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Effect of Chromium Piclonate versus L-Carnitine on High fat Diet Induced in rats

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Abstract: Introduction: The global prevalence of overweight and obesity is increasing rapidly worldwide among all ages. Several pharmacological agents such as insulin-sensitizing agents may be used to reduce or control the body weight and obesity. Obviously the need for natural supplements to decrease weight and help correction of some of complication became a very strong world need. This study try to show the effect of two natural product (LCarntine, Chromium Piclonate). Methodology: Male albino rats (n = 60) there were divided into three groups: control group (rats were fed a standard diet, Group I; rats were fed a high-fat diet for 60 days than followed with L-carnitine for 60 days, while group II; rats were fed a high-fat diet for 60 days than followed with Chromium Picolonate (Cr Pi) for 60 days. Results: As for Fasting blood sugar (FBS), there was statically significantly lower values (SD=84.3±3.7, P< 0.001) between group II Chromium group (Cr gp) over group I (L- carnitinegroup) after administration of drug. Regarding Hepatic enzymes; alanine aminotransferease (ALT) showed a statistically significantly lower values (P< 0.001) between Group II (82.8±3.7) over Group I (94.8±3.6) after administration of drugs. While total cholesterol and triglycerides showed statistically significant lower values in group II over group I. Also low density lipids (LDL) gp showed a statistically significant lowering effect [246.5±11.7], (p<0.001), after administration of Cr Pi more than L- carnitine. Conclusion: In this study we tried to compare a known drug (Chromium Picolinate) which is used a lot to improve obesity, with another drug (L- Carnitine) which is not well used for obesity or fatty liver, and discuss the effect of each of them. Each drug showed a great effect in different measurement which lead us that combination of both would have an amazing effect upon obese and fatty liver.

Keywords: Effect; Chromium; Piclonate; versus; L-Carnitine; High fat Diet; rat

1. Introduction:

The global prevalence of overweight and obesity is increasing rapidly worldwide among all ages, where high dietary fat intake leads to dramatic complications and is associated with alterations in liver chemistry and structure[1,2], hyperlipidemia[3], fatty liver[4], type II diabetes mellitus[5] and cardiovascular diseases[6], increased risk of liver damage and hepatocellular degeneration.

Several pharmacological agents such as insulin-sensitizing agents may be used to reduce or control the body weight and obesity. One of such agents, chromium (Cr) has been examined in some animal studies and clinical studies for its anti-obesity effects[7]. Cr is essential for the maintenance of normal metabolism of carbohydrate and lipids[8]. Inadequate amounts of Cr may result in improper functioning of the metabolic process and lead to a number of physiological disorders that increase risk for diabetes and cardiovascular diseases including elevated levels of glucose, triglycerides, total cholesterol, reduced HDL-cholesterol and impaired immune function[9,10,11]. Cr complexes have also been shown to reduce oxidative stress in diabetic rats[12,13]

As known, L-Carnitine, a nutritional element, Carnitine is a quaternary ammonium compound which is biosynthesized in the body from the essential amino acids lysine and methionine.[14]. It is supplemented in foods for healthy humans. It lowers lipid levels in the blood, and reduces high fat-induced obesity[15,16]. L-Carnitine is involved in long-chain fatty acids transporting from cytosol to the mitochondria matrix[17], which is required for facilitating lipid metabolism and reducing the storage oflong-chain fatty acids in adipose. It is found in animal products like meat, fish, poultry, and milk are the best sources, In general, the redder the meat, the higher its carnitine content while dairy products contain little fraction of it.[18]L-Carnitine supplementation could prevent irregular feeding-induced lipid metabolism disorder. However, whether L-Carnitine may affect the disorder of circadian rhythm and lipid metabolism of mice subjected to prolonged circadian disruption is still not reported[19]. Carnitine homeostasis reflects the balance among absorption from the diet, endogenous biosynthesis, and efficient renal reabsorption[20]. In general, L-carnitine is not required for short- and medium-chain fatty acids to enter the mitochondrial matrix as described before, but is necessary for long-chain fatty acids to do so.[21]

As a strong relationship exists between Body mass Index (BMI) and all-cause mortalityhas been

founded[22]. Obviously the need for natural supplements to decrease weight and help correction of some of complication became a very strong world need.[23]Which encourage us to study and assess the effect of organic chromium Piclonate and L- carnitine on rats feed on high fat diet with increased liver enzymes, cholesterol and triglycerides.

2. Materials and Methods

Animals and diets

Male albino rats (n = 60, 4 weeks old) weighing 120-150 g were purchased from Pharos University Laboratory Animal Research Center (Alex, Egypt). Control group (n=20), Group I (n=20), and Group II (n=20). All procedures involving rats were conducted in strict compliance with relevant laws of Animal Welfare.

The animals were housed at the temperature of 22 ± 2°C, humidity of 55 ± 5%, and with a 12/12 h light/dark cycle throughout the experiment. The experiment was conducted under the protocol approved by the Pharos University.

Rats were fed standard diet (12% of calories as fat) or high fat diet (HFD, 40% of calories as fat). During the animal experimentation, rats in the treatment group I were supplemented with L-Carnitine (Mepaco-Medifood), group II were supplemented with Chromium Picolinate (Mepaco-Medifood) viadrinking water. Ingredients and chemical composition of the basal (control) diet are shown in (Table 1). The diets were stored at 4°C cold chamber.

Experimental Design

After 1 week of adaptation period, the rats were randomly divided into three groups as (i) control group: rats were fed a standard diet (12% of calories as fat); (ii) Group I: L- carnitine group and group II: Chromium Picolinate (Cr Pi) group, both groups of rats were fed a high-fat diet (40% of calories as fat) first (according to table 1) for 60 days.

Table (1): Ingredient and nutrient composition of the diets[24]

Ingredients (g/kg)	Normal Diet	High Fat Diet (HFD)
Casein	200.0	200.0
Starch	615.0	145.0
Sucrose	-	150.0
Beef tallow	-	80.0
Corn oil	-	400.0
Cellulse	50.0	50.0
Vitamin -Mineral Premix1	50.0	50.0
DL-Methionine	3.0	3.0
Choline chloride	2.0	2.0

Vitamin-mineral premix provides the following (per kg): all-trans-retinylnacetate, 1.8 mg; cholecalciferol, 0.025 mg; all-rac-a-tocopherol acetate, 12,5 mg; menadione (menadione sodium bisulfate), 1.1 mg; riboflavin, 4.4 mg; thiamine (thiamine mononitrate), 1.1 mg; vitamin B-6, 2.2 mg; niacin, 35 mg; Ca-pantothenate, 10 mg; vitamin B-12, 0.02 mg; folic acid, 0.55 mg; d-biotin, 0.1 mg. manganese (from manganese oxide), 40 mg; iron (from iron sulfate),12.5 mg; zinc (from zinc oxide), 25 mg; copper (from copper sulfate), 3.5 mg; iodine (from potassium iodide), 0.3 mg; selenium (from sodium selenite), 0.15 mg; choline chloride, 175 mg.[25](23).

After the routine analysis showed elevation in liver enzymes and high lipid profile, L- carnitine group: rats were received L- carnitine; which was dissolved in water and administered according to (table 2) Cr Pi group: was dissolved in water and administered according to (table 2) for 60 days.

Table (2): Drug and doses

Group I	Group II
L- carnitine daily dose	Chromium Picolinatedaily dose
350mg/1ml water	24.85mg/1ml water

Laboratory Analyses

For the measurement of biochemical markers, samples were taken from the retro-orbital puncture under light ether anesthesia. Blood samples were centrifuged at 3000 g for 10 min and serum was separated. Fasting glucose concentrations, lipid profile, liver function were determined.

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp**).** The Kolmogorov-Smirnov and Shapiro wilk tests were used to verify the normality of distribution of variables, **ANOVA** was used for comparing the different studied groups and followed by **Post Hoc test (Tukey)** for pairwise comparison for normally distributed quantitative variables while **Paired t-test** was assessed for comparison between different periods. **Kruskal Wallis test** was used to compare different groups for abnormally distributed quantitative variables and followed by **Post Hoc test (Dunn-Bonferroni)** for pairwise comparison, While **Wilcoxon signed ranks test** was assessed for comparison between different periods. Significance of the obtained results was judged at the 5% level.

Table (3): Comparison between the two studied groups according to different parameters

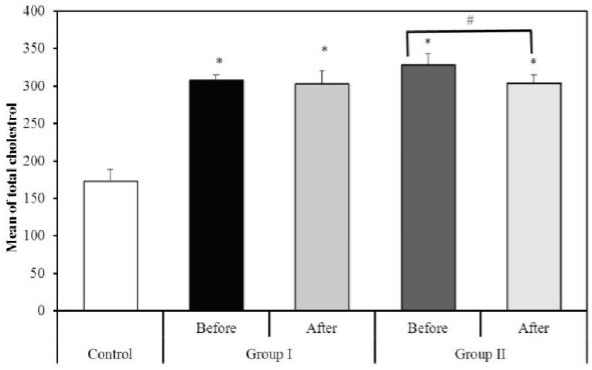
	Control (n = 30)	Group I		Group II		p_1	p_2
		Before (n = 30)	After (n = 30)	Before (n = 30)	After (n = 30)		
FBS	83.6±8.4	104.4±4.6	95.4±5.5#	105.1±3.7	84.3±3.7#		
p_3		<0.001*	<0.001*	<0.001*	0.891	0.873	<0.001*
Urea	42.0±1.8	42.0±1.8	42.0±2.0	47.3±2.6	45.8±2.6#		
p_3		0.998	1.000	<0.001*	<0.001*	<0.001*	<0.001*
Creat	1.0(0.8–1.0)	1.0(0.8–1.0)	1.0(0.8–1.1)	1.0(0.9–1.1)	1.0(0.9–1.1)		
p_3		1.000	0.486	0.001*	0.003*	0.001*	<0.001*
ALT	65.5±4.1	100.6±3.2	94.8±3.6#	104.7±4.1	82.8±3.7#		
p_3		<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
AST	83.3±4.9	173.3±7.4	157.0±4.4#	189.9±3.4	159.0±4.6#		
p_3		<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	0.211
Ch	172.9±15.4	307.4±7.2	302.5±18.1	328.3±14.9	303.7±10.9#		
p_3		<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	0.946
TG	82.0(70.0–94.0)	125(115–145)	118(100–128)#	125(115–145)	98(90–118)#		
p_3		<0.001*	<0.001*	<0.001*	<0.001*	1.000	<0.001*
HDL	38.8±3.3	32.3±1.7	34.3±2.8#	32.4±1.7	37.2±2.2#		
p_3		<0.001*	<0.001*	<0.001*	0.067	0.985	<0.001*
LDL	117.7±15.5	249.7±8.2	245.2±18.2	270.5±15.6	246.5±11.7#		
p_3		<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	0.940

Normally quantitative data was expressed in **mean ± SD**, **not normally** distributed data was expressed in **median (Min. - Max.)**

#: Statistically significant between before and after in each group, p_1: p value for comparing between Group I and Group II before

p_2: p value for comparing between Group I and Group II after, p_3: p value for comparing between control and each other groups

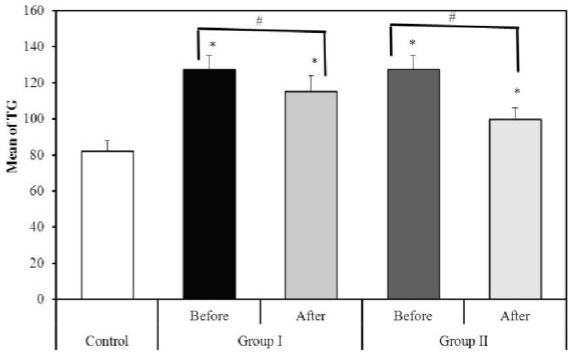
*: Statistically significant at $p \leq 0.05$



#: Statistically significant between before and after in each group

*: comparing between control and each other groups

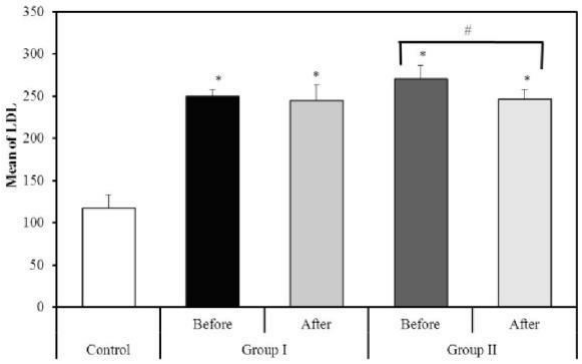
Figure (1): Comparison between the two studied groups according to Cholesterol



#: Statistically significant between before and after in each group

*: comparing between control and each other groups

Figure (2): Comparison between the two studied groups according to TG



#: Statistically significant between before and after in each group

*: comparing between control and each other groups

Figure (3): Comparison between the two studied groups according to LDL

3. Results:

Analytical results between three groups were represented in table (3). Feeding rats with high-fat diets resulted in the slightly increasing body weight gain and the significantly increasing body mass/body length ratio (by 10%).

As for Fasting blood sugar (FBS) there was statically significantly lower values (SD=84.3±3.7, P< 0.001) between group II Chromium group (Cr gp) over group I (L- carnitine group) after administration of drug.

Regarding Hepatic enzymes; alanine aminotransferease (ALT showed a statistically significantly lower values (P< 0.001) between Group II (82.8±3.7) over Group I (94.8±3.6) after administration of drugs, While AST showed a statistically significantly lower values (P< 0.001) between both Group I, Group II comparing before and after drug within the same group, but did not show statistically difference between groups after administration of drugs.

As for Total Cholesterol (Ch) there was a statistically significant decreased values between both groups and Control group, with significant lower value in group II after administration of chromium Picolinate (303±10.9, p<0.001).

Regarding Triglycerides (TG), Cr Pigp showed a great lowering effect than the L- Carnitinegp as there was a statistically significant lower values, as mean of Cr Pi gp II was [98(90-118), p<0.001] while mean for L- Carnitine gp I [118(100-128)].

As for low density lipids (LDL) Also Cr Pigp showed a statistically significant lowering effect after administration of the drug [246.5±11.7], (p<0.001), although there was a decreased difference between groups after administration of drugs, it was not statistically significant (P=0.940) between both groups after administration of drugs.

4. Discussion:

The prevalence of Fatty liver disease has been increasing worldwide and its spectrum ranges from simple steatosis, non-alcoholic NASH, advanced fibrosis and cirrhosis.[26] A number of studies both on diabetic animals and diabetic patients reported that CrPi supplementation may be beneficial, as evidenced by decreased blood glucose, glycosylated hemoglobin, and cholesterol values or decreased insulin requirements after Cr Pi supplementation.[27]On the other hand, there are also clinical trials showing that supplementary CrPi did not improve significantly blood biochemistry indices[28]. While the essentiality of chromium for humans has been recently questioned by researchers; the pharmacological dosages of this element improved insulin sensitivity in experimental animals and diabetic subjects[29], which need more investigation to fill the gap between experimental and application to human beings.

Mitochondrial abnormality is well documented in Non-alcoholic Fatty Liver Disease

Nonalcoholic Fatty Liver Disease (NAFLD) and a suggested target for treatment[30] therefore the choice of L- carnitine was made to improve the oxidation of fatty acid deposited in liver which was documented in several studies to improve mitochondrial function[31] and biosynthesis[32].

In our study Chromium Pollinate showed significantly and statistically decreased in FBS. Which agree with the results done by Jaroslav Racek et al done on diabetic patients receiving chromium FBS levels decreased significantly during the first supplementation period (period B, 100 µg of chromium daily); doubling the chromium dose in period C led to a further decrease of FPG level; however, this decrease was not statistically significant[33].

Chromium Pollinate also showed significantly and statistically decreased level of both AST and ALT. This is also in agreement with Doddigarla Z et al, as they deduced that chromium Pollinate showed a significant effect on rat fed on it for 8 weeks and was on high carbohydrate diet where total cholesterol, triglyceride significantly decreased while HDL increased, also when chromium combined with melatonin showed even better results. This was documented with histological changes in different groups.[34]

As for L-carnitine in the present study there were significantly and statistically decreased in the level of FBS, hepatic enzymes (AST and Alt), and lipid profile. this agree with Ji Cheol Bae et al[35], where Treatment with Carnitine-orotate complex improves serum to the normal range, a significant decrease from baseline in HbA1c, However, no significant changes

were seen in fasting glucose, HOMA-IR, HOMA-B, lipid profile.

This is in agreement with Xiaoxian Xie et al; who feed mice with L-Carnitine where they was subjected to chronic jet-lag, the serum GPT and GOT activities were decreased as compared with those in the jetlag group that were not on L Carnitine, but they did not exhibit obvious differences in the concentrations of serum total cholesterol and TC/HDL-C ratio among different groups. More importantly, quantitative real-time polymerase chain reaction (qRT-PCR) analysis indicated that L-Carnitine supplementation would effectively counteract the negative alterations in gene expression which related to lipid metabolism and circadian rhythm.[36]

Wu T et al also deduced that L-Carnitine supplementation showed reduced obesity caused by high-fat diet and irregular feeding-induced obesity, and it is beneficial for lowering blood and hepatic lipid levels namely GPT, GOT and TG.[37]

Conclusion:

As the number of patients with a fatty liver is increasing and studies with the long-term objective of improving the fatty liver is strongly needed, therefore new therapies must be developed to combat such illness. Again this emphasizes the importance of such research to encourage more researchers to combine more pharmacological items to solve such an issue.

In this study we tried to compare a known drug (Chromium Picolinate) which is used a lot to improve obesity, with another drug (L- Carnitine) which is not well used for obesity or fatty liver. We recommend strongly associating both drugs with each other using different doses in Vivo study, which may ultimately assist clinicians in controlling fatty liver and hyperglycemia.

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