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High salt intake does not aggravate glucose dysregulation and dyslipidemia induced by estrogen-progestin oral contraceptive

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ABSTRACT

Background: Estrogen-progestogen combined oral contraceptive (OC) use has been associated with increased cardiometabolic risk factors, including glucose dysregulation, dyslipidemia, hypertension, and pro-inflammatory state. However, the effect of a high-salt diet on these risk factors during OC use is not yet investigated. We therefore hypothesized that a high-salt diet would increase cardiometabolic risk factors in female rats treated with a combination of OC steroids, levonorgestrel (L) and ethinylestradiol (EE), and that elevated plasma levels of pro-inflammatory markers are associated with the cardiometabolic effects.
Methods: Female Wistar rats were given (*p.o.*) vehicle, high-dose (1.0 μg EE plus 5.0 μg L) or low-dose (0.1 μg EE plus 0.5 μg L) OC with or without a high-salt diet (8%) daily for 8 weeks. Insulin resistance (IR) was estimated using the homeostatic model of assessment (HOMA).
Results: Results showed that OC treatment or high salt diet led to significant increases in insulin resistance, plasma insulin, total cholesterol (TC), triglyceride (TG), TC/HDL-cholesterol, uric acid levels, and decreased glucose tolerance. OC treatment but not a high-salt diet resulted in increased plasma C-reactive protein and TG/HDL-cholesterol. However, a high-salt diet did not aggravate the effects of OC treatment.
Conclusion: The results from the present study indicate that glucose dysfunction and dyslipidemia induced by OC use, but not those induced by increased dietary salt are associated with elevated plasma C-reactive protein. Besides, increased dietary salt does not worsen abnormal cardiometabolic impact of OC use.

1. Introduction

Contraception is one of the keystones of reproductive health, which enables the individual to choose when and how many children he/she has [1]. Increasing population puts strain on the world's limited resources. In the last decade, the prevalence of contraceptive usage has increased worldwide. The health benefits of avoiding unintended pregnancy and the ability to extend inter-birth intervals have been well documented [2]. Estrogen-progestogen oral contraceptives (OC) have been in use for over five decades, particularly in the developed countries due to their ease of use, proven efficacy, low occurrence of side effects, relative safety compared with pregnancy and capability of returning fertility soon after discontinued use [3]. They are used by over 100 million women primarily for contraception and are also in the treatment of menstrual disturbances and hyperandrogenism in women with polycystic ovary syndrome worldwide [4]. Since the introduction, the impact of estrogen and progestogens exposure on cardiometabolic morbidity remains unresolved [5,6].

Mortality due to cardiovascular disease (CVD) is several times lower in women than in men of reproductive age. The incidence of death due to myocardial infarction is 3–5 times higher in men than in premenopausal women of the same age group. Similarly, the prevalence of stroke-related deaths in women is only about half that of men of the same age [7]. In premenopausal women, estrogens play a major role in protecting against the development of atherosclerotic cardiovascular event [8]. However, studies have indicated that increased levels of estrogens and progestogens, particularly during pregnancy [9] and during OC use [10] are associated with glucose dysregulation. Studies have also shown that use of OC

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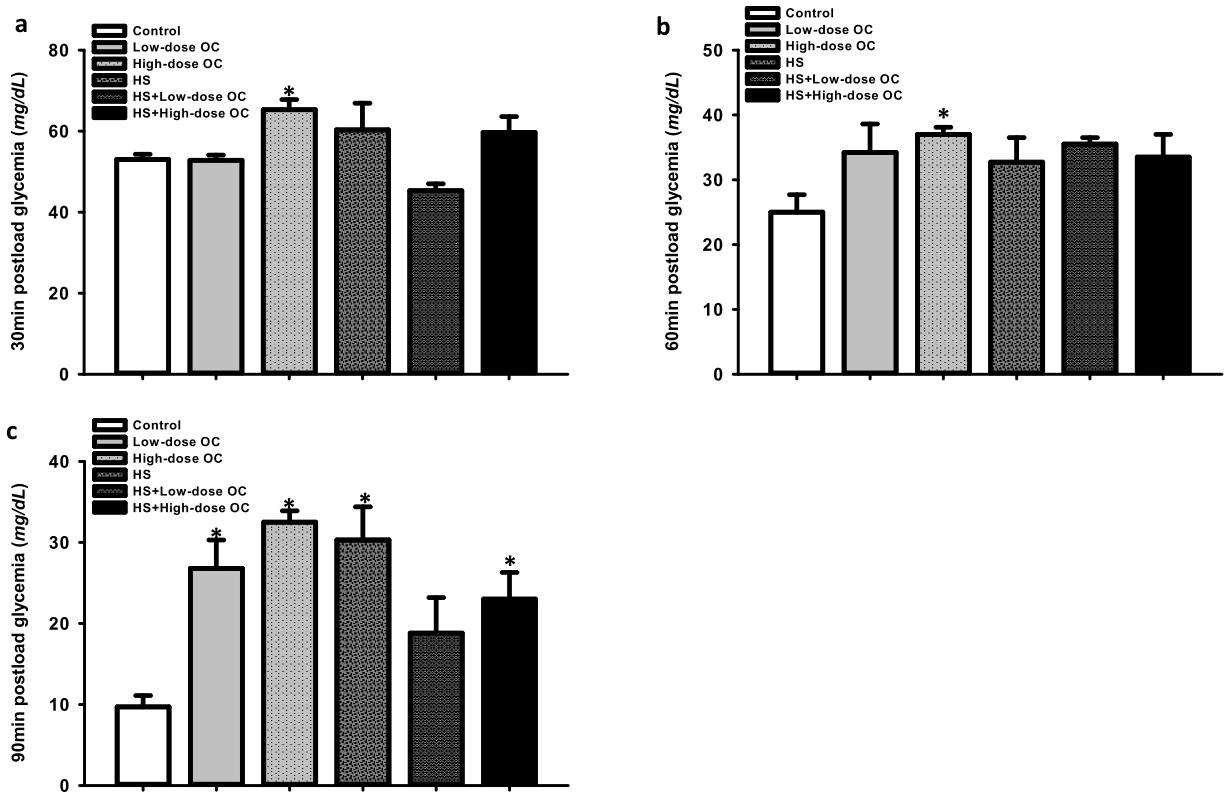

Fig. 1. Effect of treatment with estrogen-progestin oral contraceptive and high salt on post-load glucose response at (a) 30 min (b) 60 min and (c) 90 min in female Wistar rats. 30 minutes and 60 min post-load glucose response was elevated in high salt treated rats. 90 min hour post-load glucose response was elevated in low-dose OC, high-dose OC, high salt and high salt with high-dose OC-treated rats. Data are expressed as the mean ± SEM of 6 rats in each group. Data were analyzed by one-way ANOVA followed by followed by Bonferroni post hoc test (*$P < 0.05$ vs control).

Table 1
Physiological and biochemical parameters in female rats treated with combined oral contraceptive (OC) containing levonorgestrel and ethinyl estradiol with or without high-salt (HS) diet.

	Control	Low-dose OC	High-dose OC	HS	HS + Low-dose OC	HS ± High-dose OC
Body weight (g)						
Initial	163.8 ± 6.7	172.7 ± 8.6	166.1 ± 5.1	187.5 ± 9.9	180.0 ± 7.2	178.3 ± 4.8
Change	62.4 ± 6.7	25.2 ± 7.7*	18.7 ± 4.5*	29.2 ± 7.5*	30.0 ± 8.2*	20.0 ± 8.6*
Food (g/100 g bw/day)						
initial	10.1 ± 1.0	9.8 ± 1.1	9.2 ± 0.8	9.6 ± 0.9	8.2 ± 0.6	9.3 ± 0.7
Final	10.6 ± 0.9	9.7 ± 0.6	10.1 ± 1.0	7.8 ± 0.8	6.9 ± 0.8	6.4 ± 0.9

Data are expressed as mean ± SEM of 6 rats per group. Data were analyzed by one-way ANOVA followed by Tukey's test.
*p<0.05 vs control.

Table 2
Plasma lipid parameters in female rats treated with combined oral contraceptive (OC) containing levonorgestrel and ethinyl estradiol with or without high-salt (HS) diet.

	Control	Low-dose OC	High-dose OC	HS	HS ± Low-dose OC	HS ± High-dose OC
Fasting Insulin (ng/mL)	9.6 ± 0.2	11.9 ± 0.6*	14.6 ± 0.5*	15.4 ± 0.4*	10.6 ± 0.7	13.7 ± 0.4*
Fasting glucose (mg/dL)	2.0 ± 0.1	67.0 ± 1.6*	68.1 ± 1.8*	67.2 ± 2.1*	69.8 ± 1.1*	72.7 ± 1.0*

Data are expressed as mean ± SEM of 6 rats per group. Data were analyzed by one-way ANOVA followed by Tukey's test.
*$p < 0.05$ vs control.

containing high dose of estrogen caused marked impaired glucose tolerance and increases in serum triglycerides and total cholesterol [11,12].

In an attempt to circumvent the untoward occurrences, OCs with lower doses of estrogen and less androgenic progestins were developed [5]. However, these preparations are still associated with increased incidence of vascular events [13,14]. Although this led to a better metabolic profile, cardiometabolic risk factors have not been eliminated [15,16], a trend toward an increased risk of atherothrombotic disease still occurred [17], especially among women with concomitant risk factors such as smoking [18] and hypertension [15].

Insulin resistance (IR) has been proposed as a metabolic link between hypertension, type 2 diabetes, obesity, dyslipidemia, coro-