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EFFECT OF NUTRITIONAL AND EXCESSIVE LEVEL OF SELENIUM ON ANTIOXIDANTS STATUS AND LIPID PROFILE OF RATS FED A HIGH CHOLESTEROL DIET

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ABSTRACT

This study was carried out to investigate the effect of nutritional and excessive supplementation of selenium on antioxidants & lipid profile in the presence and absence of high cholesterol diet (HCD).The effect of two different doses (6mg (LD Se) and 300mg (HD Se) Se/kg/body weight) on HCD-induced oxidative stress was investigated. At the end of experiment, serum samples were collected for analysis of serum lipid profile and rats were dissected for collection of tissues of liver, heart and kidneys for tissue antioxidant status determination. The obtained results revealed that administration of Se with low doses caused a significant decreased in serum total cholesterol, triglycerides, LDL-cholesterol levels and caused increase in HDL-C levels compared to HD-Se group.

A significant decrease in CAT activity in HD-Se group in Liver and heart tissue . The obtained results revealed a significant increase in hepatic GSH level in G3 in comparison with G2 and a significant decrease in GSH in kidney Level in G2,G4 in comparison with G1 .Our results revealed a marked increase in liver and kidney GST activity of G5 fed LD-Se in comparison with G1and G2. Heart GPx activity increased in G5 in comparsion with G2 The results of the Current Study revealed a non significance changes in Kidney ,liver and heart SOD activities.

INTRODUCTION

Selenium is an essential trace element that is an integral part of many selenoproteins**.** Selenium has been observed to have antiatherogenic function that suppressed peroxidation of lipids **(Alissa et al., 2003).**

Functionally, there are two families of selenium-containing enzymes, including glutathione peroxidases **(Arthur, Bermano et al. 1995)** and thioredoxin reductase**(Howie, 1998)** which control tissue concentrations of highly reactive oxygen-containing metabolites. Selenoenzymes may protect against the damaging effects of hydrogen peroxide or oxygen-rich free radicals as they catalyses the destruction of hydrogen peroxide or lipid hydroperoxides

Se dietary intake may influence the pathogenesis of various CVDs **(Blankenberg, et al. 2003, Zhou, Ji. 2007,Wu and Huang 2004)**. They reported that long-term Se deficiency in the rat is significantly decrease T-AOC, GPx, and CAT level and activities in arterial wall, and a subsequent Se supplementation led to an antioxidant capacity increase in both arterial wall and vascular tissues.

Se supplementation for 3 days through intraperitoneal injection of sodium selenite increased ACh-induced endothelium-dependent relaxation of rat aortic rings in comparison with those of control rats **.**

During selenium deficiency hepatic stores of Se might be insufficient to allow the synthesis of 5'-DI. 1 ppm of Se supplementation caused GSH-Px and 5'-

deiodenase levels to increased in control rat as well as HCD fed groups. This could be due to the level of these two enzymes increased after Se supplementation. During Se depletion, the level of T3 was decreased as well as on HCD feeding due to decreased T4 conversion to T3 in the liver and other parts as 5'- DI expression decreased **(Dhingra and Bansal 2005)**.

Se deficiency caused the LDL-R activity and mRNA expression down regulation compared to adequate Se diet this could be due to the decreased T3 level during Se deficiency. T3 regulates LDL-R expression via modulation of SREBP-2 (sterol regulatory element-binding protein- 2) gene expression. SREBP-2 is a major transcriptional regulator of cholesterol uptake through LDL-R **(Shin and Osborne 2003 , Dhingra and Bansal 2005**).

Iizuka, Sakurai et al. (2001) evaluated the influence of inorganic selenium on metabolism of lipid in rats fed a HCD and showed that Se repressed total cholesterol, free fatty acid and triacylglycerol concentrations in the serum a Consequently **Asha and Indira (2004)** concluded that Se and ascorbic acid supplementation minimized hyperlipidemia by enhancing catabolism and lowering synthesis.

Se supplementation lowered plasma total and LDL cholesterol levels and increased HDL- c levels, while Se deficiency had an obverse effect **(Mazur et al., 1996 ; Wojcicki et al., 1991 ; Dhingra & Bansal , 2005).** Previous studies examined the selenoprotein function in cardiovascular disease by analysis of oxidative stress under states of selenium deficiency or supplementation and showed that LDL-receptor activity and mRNA expression were increased significantly after Se supplementation, which mediated by the iodothyronine deiodinases (DIOs) **(Ness, et al,. 1998; Dhingra & Bansal . 2004).**

Abnormally high cholesterol levels are strongly linked to the cardiovascular diseases. High cholesterol diet results in deposition of cholesterol in the arterial walls **(Descamps, et al,.2003 and Castro, et al,. 2005).** It was found that 1 ppm selenium supplementation with high fat diet (HFD) fed rats prohibited the atherosclerosis occurence as studied by Scanning electron microscopy (SEM) of aorta in which the serum selenium levels lowered in HFD group compared to the control group. It is known that high selenium levels lead to tissue damage due to the elevated production of reactive oxygen species (ROS**) (Gad and Abd El-Twab 2009; Spallholz et al., 2004)** .The purpose of this study is aimed to find effect of nutritional and excessive level of selenium on antioxidants status&lipid profile of rats fed a high cholesterol diet.

MATERIAL AND METHODS

Experimental design:

Animals grouping:

In order to establish the aim of this experiment, thirty rats weighed from 180 to 210g, divided into six groups, each of five rats. GroupI (control negative group) where rats have received standard diet pellets for one month. GroupII(control positive) where rats were fed a HCD (6gm/kg/body weight) .Group III Rats were fed 300mg/kg/bodyweight dose of selenium bi selenite (High diet selenium) daily for one month . the wanted selenium dose was made by dissolving wanted amount of sodium selenite in distilled water and administered daily using an oral stomach tube for one month. Group IV: Rats of the present group received an experimental ration containing (HCD) plus (HDSe) with doses 6gm cholesterol/kg/bodyweight and 300mg selenium/kg/body.GroupV: rats were provided with daily doses of 6mg selenium/kg/body weight (Low dose selenium) GroupVI: rats were administered by High cholesterol diet plus LDSe(LD-Se-HC) with potions 6gm cholesterol/kg/bodyweight and 6mg selenium/kg/body weight. At the end of experiment, blood samples were collected from rats under diethyl-ether anesthesia. Serum samples were collected for determination of total cholesterol concentration in whole blood ,

high density lipoprotein - cholesterol concentration, triglycerides concentration **,**low density lipoprotein concentration **(Burstein M. et al. ,1970).**

At the end of experiment rats were dissected to obtain (liver, heart,kidney,wich then divided longitudinally into two equal parts .The first part of each organ was homogenized according to **Fernandez-Botran et al., (2002)** for determination of catalase activity **(Aebi, 1984),** reduced Glutathione level **(Beutler et al., 1963),** Glutathione S-transferase activity**(Habig et al., 1974),** Glutathione Peroxidase activity **(Paglia and Valentine 1967).** Superoxide Dismutase activity **(Nishikimi et al.,1972)** The second part was kept in 20% formalin for histopathology examination using Hematoxylin and Eosin**.**

Table (1): The effect of Se supplementation on lipid profile of rats (mg/dl)

Groups	Total cholesterol	HDL-C	Triglycerides	LDL-C
Group I	81.41 ± 4.56^{bc}	40.58 ± 3.85^{b}	83.26 ± 5.56^{d}	36.66 ± 9.16^{b}
Group II	122.1 ± 18.93^{ab}	52.70 ± 2.29^{ab}	122.17 ± 8.48^{bc}	123.2 ± 7.95^{a}
Group III	76.13 ± 2.53^{c}	48.16 ± 3.97^{b}	139.6 ± 8.26^{b}	101.9 ± 9.31^{a}
Group IV	143.1 ± 6.18^{a}	45.00 ± 2.01^{b}	177.7 ± 8.47^{a}	132.7 ± 16.57^{a}
GroupV	45.6 ± 3.5^{c}	48.5 ± 3.99^{b}	90.47 ± 8.10^{cd}	41.43 ± 7.31^{b}
GroupV I	85.27 ± 2.14^{bc}	71.55 ± 9.12^{a}	101.8 ± 1.83^{cd}	29.41 ± 1.91^{b}

The different letters superscripts in the same column means significant changes
The same letters superscripts means in the same column means a non significant changes

Table (2) : The effect of Se supplementation on tissue antioxidant in rats

Antioxidant	Organ	Group I	Group II	Group III	Group IV	Group V	Group VI
CAT Activity	**Liver**	$0.56\pm.02^{a}$	$0.58\pm.01^{a}$	$0.19\pm.19^{b}$	$0.65\pm.02^{a}$	$0.56\pm.02^{a}$	$0.50\pm.00^{a}$
	Kidney	$0.31\pm.02^{b}$	$0.60\pm.02^{a}$	$0.33\pm.05^{b}$	$0.26\pm.02^{b}$	$0.33\pm.02^{b}$	$0.41\pm.089^{ab}$
	Heart	$0.49\pm.04^{ab}$	$0.59\pm.01^{a}$	$0.30\pm.03^{b}$	$0.61\pm.098^{a}$	$0.61\pm.01^{a}$	$0.54\pm.04^{ab}$
GSH Level	**Liver**	$32.36\pm.23^{ab}$	$23.1\pm.58^{b}$	33.26 ± 1.036^{a}	$32.8\pm.58^{ab}$	29.26 ± 1.39^{b}	$32.16\pm.43^{ab}$
	Kidney	33.7 ± 1.17^{a}	25.29 ± 1.66^{b}	$34.41\pm.58^{a}$	25.99 ± 2.26^{b}	30.73 ± 1.00^{ab}	32.83 ± 1.24^{a}
	Heart	$32.13\pm.23^{ab}$	$28.34\pm.95^{b}$	$31.93\pm.37^{ab}$	$32.16\pm.59^{a}$	$32.21\pm.80^{a}$	33.5 ± 1.33^{a}
GST Activity	**Liver**	$0.31\pm.02^{b}$	$0.2\pm.03^{b}$	$0.53\pm.12^{ab}$	$0.20\pm.09^{b}$	$0.73\pm.05^{a}$	$0.43\pm.08^{ab}$
	Kidney	$0.08\pm.056^{c}$	$0.27\pm.03^{bc}$	$0.8\pm.04^{a}$	$0.22\pm.06^{c}$	$0.64\pm.12^{a}$	$0.60\pm.09^{ab}$
	Heart	$1.11\pm.321^{a}$	$0.39\pm.05^{b}$	$0.23\pm.03^{b}$	$0.26\pm.06^{b}$	$0.19\pm.017^{b}$	$0.084\pm.016^{b}$
GPx Activity	**Liver**	183.9 ± 15.19^{b}	211.9 ± 2.48^{ab}	255.02 ± 11.40^{a}	105.6 ± 16.94^{c}	259.6 ± 23.44^{a}	245.2 ± 6.028^{ab}
	Kidney	136.3 ± 19.47^{c}	145.3 ± 5.12^{c}	547.05 ± 22.54^{a}	419.1 ± 17.04^{ab}	395.5 ± 17.20^{b}	182.6 ± 57.53^{c}
	Heart	101.6 ± 22.89^{bcd}	54.47 ± 5.15^{d}	173.1 ± 29.11^{ab}	146.4 ± 5.96^{ac}	214.9 ± 2.90^{a}	90.79 ± 23.44^{bc}
SOD Activity	**Liver**	365 ± 2.17^{a}	343.3 ± 15.19^{a}	356.3 ± 2.59^{a}	$369.5\pm.96^{a}$	366.6 ± 2.82^{a}	369 ± 2.59^{a}
	Kidney	90.62 ± 4.28^{a}	83.1633 ± 7.99^{a}	82.2867 ± 2.86^{a}	87.1 ± 2.39^{a}	95.18 ± 1.24^{a}	87.4967 ± 3.32^{a}
	Heart	97.62 ± 1.054^{a}	85.65 ± 4.68^{a}	87.39 ± 5.90^{a}	83.8 ± 6.10^{a}	93.87 ± 2.25^{a}	97.12 ± 1.11^{a}

The two different letters superscripts in the same raw means significant changes

The same letters superscripts means in the same raw means a non significant changes

RESULTS & DISCUSSION

In table (1),**(CHOL)** levels increase in G2,G4 due to HCD and decrese in G3,G5 due to due to supplementation of different doses of selenium and these results agree with the findings of **Dhingra and Bansal (2006)** who studied the role of Se supplementation in modulation of hyper-cholesterolemia induced changes in apolipoprotein B (apoB).Their result reveled that ApoB levels increased significantly on 2% cholesterol-supplemented diet feeding. 1 ppm Se supplementation, apoB levels decreased significantly.

HMG-CoA reductase mRNA expression decreased significantly on cholesterol-supplemented diet feeding and on 1 ppm Se supplementation.

Since HMG-CoA reductase is the rate-limiting enzyme in cholesterol biosynthesis, this observation suggests an increased hepatic cholesterogenesis in Se deficient animals. As previously discussed by **SCrougne et al., (1995).** The concentration of **HDL** were increased in G6 in comparison to G1 due to supplementation of selenium is responsible for the up regulation of LDL receptor(LDL-R) activity as explained by **Dhiangra and Bansal., (2006)**

levels of TG increase significantly in G3 and G4 due to hypertriglyceridemia, which is usually associated with decreased HDL-cholesterol (HDL-C) and increased LDL

The group of rats fed on high cholesterol diet and low doses of Se, TAG levels were decreased and lowered than those of G2 that indicated that high doses of Se may have an adverse side effect on the TG metabolism. TAG concentrations were inversely correlated with the predominant LDL and the concentration of LDL was markedly increased in G4 in comparison to G2, where rats fed on high cholesterol diets and high doses of Se in comparison to G5 and G6.

LDL- C levels were markedly lowered in comparison to G2, which is suggested due to supplementation of Se.

The supplementation of selenium is responsible for the up regulation of LDL- C levels due to Apolipoprotein B (apoB) contains ligand-binding domain for the binding of LDL to LDL-R site, which enables the removal of LDL. Selenium regulates Apo lipoprotein B expression through selenoenzyme**,(Dhiangra and Bansal.,2006**)nd HDL-Concentration. The relationship between TAG concentration and LDL particles' size was evaluated by measuring MDA-LDL **(Kondo et al., 2001).**

In table(2), the results of the current study revealed a marked significant decrease in hepatic **CAT** activity in G3 in comparison with G1 and G2 . This is suggested to be due to the impairment of the process and activity of the biological antioxidant defense mechanism through oxygen free radical generating processes **(Yan and Spallholz**, **1993)**. A significant decrease in the renal catalase activity in all experiment groups G3,G4,G5 and G6 in comparison with G2 . This is suggested to be due to oxidative stress on renal tissue which is due to oxygen free radicals which is generated due to Selenium as excess amount of selenium generates and reacts with thiol compounds such as reduced glutathione, composing seleno-diglutathione **(BALOGH & Miklossa ., 2004)** . Cardiac catalase activity was decreased in G3 in comparison to G1 and G2. This is suggested to be due to the toxic effect of Se on myocardium as suggested by **Latheef et al., (2014)**

Se supplementation was significantly increased ($p<0.05$) the antioxidant capacity GSH in rats in G3,G4, G5 and G6. Hepatic GSH is an essential tripeptide which plays an important role in inhibiting the lipid peroxidation and detoxification of hydrogen peroxide with the added glutathione peroxidase enzyme **(Peuchant et al., 1994).** This is suggested due to Se increased antioxidant enzymatic activities, and GSH was able to remove reactive oxygen species and the levels of renal GSH in G3 were increased in comparison to G1($p\leq0.001$), it may indicate the effectiveness of Se in increasing cellular GPx activity and plasma Se level as suggested by (**Sedighi et al.,2014**)

There is a significant (P<0.05) increase in hepatic GST activity in G5 in comparison with G1 and G2. This is due to multiple mechanisms involving free radical scavenger properties, attenuating lipid peroxidation and increasing the antioxidant status as suggested by **Winston and Di Giulio, (1991)**

While in G4 the levels of Hepatic GST were markedly decreased in comparison to G1.It may indicate the toxic effect of high selenium dose on liver as suggested by(**Latheef et al., 2014)**

There is a significant increase in hepatic GPx activity in G3 in comparison with G1.This due to Selenium-dependent glutathione peroxidase (Se-GPx) activities in plasma, erythrocyte and supernatants of centrifuged tissue homogenates . Amarked increase in renal GPx activity in G3 in comparison with G1 and G2. The result of this study showed a non-significant change between groups in SOD activity so further investigation is needed.

Histopathological examination of liver was normal in G I showed a normal hepatocytes in normal radial arrangement around central vein, where G2 showed lytic necrosis of hepatocytes with focal hemorrhage in hepatic parenchyma due to degenerative changes of the hepatocyte due to high CHOL diet leading to the Fatty liver degeneration . This is an agreement with **Kengkoom et al., (2013)**where in G3,G5,G6 the liver showed a normal hepatocytes , normal portal area and normal hepatic architecture.

Histopathological structure of heart was normal in all groups except in G2 .It showed hemorrhage in myocardium and in coronary arteries of G2 of rats, granulomatous inflammation in perivascular tissue of coronary artery with vacuolation in the tunica intima of it, due to mononuclear phagocytes differentiation to macrophage after insertion in the intima. This is an agreement with the results of **Nassir et al., (1997)** and **Rafieian-Kopaei et al., (2014); Nelson, (2001) & Singh et al., (2002).** In Group 6, the histopathological structure of heart showed Severe hemorrhages around coronary artery displacing and necrotizing myocardial fibers, due to the induced hypercholesterolemia, which led to ischemic stroke in the heart **(Fitchett et al., 2008)**

Histopathological structure of kidney showed normal renal glomeruli and normal renal tubules lined by normal renal tubular epithelium in all groups except G2. In figure 6, a proliferation of mesangial cells and forming epithelial crescent of the renal glomeruls . Kidneys of G6 showed normal renal glomeruli with degeneration and necrosis of renal tubular epithelium due to induced hypertensive nephropathy caused by hyperlipidemia and atherosclerosis a explained by(**Wang et al., 2013)**

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الملخص العربي

تاثير مستوى التغذيه و المستوى الزائد من السيلينيوم على مضادات الاكسده وصورة الدهون فى الفئران المغذاه على عليقه عالية الكوليستيرول

الاء مصطفى - فهيم وحيش - محمد العدل

اجريت هذه الدراسة لاستبيان تاثير التغذية وزيادة معدل السيلينيوم علي حالة مضادات الاكسدة ومستوي الدهون في الفئران المغذاة علي عليقة غنية بالكوليسترول وقد تمت التجربة علي هذه الفئران في معمل الفسيولوجيا بكلية الطب البيطري- جامعة المنصورة علي عدد ثلاثين فار تم تغذيتها لمدة ثلاثين يوم وتم تقسيمها الي ستة مجاميع متساوية كل مجموعة مكونة من خمسة فئران وكانت المجموعة الاولي هي المجموعة الضابطة وتم تغذيتها بعليقة خالية من السيلينوم والكوليسترول والمجموعة الثانية تم تغذيتها بعليقة غنية بالكوليسترول بجرعة6 جم لكل كجم من وزن الجسم والمجموعة الثالثة تم تغذيتها بعليقة غنية بالسيلينيوم بجرعة تقدرب ٣٠٠مجم لكل كجم من وزن الجسم والمجموعة الرابعة تم تغذيتها بعليقق غنية بكل من السيلينيوم والكولوسترول بجرعة تقدر ب ٣٠٠مجم سيلينيوم لكل كجم من وزن الجسم و٦جم كوليسترول لكل كجم من وزن الجسم والمجموعة الخامسة تم تغذيتها بعليقة تحتوي علي جرعة قليلة من السيلينيوم بمعدل ٦مجم سيلينيوم لكل كجم من وزن الجسم والمجموعة السادسة تم تغذيتها بعليقة تحتوي علي جرعة عالية من الكوليسترول تقدر ب ٦جم كوليسترول لكل كجم من وزن الجسم وجرعة قليلة من السيلينيوم تقدر ب ٦مجم لكل كجم من وزن الجسم .

في نهاية التجربة تم تجميع عينات الدم لقياس مستوي الدهون ومستوي الكوليسترول والليبوبروتين كوليسرول عالي الكثافة ومنخفض الكثافة وايضا مستوي الدهون ثلاثية الجلسرول

وتم تجميع عينات الانسجة(الكبد والكلي والقلب) لقياس مستويات الكتاليز ومستويات الجلوتاثيون الناقل والجلوتاثيون المختزل والجلوتاثيون بيرواكسيديز و سوبر اكسيد ديسميوتيزبالاضافة الي ذلك تم التعرف علي التغيرات التي تمت في انسجة الكبد والكلي والقلب عن طريق عمل شرائح الهستوباثولوجي (التشريح المرضي) ولقد كانت النتائج كالتالي .

زيادة معدل الكوليسترول فى المجموعة الثانية والرابعة والخامسة والسادسة مقارنا بالمجموعة الضابطة وزيادة مستوى الليو بروتيين كولستيرول عالى الكثافة فى المجموعة السادسة وزيادة الليبوبروتين منخفض الكثافة فى المجموعة الثالثة والرابعة وزيادة الدهون ثلاثية الجلسرول ى المجموعة الثالثة والرابعة. وكذالك زيادة مستوى الجلوتاثيون المختزل فى نسيج الكبد فى المجموعة الثالثة بينما فى نسيج الكلى اظهر نقص فى المجموعة الثانية والرابعة كما حدث زيادة متوسط نشاط الجلوتاثيون الخامل فى نسيج الكبد فى المجموعة الخامسة .

واظهر التشريح المرضى نزيف فى عضلة القلب والشريان التاجى وفى الكلى فى المجموعة الثانية وجد تكاثر لخلايا المسينجيال المكونة لانابيب الكلية بسبب انحلال الكلية نتيجة ارتفاع ضغط الدم وسببه زياده فى تركيز الدهون وتصلب الشرايين.