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Effects of 5% Coca-Cola Consumption on Metabolic, Renal, and Hepatic Markers in Adult Balb/c Mice

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ABSTRACT

The impact of consuming Coca-Cola increases the energy and the weight at the same time, however, the 5% refers to consuming one can of Coca-Cola daily in the long term. The consumption of 5% Coca-Cola increases food intake, body weight, and contributes to various other disorders in young mice. This work aims to find the effect of Coca-Cola consumption on leptin and insulin resistance, lipid profile, and changes in renal and liver functions in adult mice. In this study, 30 adult male Balb/c mice (8-10 weeks old, weighing 25-30g) were used and divided into three groups. Ten mice received tap water and serve as control group, the other 20 mice received 5% Coca-Cola daily instead of water for different durations and served as restricted groups, ten for 10-day (restricted 1) and the other ten for 30-day (restricted 2). Body weight of all mice was measured at the start and end of the experiment, while the food intake was recorded daily. The mice were killed at different time-points. Blood was collected and used to determine the levels of FBG, HbA1c, leptin and insulin hormones, lipid profile, and liver and kidney function parameters. The insulin resistance was also calculated. The results indicate significant increases in food intake, body weight, leptin, insulin, FBG, HbA1c, and insulin resistance in groups exposed to Coca-Cola. Lipid profiles and liver and kidney function markers also deteriorated, particularly in the group with longer exposure. Prolonged consumption led to increased body weight and leptin levels (indicating leptin resistance), insulin resistance with elevated FBG and HbA1C (suggestive of type 2 diabetes), altered lipid profiles (raising cardiovascular risk), elevated kidney (BU and SCr) and liver function markers (GOT, GPT, ALK), with these effects intensifying over 30 days compared to 10 days.

1. INTRODUCTION

A soft drink is a type of beverage that usually consists of carbonated water, sugar, and either artificial or real flavour. Sugar, high-fructose corn syrup, fruit juice, sugar substitutes, or any combination of these may be used as a sweetener. In addition, caffeine, colourings, preservatives, and other substances may be included in soft drinks [1].

Coca-Cola is a well-known soft drink and probably consumed by every country in the world [2] because of its supposed benefits since Coca-Cola contains phosphoric acid which is cited in the pharmacology literature as having an antiemetic [3]. Therefore, the rate of consumption of these drinks is alarming, especially in affluent countries [4]. This large increase in the consumption of these drinks raises concerns about potential health risks, especially since caffeine is deliberately added to enhance dependency and is absorbed more quickly than in other beverages. In addition, Coca-Cola is unique from other soft drinks in that the water used to prepare Coca-Cola is more carbonated than that in other soft drinks, and it also contains higher percentages of salts and calories [5]. As a result, researchers have started investigating the harmful effects of these beverages and have identified several serious health issues linked to regular soft drink consumption, including obesity, type 2 diabetes mellitus, cardiovascular disease [6], heart attacks [7], kidney damage and a high risk of kidney stone formation [8], as well as bone fractures and reduced bone mineral density [9].

To our knowledge, previous researchers have studied the harmful effects of 100% or 50% Coca-Cola on adult mice or rats. Moreover, based on these studies, it was found that the consumption of 5% Coca-Cola increases food intake and body weight in young mice.

This work aims to study the impact of 5% Coca-Cola, which is equivalent to approximately one can of Coca-Cola per day for humans, on leptin and insulin resistance, lipid profile, and changes in renal and liver functions in adult mice.

2. MATERIALS AND METHODS

This study is conducted on 30 male Balb/c mice. The animals were purchased from the Iraqi Centre for Cancer and Medical Genetic Research. These mice weighed between 25 and 30 g and were 8 to 10 weeks old. The mice are housed in six clean plastic cages (40*25 cm) every cage contain 5 mice with metal network covers found in the animal house in Mustansiriyah University with controlled climate, a temperature between 22-25℃ and 12h light-dark cycle. These mice were fed Standard mouse pellet and drank tap water (ad libitum).

After the mice were left for one week for adaptation, they were divided into three groups， each of them has ten mice; the first received tap water and serve as control group. The other groups received 5% (7 ml Coca-Cola diluted with 140 ml water) daily instead of water and serve as restricted groups, one received it for 10-day (restricted 1) and the other for 30 day is (restricted 2).

While daily food intake was recorded every day, mice body weight was measured at the beginning and the end of experiment. Mice body weight changing was calculated by subtracting the weight of mice at the beginning of experiment from its weight after the end of the experiment. Mice were killed by cervical distraction (Pop the mouse's eye to extract blood) at different times. Blood was collected from eyes in two types of sterile tubes. One had EDTA for the direct detection of HbA1con ichroma TM instrument testing. The other tube was gel tube and the blood was left to clot. The serum was separated by centrifugation 3000 rpm for 10 min, then the eloquent was stored in -20℃ until used to determine biochemical parameters.

The leptin and insulin hormones levels were measured by a sandwich enzyme-linked immune sorbent assay (ELISA) technique using a kit from Shanghai YL Biont China while FBG level was measured by enzymatic methods using laboratory kit glucose MR Giesse/Italia. For calculate the level of IR, the equation below was used [10]:

$$IR = [Fasting\ Serum\ Insulin\left(\frac{mU}{mL}\right) \times Fasting\ Blood\ Glucose\ (\frac{mmol}{L}) \quad (1)$$

The levels of Chloe, Tri, HDL, LDL and VLDL were also Measured by enzymatic end point method supplied using the kits from Bio labocompany, France.

Glutamate pyruvate transaminase (GPT), Glutamate oxaloacetate transaminase (GOT), Alkaline phosphatase (ALP), and Blood urea (BU) levels in serum were measured by the enzymatic colorimetric method while Serum creatinine (SCr) levels in serum was determinate by kinetic colorimetric method using kits form linear company/Spain.

2.1 Statistics

The results are presented as mean ± standard error (M ± SE). Data analysis was performed using one-way analysis of variance (ANOVA), followed by Fisher's test for multiple comparisons, utilizing StatView version 5.0. A p-value of less than 0.05 was considered statistically significant.

3. RESULTS

Figure 1 shows the differences in the food intakes (A), the body weight changing (B) and the leptin levels (C) of restricted mice compared to control group. Significantly differences in the food intakes of restricted groups compared to control group were obtained in Figure 1(A). After zero-time, restricted mice start to eat more than the control with the time. The food intake of each mouse drank coca cola until 10 days was about 5g compared to 4 g in control groups. This amount gradually increased as a fallowing: after 20 days, 6.5 g compared to 4.5, and finally after 30 days, 7 g compared to 5. However, a significant rise in the body weight changes was noted of the mice groups drank Coca-Cola instead of water for 10 and 30 days compared to control group (1.13±0.093, 1.18±0.073 and 0.99±0.086 g, respectively), as shown in Figure 1(B). Moreover, Figure 1(C) shows that there was also significantly increase in the leptin levels of restricted groups after 10 and 30 days compared to control (2.3±0.66, 3.2±0.16 and 1.98±0.69ng/ml, respectively).

Table 1 shows the differences in FBG (mg/dl), HbA1c%, insulin (µU/ml) and IR of restricted and control mice groups. Significant increase in the FBG, HbA1c%, insulin and IR level of the mice groups drink Coca-Cola for 30 days (150.2±2.9 mg/dl, 4.4±0.67%, 0.37±0.068 µU/ml and 0.138±0.011,respectively),compared to restricted group 10 days (117.8±22.9 mg/dl, 3.0±0.68%, 0.33±0.05 µU/ml and 0.095±0.01, respectively) and control group (103.7±13.2 mg/dl, 1.1±0.27%, 0.25±0.017µU/ml, 0.063±0.009, respectively). However, these parameters were significantly higher in the restricted group after 10 days than control except FBG which was non-significantly higher in the restricted group after 10 days compared to control.

Table 2 shows that in both restricted groups (after 10 and 30 days), there was an increase in the levels of Cholesterol (124.7±23.9 and 129.1±3.7 mg/dl, respectively) and Triglycerol (166.2±31.2 and 180.8±28.8 mg/dl, respectively) compared to control (62.0±15.2 and 99.5±21.1 mg/dl, respectively) while there was significant decrease in HDL level of restricted group after 10 and 30 days compared to control (79.9±3.5, 67.6±9.1 and 95.3±7.1mg/dl, respectively), which was significantly higher in the restricted group after 10 than 30 days. However, the level of LDL and VLDL was significantly increased in restricted group after 30 (78.4±14.7 and 38.6±1.1 mg/ml, respectively) compared to restricted group after 10 days (47.9±9.6 and 23.0±2.4 mg/ml, respectively) and control (37.5±1.3 and 19.7±6.6 mg/ml, respectively).

Table 3 shows the differences in the blood urea (BU) and serum creatinine (SCr) of the three mice groups. While there was no significant difference in BU levels of the mice group drank Coca-Cola for 10 days, a significant increase in the BU level of the mice groups drank Coco-Cola for 30 days (32.7±1.3 and 64.4±9.4 mg/dl, respectively) compared to control group (27.7±0.7 mg/dl) was observed. This increase was also observed in the SCr levels, as the SCr levels for mice groups drank Coca-Cola for 10 days and 30 days were significantly higher than control (0.99±0.19, 1.6±0.19, and 0.36±0.05 mg/dl, respectively). The levels of these parameters were also significantly higher in the restricted 2 compared to 1.

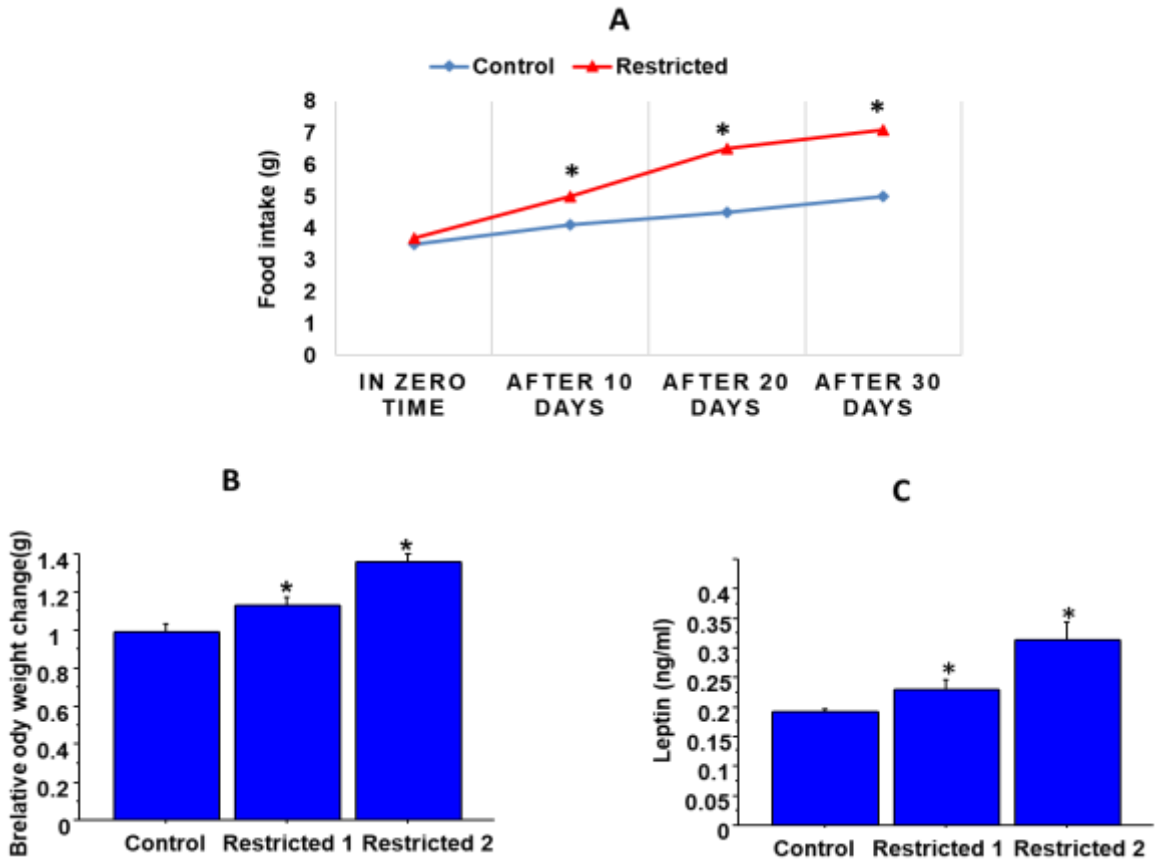

Figure 1. The changing in the (A) Food intakes, (B) body weights, and (C) Leptin levels of the restricted and control mice groups

Table 1. The levels of FBG, HbA1c, Insulin and IR in the control and restricted groups

Groups	FBG (mg/dl)	HbA1C%	Insulin (µU/ml)	IR
Control	103.7±13.2	1.1±0.27	0.25±0.017	0.063±0.009
Restricted 1	117.8±22.9	3.0±0.68	0.33±0.05	0.095±0.01
Restricted 2	150.2±2.9	4.4±0.67	0.37±0.068	0.138±0.011
P. value	R1 vs. C=0.23 R2 vs. C=0.003 R1 vs. R2=0.015	R1 vs. C=0.0007 R2 vs. C<0.0001 R1 vs. R2=0.005	R1 vs. C=0.042 R2 vs. C=0.005 R1 vs. R2=0.196	R1 vs. C=0.035 R2 vs. C=0.0003 R1 vs. R2=0.008

Table 2. The levels of Chol., Tri., HDL, LDL and VLDL in the restricted and control groups

Groups	Chol. (mg/dl)	Tri. (mg/dl)	HDL (mg/dl)	LDL (mg/ml)	VLDL (mg/ml)
Control	62.0±15.2	99.5±21.1	95.3±7.1	37.5±1.3	19.7±6.6
Restricted 1	124.7±23.9	166.2±31.2	79.9±3.5	47.9±9.6	23.0±2.4
Restricted 2	129.1±3.7	180.8±28.8	67.6±9.1	78.4±14.7	38.6±1.1
P. value	R1 vs. C=0.0002 R2 vs C=0.0004 R1 vs. R2=0.7	R1 vs. C=0.04 R2 vs. C=0.02 R1 vs. R2=0.6	R1 vs. C=0.007 R2 vs. C=0.0002 R1 vs. R2=0.02	R1 vs. C=0.32 R2 vs. C=0.003 R1 vs R2=0.01	R1 vs. C=0.23 R2 vs. C<0.0001 R1 vs. R2=0.0002

Table 3. Levels of BU and SCr in the control and treated (T1 and T2) groups

Groups	BU (mg/dl)	SCr (mg/dl)
Control	27.7± 0.7	0.36± 0.05
Restricted 1	32.7± 1.3	0.99± 0.19
Restricted 2	64.4± 9.4	1.6± 0.19
P. value	R1 vs. C=0.537 R2 vs. C=0.001 R1 vs. R2=0.003	R1 vs. C=0.020 R2 vs. C= 0.0004 R1 vs. R2=0.023

Table 4 shows the differences in the liver enzymes; Glutamate pyruvate transaminase (GPT), Glutamate oxaloacetate transaminase (GOT) and alkaline phosphatase (ALP) of the three mice groups. While there was no significant difference in level of GOT in mice groups drank Coco-Cola for 10 days, a significant increase in GOT of mice groups drank Coco-Cola for 30 days compared to control (248.8±20.6, 466.8±82.0, and 189.8±20.6 U/I, respectively). Moreover, significant increasing was observed in the other two enzymes (GPT and ALK) in restricted group 1 and 2 compared to control group (49.0±5.12, 80.8±8.7, and 299.8±0.95 U/I GPT, respectively) and (973.3±110.2, 1287±29.9, and 602.8±25.3 U/I ALK, respectively). The levels of these parameters were also significantly higher in the restricted 2 compared to 1.

Table 4. Levels of GOT, GPT, and ALK in the control and treated (T1 and T2) groups

Groups	GOT (U/L)	GPT (U/L)	ALK (U/L)
Control	189.8± 20.6	1.1±0.27	0.25±0.017
Restricted 1	248.8± 7.4	3.0±0.68	0.33±0.05
Restricted 2	466.8± 82.0	4.4±0.67	0.37±0.068
P. value	R1 vs. C=0.42 R2 vs. C=0.003 R1 vs. R2=0.012	R1 vs. C=0.045 R2 vs. C= 0.0002 R1 vs. R2=0.004	R1 vs. C=0.0037 R2 vs. C<0.0001 R1 vs. R2=0.009

4. DISCUSSION

Worldwide, adults and young adults are consuming more carbonated soft drinks like Coca-Cola on a variety of occasions [11]. The consumption of high concentration of Coca-Cola, however, has a number of harmful impacts, according to various research articles [2, 3, 6, 8]. So, we focused on the effects that can be caused by a daily small concentration of Coca-Cola (5%) on adults mice.

When compared to the control, the mice that consumed 5% Coca-Cola have gained weight as the period of consumption increased. This finding was consistent with other studies that found a substantial correlation between Coca-Cola consumption and the prevalence of obesity [6, 8]. This weight gain reported in current work could be caused by the increasing of food intake of the mice consumed 5% Coca-Cola with increasing period of consumption compared to control. There is growing evidence linking the consumption of soft drinks containing artificial sweeteners to increased food intake and weight gain [12].

On the other hand, another study demonstrates clearly that the carbon dioxide gas causes ghrelin production, which in turn causes an increase in food intake and a higher risk of weight gain, obesity [13]. Other research, however, found no connection between use of soft drinks and BMI changes [14]. Interestingly, the mouse groups drank 5% Coca-Cola that had an increase in food intake and body weight also had an increase in the leptin noted in this study. This elevation in leptin level my contradict other results, the elevation in food intake and body weight, that observed in this study in addition to increase the level of ghrelin [14]. However, as an explanation for this phenomenon, these mice could be developed leptin resistance which may lead to all these changes.

It is well known that Cola is a fructose-containing beverage and according to a study by de Farias Lelis et al. [15], fructose causes hyperinsulinemia, decreased glucose tolerance, insulin resistance syndrome, and weight gain. These results agree with ours in this study in same conditions since the level of FBG, HbA1C, insulin and insulin resistance were elevated with Cola consumption. Furthermore, because insulin responses to meals influence the generation of leptin, cola consuming raises circulating leptin concentrations. Moreover, leptin controls oxidation of free fatty acids, insulin action, and food intake [16].

Leptin levels exhibit a strong positive correlation with obesity, which, in turn, may lead to the development of leptin resistance. Emerging evidence suggests that the dysfunction or inactivation of leptin receptors in the central nervous system plays a pivotal role in leptin resistance, further amplifying the risk of obesity [17]. This phenomenon may account for the simultaneous increase in leptin levels and food intake observed in mice consuming a 5% Coca-Cola diet, ultimately contributing to a rise in body weight. Furthermore, studies have established a positive correlation between leptin concentration, insulin levels, and insulin resistance, highlighting the intricate interplay between these metabolic factors. Study [18] found in this work either.

There is a lot of caffeine in the carbonated soft drinks. According to Harpaz et al. [19], caffeine is an adenosine antagonist that triggers the release of neurotransmitters, a phosphodiesterase inhibitor that modifies intracellular cAMP levels, and a stimulant of both lipolysis and glucose metabolism. Furthermore, this sugar-sweetened beverage comes in cans with about 30 grams of sugar per can, which is a lot higher than the WHO's most recent recommendations.

According to Manolis et al. [20], several metabolic pathways involving glucose, lipids, ketone bodies, and proteins are adversely affected by the high sugar level. According to research by Meng et al. [21], consuming beverages containing both sugar and caffeine was found to be substantially linked to an increased risk of many ailments linked to the metabolism of glucose, such as obesity, type 2 diabetes, and cardiovascular diseases. Actually, the high levels of carbohydrates in the drinks under study raised blood glucose levels, which led to hyperinsulinemia and ultimately damaged the overall metabolic process.

Caffeine has been shown to increase hyperinsulinemia through a number of mechanisms, including improving levels of cortisol and circulating epinephrine, minimizing tissue sensitivity, inhibiting glucose uptake, and maintaining high blood glucose levels. This explains the increase in levels of blood sugar, HbA1c, Insulin and Insulin resistance observed in mice that consumed 5% Coca-Cola in this study.

Because of the sugar-caffeine combination's increased hyperglycaemia and hyperinsulinemic state, Coca-Cola consumption affects lipid metabolism by favouring glycolytic pathways and preventing lipolysis via the inhibitory effect of insulin on hormone-sensitive lipase [22]. Softic et al. [23] have observed that when fructose is consumed in big quantities, it offers a somewhat uncontrolled source of carbon precursors for the hepatic lipogenesis process. Moreover, a recent study on mice revealed that drinking liquids sweetened with fructose causes a greater increase in adiposity than drinking beverages sweetened with sucrose or artificial sweeteners.

Furthermore, it has been suggested that Coca-Cola soft drinks' impacts on lipid levels by stimulates the liver's synthesis of triglycerides, fatty acids, and cholesterol which may be generate hypertriglyceridemia and hypercholesterolemia, respectively, making them powerful in the induction of diabetes mellitus and cardiovascular diseases [24]. Furthermore, epidemiological research has shown that elevated blood levels of LDL and/or total cholesterol are important risk factors for coronary heart disease [25]. Since low levels of LDL are beneficial; it is sometimes referred to as bad cholesterol [26].

It has been established that this function of HDL-cholesterol is what gives it a theroprotective qualities. HDL cholesterol also controls the transfer of lipids and proteins between various lipoproteins. HDL cholesterol also supplies the protein components required to activate lipoprotein lipase, which releases fatty acids that can be oxidized by the ß-oxidation

pathway to produce energy [27]. Most notably, HDL cholesterol's antioxidant property allows it to prevent LDL cholesterol from oxidizing as well as the atherogenic effects of LDL cholesterol that have been oxidized. Our outcomes were in line with the study's findings [28] that suggested that the level of bad cholesterol (LDL) had increased and the level of HDL cholesterol (HDL) had decreased.

Fructose is quickly converted to hepatic glycogen or fat in the liver, which encourages lipogenesis and exacerbates insulin resistance [28]. As a result, eating fructose is known to increase the risk of obesity or other cardiometabolic diseases, muscles are the main tissue that responds to insulin after glucose tolerance.

A study has shown that rats exposed to soft drinks show weakness in insulin signals in the muscles, because eating a lot of fructose has negative effects on muscles' mitochondrial function and energy metabolism. Additionally, they observed that the muscles' poor glucose metabolism might have contributed to the onset of diabetes [29]. This is due to the relationship between the endoplasmic reticulum, cytokines like adiponectin, chemicals involved in oxidative stress, and plasminogen activator inhibition in the metabolism of glucose and fat [30].

In the current study, there were significant increase in the BU and SCr levels in mice group consumed Coca-Cola compared to the control. The serum creatinine level is used as an indicator of renal failure and Blood urea is also used to evaluate kidney function [31]. Many researchers suggested that carbonated beverage consumption might increase the risk of chronic kidney disease, which could cause an elevation in the levels of blood urea and serum creatinine [32] that agree with our results.

The current results also revealed a significant increase in liver enzymes (GOT, GPT and ALK). Elevating in liver enzymes often indicates inflammation or damage in liver cells which due to increase the amounts of certain chemicals more than normal, including liver enzymes, into the blood stream [33].

5. CONCLUSION

The study revealed that long-term daily consumption of a single can of Coca-Cola by healthy individuals in Iraq negatively impacts body chemistry and physiology, including increased body weight and leptin levels (suggestive of leptin resistance), elevated insulin resistance, FBG, and HbA1C (indicative of type 2 diabetes), altered lipid profiles (raising cardiovascular risk), elevated kidney function markers (BU and SCr) linked to renal issues, and increased liver function markers (GOT, GPT, ALK) associated with liver dysfunction, with these effects worsening significantly over 30 days compared to 10 days.

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NOMENCLATURE

FBG	Fast blood sugar
HbA1c	Hemoglobin A1c
Tri	Triglycerides Test
HDL	High-density lipoprotein
LDL	Low-Density Lipoprotein
VLDL	Very Low-density Lipoprotein