l, 2023) .

Another striking observation from our study was a significant increase ($p<0.05$) in the plasma levels of total cholesterol and LDLc of animals treated with COCs for a short duration (14 days) (1.86±0.06) and (2.83±0.43) respectively when compared with control (1.59±0.01) and (0.37±0.18) respectively, and a significant increase ($p<0.05$) in high density lipoprotein (HDL) cholesterol (1.99±0.09) as compared to control (1.67±0.03) This agrees with some studies that found that even short-term use of COCs in healthy young women can lead to increased unhealthy cholesterol levels and inflammation markers (Bandeira *et a*l, 2023,Gerard *et a*l, 2022) .

The results indicate that short-term administration of oral contraceptives containing progestins and EE does not exert a deleterious effect on lipoprotein metabolism, as high HDL-cholesterol and low LDL-cholesterol levels are known as low-risk factors of cardiovascular disease. These changes in lipid metabolism appear to reflect a predominance of the effect of the estrogen component. ER actions generally favor a lipid profile that is metabolically protective (higher HDL, lower ectopic lipid

deposition), though oral estrogen formulations can alter hepatic lipoprotein production via first-pass hepatic effects. The progestin type in combined therapies strongly influences net lipid effects; some progestins are androgenic (worsen LDL), others are neutral or anti-androgenic. Clinical studies of combined oral contraceptives show variable changes in LDL, HDL, and triglycerides that map to formulation differences (Ighodaro *et a*l, 2018, Hashemi *et a*l, 2023,Silva-Bermudez *et a*l, 2020)

The absence of exogenous hormonal influence in the untreated diabetic group (group 5), with slight elevation in TC level (2.62±0.17) when compared with the control (2.59±0.01) might lead to unopposed endogenous hormonal activity, potentially driving cholesterol synthesis through mechanisms such as increased hepatic hydroxymethylglutaryl-CoA reductase activity. This hypothesis aligns with studies suggesting that endogenous estrogen fluctuations can modulate lipid metabolism, potentially leading to higher total cholesterol levels in certain populations (Bandeira *et al*.2023). These results highlight that while COCs can enhance protective HDL-C levels, they may simultaneously elevate atherogenic lipids, especially in diabetic individuals whose hepatic lipid clearance mechanisms are already impaired.

CONCLUSION

This study provides valuable insights into the biochemical effects of the use of COCs on glucose levels and lipid profiles in diabetic female Wistar rats. Our findings revealed some of the negative effects of the drug, which include an increase in glucose levels and lipid profile, and prolonged COCs use may be associated with significant elevations, suggesting a compromised antioxidant defense, potentially increasing the risk of oxidative stress-related conditions. Moreover, the study revealed significant alterations in lipid metabolism, with higher levels of TG and LDL cholesterol observed in COCs use. These changes heighten the risk of cardiovascular diseases, emphasizing the need for careful monitoring of lipid profiles in women using COCs. In light of these findings, healthcare providers must monitor the antioxidant status via glucose level and lipid profiles of women using COC therapy. Further research is needed to explore potential protective strategies, such as antioxidants.

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