EXPERIMENTAL CLINICOPATHOLOGICAL STUDIES ON SELENIUM TOXICITY IN RATS

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ABSTRACT

This work aimed to study the effect of increasing selenium on some hematological, biochemical and immunological parameters in addition to study their effects on some pathology in albino rats. This study performed on 75 male albino rats, which divided into 3 equal groups (each one contains 25 rats).The first group (control group), received no treatment. The second group (Se1group), received low dose of selenium, 2ppm sodium selenite/liter in drinking water for 3 months. The third group (Se2 group), received high dose of selenium, 4ppm sodium selenite/liter in drinking water for 3 months. Collection of blood samples and separation of serum samples at the end of the 1st, 2nd and 3rd month of experiment for hematological, serum biochemical and immunological analysis. Tissue specimens were collected at the end of the 1st, 2nd and 3rd months of experiment for histopathological examination. Administration of high dose of selenium (4ppm) at the third group resulted in, significant decrease in live body weight of rats, anemia which was macrocytic hypochromic, also we recorded decrease in total leukocytic count with significant decrease in neutrophil count. Regarding serum biochemical analysis we reported, significant elevation in ALT, AST, ALP and total bilirubin.

On the other hand there were significant decrease in total protein and albumin. IL 1β was increased after 2months then decreased after 3months.

Hisopathological examination of tissue specimens showed serious lesions in liver, kidney, thymus, intestine and spleen. It concluded that high doses of selenium revealed regenerative anemia, significant undesirable changes in serum biochemical and immunological parameters. Also, there were multiple pathological lesions in different organs.

INTRODUCTION

Selenium, an essential trace element, plays an important role in mammalian biology. The best known role of selenium is attributed to its presence in glutathione peroxidases (GPx) and thioredoxin reductase (TrxR). GPx catalyzes the reduction of hydrogen peroxide and a variety of organic hydro-peroxides using glutathione (GSH) as the hydrogen donor to water and corresponding alcohols. TrxR exerts antioxidant action through catalyzing the reduction of oxidized thioredoxin by using NADPH as the electron donor. Addition-ally, TrxR possesses a number of other antioxidant functions, such as reduction of selenium-containing compounds; regeneration of ascorbyl radical, lipoic acid, and ubiquinone; and directly scaven-ging lipid peroxides and hydrogen peroxide **(Rayman 2000).** Desp-ite being an essential trace element, selenium in fact is toxic at a level not much higher than the beneficial requirement. For insta-nce, chemopreventive effects of selenium in animals usually occur in the range of 1–3 μg Se/g diet **(Ip and Ganther 1990).** Whereas chronic dietary selenium toxicity begins at 3–5 μg Se/g diet **Martin and Hurlbut (1976).** Moreover there is almost no survival of rats fed 16 μg Se/g diet and **(Koller and Exon 1986).** The present study was designed to investigate the toxic effects of selenium on the hematopoietic system, biochem-istry, immune system function and histopathology in rats.

MATERIALS AND METHODS:

Experimental design:

Seventy five male albino rats of Wistar strain (130±10 g, 10 to 12 weeks old) purchased from Laboratory Animal institute in Hellwan were used for the study. Animals were fed with comm.-ercially available standard and balanced rat ration and water was provided ad libitum. All animals were acclimatized for 2 week before experimentation.

The 75 rats were randomly divided into 3 equal groups (each 25 rat). The first group (Con) was control group, the second group (Se1) received selenium as sodium selenite (Na2SeO3, Loba Chemie, India. Batch No. G 065106) at a dose of 2ppm/liter in drinking water for 3 months, and the third group (Se2) received selenium as sodium selenite at a dose of 4ppm in drinking water for 3 months.

Blood samples were collected from heart puncture in heparinized tubes for the estimation of RBCs count, hemoglobin content, PCV value, TLC count and DLC of rats of different groups after 1st, 2nd and 3rd month of the expe-

riment. Blood samples were also collected in separate tubes and serum was separated for biochemical and immunological investigations. Tissue specimens were collected at the end of 1st, 2nd and 3rd month (kidney, liver, spleen, thymus, heart, intestine and pancreas) and fixed in 10% neutral formalin for histopathological examination.

HEMATOLOGICAL STUDIES:

Erythrocytes, Hb, PCV, MCV, MCH, MCHC, TLC and differential leucocytic count were performed according to **Jain (1986)**.

BIOCHEMICAL STUDIES:

Both ALT and AST activeities were assayed according to **Reitman and Frankel (1957)** using kits obtained from Quimica Clinical Aplicada (Spain).

Determination of ALP according to **Tietz (1976)** using kites provided by Scalvo diagnostic Italy. Amylase activity was assayed according to **Caraway et al., (1959)** using kits obtained from Scalvo diagnostic Italy. Total pro-tein was measured according to **Young (2001)** by kits provided by Scalvo diagnostic Italy. Albumin was assayed according to **Dumas and Biggs (1972)** using kits obta-ined from Scalvo diagnostic Italy. Serum uric acid was determined according **Caraway (1963)** using kits obtained from Bio Analytics USA. Creatinine was measured according to **Henry (1974)** using kits provided by Bio Analytics USA. Total bilirubin determined according to **Wahlefeld et al (1972)** using kits obtained from Bio Analytics USA. Calcium and phosphorus were measured according to (**Tiez 1976**) using kits obtained from Bio Analytics USA.

IMMUNOLOGICAL STUDIES:

Measurement of level of Interleukin-I beta according to **Chan and Perlstein (1987)** by kits purchased from Pierce Biotechnology, USA. Serum lysozyme activity was assayed according to **Parry et al., (1965)** using kits obtained from Sigma Aldrich, USA.

VI-STATISTICAL ANALYSIS:

Hematological, serum biochemical and immunological parameters were analyzed by analysis of variance (**ANOVA**) using SPSS 16 for window. Two groups were significantly different if P was statistically lower than 0.05 Statistical analysis was carried out with one way NOVA test (**Snedecor and Cochran, 1982).**

RESULTS

HEMATOLOGICAL RESULTS:

Selenium administration caused no changes in hematological parameters after the 1st month, while after 2nd and the 3rd month there were significant reduction in RBCs, Hb and PCV in Se2 group in compare with control group. On

the other hand there was significant increase in MCV value together with decrease in MCHC value in Se2 group in compare with control group. Total and differential leukocytic count revealed no significant change after the 1st month, but after the 2nd and 3rd month there were significant decrease in WBCs and neutrophil count in Se2 group in compare with control group **tables (1-4)**.

Table (1): Erythrogram in control, low selenium and high selenium groups (Mean ± S.E.) after two months.

Parametes & groups	RBC $10^6/\mu L$	Hb g/dL	PCV %	MCV fl	MCH pg	MCHC %
Con	7.84± 0.17a	13.87± 0.13a	40.7± 0.67a	51.90± 1.04c	17.7± 0.22a	34.11± 50.48a
Se1	7.69± 0.34a	13.36± 0.68a	42.0± 1.15a	54.99± 4.01c	17.4± 0.72a	31.86± 1.91a
Se2	5.0± 0.0b	8.17± 0.17b	36.33± 0.33b	72.67± 0.67b	16.33± 0.33a	22.48± 0.59b

The same Column not followed by the same letter differ significantly (P<0.05)

Table (2): Erythrogram in control, low selenium and high selenium groups (Mean ± S.E.) after three months.

Parameters & groups	RBC $10^6/\mu L$	Hb g/dL	PCV %	MCV fl	MCH pg	MCHC %
Con	8.27± 0.16a	13.53± 0.42a	41.0± 0.58a	49.58± 0.88d	16.37± 0.61a	33.05± 1.44a
Se1	8.17± 0.17a	13.33± 0.33a	40.0± 0.58a	49.04± 1.62d	16.35± 0.64a	33.33± 0.48a
Se2	5.7± 0.15b	7.33± 0.33b	35.33± 0.88b	62.0± 0.86c	12.9± 0.86b	20.79± 1.14b

The same Column not followed by the same letter differ significantly (P<0.05)

Table (3): Leukogram in control, low zinc and high zinc groups (Mean ± S.E) after two months.

Parameters & groups	TLC 10^3 / µL	Neutroph. 10^3 / µL	Lymph. 10^3/µL	Monocyt. 10^3/µL	Eosino. 10^3 / µL	Basophil 10^3 / µL
Con	10.04± 0.03a	3.69± 0.23b	6.62± 0.2a	0.06± 0.02aa	0.01± 0.01a	0.00± 0.00a
Se1	9.83± 1.02a	3.3± 0.08b	6.45± 0.03a	0.06± 0.02	0.001± 0.00a	0.00± 0.00a
Se2	8.67± 0.38b	2.22± 0.15c	6.38± 0.28a	0.06± 0.01a	0.01± 0.00a	0.00± 0.00a

The same Column not followed by the same letter differ significantly (P<0.05).

Table (4): Leukogram in control, low zinc and high zinc groups (Mean ± S.E) after three months.

Parameters & groups	TLC 10^3 / µL	Neu.roph. 10^3 / µL	Lymph. 10^3/µL	Monocyt. 10^3/µL	Eosino. 10^3 / µL	Basophil 10^3 / µL
Con	9.67± 0.67a	3.17± 0.12b	6.75± 0.46a	0.05± 0.01a	0.04± 0.01a	0.00± 0.00a
Se1	9.68± 0.16a	3.23± 0.13b	6.53± 0.16a	0.05± 0.01a	0.02± 0.01a	0.00± 0.00a
Se2	8.0± 0.29b	1.77± 0.15c	6.15± 0.23a	0.07± 0.00a	0.01± 0.01a	0.00 ±0.01a

The same Column not followed by the same letter differ significantly (P<0.05).

BIOCHEMICAL RESULTS:

There were no significant changes in ALT, AST, ALP, amylase, TP, Albumin, UA, creatinine, total bilirubin, Ca and Ph all groups after the 1st month. Meanwhile after the 2nd and 3rd months group Se2 showed significant elevation of ALT, AST, ALP, creatinine, uric acid and total bilirubin together with significant decrease in both total protein and albumin. Amylase, Ca and Ph showed no significant change in any group after the 1st and 2nd month **tables (5 and 6)**.

Table (5): Some serum biochemical parameters profile in control, low selenium, high selenium groups (Mean ± S.E) after two months.

Prameters & goups	ALT U/L	AST U/L	ALP (U/L)	Amylase (U/L)	TP gm/dl	Albumin gm/dl	Creatin mg/dl	Uric acid mg/dl	T. Bili. mg/dl	Ca mg/dl	Ph mg/dl
Con	33.67± 10.22c	42.67± 1.76c	165± 12.56b	862± 56.01b	6.17 ± 0.13a	3.50± 0.13a	0.48± 0.08b	2.63 ± 0.09c	0.22 ±0.04c	8.98± 0.69a	6.9± 0.65a
Sel	30± 3.84c	42.± 0.88c	181.67± 6.01b	858.33 ± 36.43b	5.93 ± 052a	3.58± 0.29a	0.52± 0.04b	2.53 ± 0.09c	0.18± 0.053c	9.33± 0.90a	8.23 ± 0.43a
Se2	61.67± 2.52a	88± 1.53a	266.67± 14.53a	772.67 ± 36.07b	3.4± 0.21b	1.6± 0.06b	0.75± 0.03a	3.6± 0.15a	1.23± 0.15b	8.61± 0.27a	7.1± 0.21a

The same Column not followed by the same letter differ significantly (P<0.05)

Table (6): Some serum biochemical parameters profile in control, low selenium, high selenium groups (Mean ± S.E) after three months.

Prameters & groups	ALT U/L	AST U/L	ALP (U/L)	Amylase (U/L)	Total p. gm/dl	Albumin gm/dl	Creatin mg/dl	Uric acid mg/dl	T. Bili. mg/dl	Ca mg/dl	Ph mg/dl)
Con	33.33± 2.73b	39± 0.58c	168.33± 4.41	591.33± 39.60c	6.07 ± 0.06a	3.93± 0.45a	0.51± 0.03c	1.83 ± 0.22c	0.21± 0.03c	8.96± 0.54a	8.09 ± 0.56a
Sel	34± 6b	38.33± 0.73c	166.33± 5.36	556.67± 28.48c	5.63 ± 0.09a	3.13± 0.59a	0.51± 0.05c	1.79 ± 0.20c	0.39± 0.09c	9.1± 0.09a	7.87 ± 0.40a
Se2	48.33± 1.67a	77± 1.53a	296.33± 2.33a	523± 33.95c	3.43 ± 0.29b	1.47± 0.12b	0.97± 0.07a	3.83 ± 0.08a	2± 0.29b	8.25± 0.06a	7.92 ± 0.64a

The same Column not followed by the same letter differ significantly (P<0.05)

IMMUNOLOGICAL RESULTS:

There were no significant changes in IL 1β and serum lysozyme after one month. After 2 month IL 1β showed significant increase in group Se2 in compare with control group, but after 3 months Se2 group showed significant decrease in IL 1β value in comparison with control group. Serum lysozyme showed no change after1, 2 and 3 months in all treated groups **tables (7 and 8)**.

Table (7): IL 1 β value in control, low selenium and high selenium groups(Mean ± S.E) after one, two and three months.

Time & groups	con	Se1	Se2
One Month	59.68± 2.5a	54.83± 2.89a	56.67± 3.71a
Two months	49.15± 1.37b	53.21± 1.74b	84.00± 2.65a
Three months	50.40± 0.77b	83.33± 2.40a	39.33± 0.67c

Table (8): Serum lysozyme value in control, low selenium and high selenium groups (Mean ± S.E) after one, two and three months

Time & groups	con	Se1	Se2
One month	2.15± 0.18a	2.19± 0.16a	2.42± 0.22a
Two months	2.73± 0.13a	2.74± 0.11a	2.80± 0.06a
Three months	1.96± 0.07a	1.87± 0.09a	2.00± 0.17a

The same Column not followed by the same letter differ significantly (P<0.05)

HISTOPATHOLOGICAL RESULTS:

Liver, at concentration of **4 ppm** (Se2) after 1- month showed severe, diffuse vacuolar degeneration along with congestion of hepatic blood vessels. After 2- months degeneration, congestion and mild to moderate hyperplasia of bile duct with mild fibrosis were observed. After 3-months diffuse, massive fatty change was the con-sistent finding in all examined cases (photo 1). **Kidney,** at con-centration of **4 ppm**(Se2) after 2-months,mild to moderate focal areas of Hydropic degeneration and congestion were existed. After 3-months, severe congestion, perivascular edema and degenerative changes were prominent (photo 2). **Spleen,** at concentration of **4ppm** (Se2), at one - and 2-months spleen showed congestion and hyperplasia of white pulp. At 3-months, there were severe congestion of blood vessels with perivascular edema and fibrosis (photo 3). **Thymus,** after 3-months, congestion, and mild depletion was observed. Concentration of **4ppm**(Se2) after one and two months, there were congestion, mild to moderate depletion and mild solitary focal necrosis of lymphocytes. Besides the mentioned lesi-

ons, there were congestion, hemorrhage and multifocal areas of hemosidrosis after 3 months (photo 4). **Intestine,** at concentration of **4ppm**(Se2) at 2 and 3-months, there were degeneration and desquamation of intestinal villi, congestion of intestinal blood vessels along with leukocytic infiltration mainly lymphocytes and few macrophages.

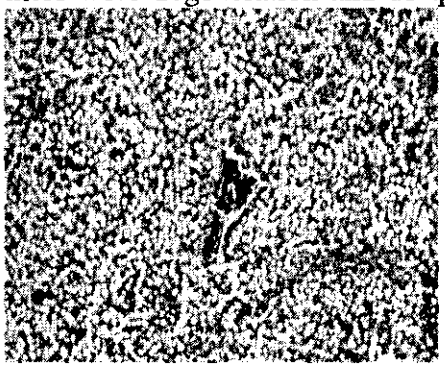


Photo (1): Liver, of Se treated group at dose **4 ppm** of after 3-months diffuse, showing massive fatty change and congestion of blood vessels. H&E Stain X 100.

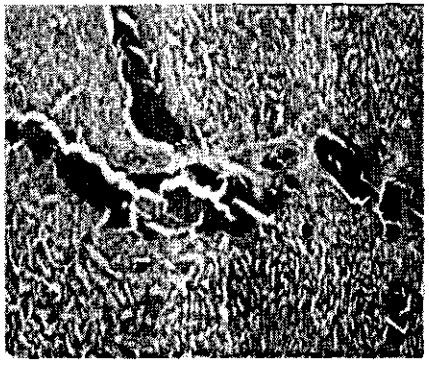
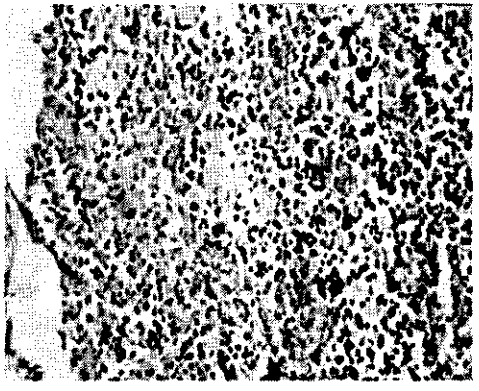


Photo (2): Kidney, of selenium treated group at done of **4 ppm** after 3-months, showing severe multiple congestion, peri-vascular edema and degenerative changes. H&E Stain X 100.

Photo (3): Spleen, at concentration of **4ppm,** at 3-months, showing severe congestion of blood vessels with perivascular edema and mild fibrosis. H&E Stain X 10.



Photo(4): Thymus, at concentration of 4ppm after 3 months, shows congestion, depletion, solitary focal necrosis of lymphocytes and hemosidrosis. H&E Stain X 40.

DISCUSSION:

Administration of different doses of selenium for 3 months resulted in macrocytic hypochromic anemia (regenerative), it appeared at 2nd and 3rd months post high dose of selenium administration. The regenerative anemia in our work evidenced by erythrocytes polychromasia. Our results confirmed histopathologyically by the presence of hem-orrhage in the thymus and multifocal areas of hemosidrosis in spleen. Our result in match with **Baumann et al., (2000)** who said that selenium interfere with the functional capability of membrane sulfhydryl groups, either by their oxidation or by their blockade, was found to induce premature RBC destruction in living animals and to interfere with the transport and metabolism of glucose as well as in the membrane permeability to cations *in vitro*, thus leading to osmotic swelling and hemolysis.

Our data about leukogram in the present study revealed that the prolonged exposure to sodium selenite reduced the peripheral total leucocyte count, which was in agreement with the **Satyavan et al., (2008)** who recorded that Selenosis has been reported to reduce the number circulating leu-cocytes in different species (**Kaur et al., 2005**). The decline in the number of circulating peripheral leucocytes was due to progressive decline in the neutrophil count. **Hogan (1986)** found that the decrease in neutrophils was resp-onsible for decline in leucocyte count. Sodium selenite probably induced decrease in the neutron-phils count by its cytotoxic action or by decreasing their product.

The elevated enzymes activeeeity in the present study are in accordance with those of **Huali et al., (2007)** who recorded that oral administration of selenium to rats resulted in significant elevation of AST and ALT. Also, **Spallholz and Hoffman (2002)** showed that sodium selenite (3.5 mg/l) in drinking water increased ALT activity in serum of adult mallard ducks by another possible mechanism which involve in the inhibition of selenium methylation metabolism in birds receiving excess selenium resulting in the accumulation of hydrogen selenide, an intermediate metabolite, which has hepatotoxic effects. The elevated serum enzymatic activities generally reflect cellular damage, because these enzymes are released into the circulatory fluid when cell membrane integrity is damaged as a result of toxemia (**Kim and Mahan, 2001**). Also, the elevated levels of hepatic enzymes may be ascribed to the increased synthesis of these enzymes (**Feilleux-Duche et al., 1994**). Our result confirmed histopath-

ologically by diffuse vacuolar degeneration along with congestion of hepatic blood vessels. Our results disagree with those of **Meotti et al., (2003)** who reported that IP injection of rats with diphenyl diselenide, resulted in no change in ALT or AST activity.

Regarding to renal toxicity markers creatinine and uric acid, our result revealed elevation in level of both markers; this elevation may be attributed to renal disease. This result is confirmed histopathologically by mild to moderate focal areas of hydropic degeneration and congestion were existed. After 3-months, severe congestion, perivascular edema and degenerative changes this in accordance with **Fair et al., (1985)** who recorded that the elevation in renal markers in mice admistered selenium daily for 20 days. Our result disagree with those of **Andreza et al., (2006)** who said that diphenyl diselenide, caused no change in creatinine level in rabbits.

Recent studies suggest oxidative stress as one of the important mechanisms of toxic effects of selenium **(Spallholz and Hoffman, 2002)**.

The oxidative stress has also been implicated to contribute to selenium-associated liver injury **(Albers et al., 1996)**. The decrease in serum total protein concentr-ation seen in the present study may be due to an inhibition in hepatic protein synthesis resulting from a depletion of thyroxine (T4) transport, necessary for protein synthesis, into the hepatic cells **Schreiber and Richardson (1997)**. Also, the decreased total protein concentration may be an indirect effect of the decreased albumin concentration, involved in selenium detoxification, which aids in the transport of thyroxine into the liver cells **(Preedy et al., 2002)**. The decreased serum protein was parallel to that of **Hoffman et al. (1989)** who indicated that dietary selenium as sodium selenite (20 and 40 ppm, w/w) decreased hepatic protein concentration in mallard ducks. The increase in the level of total bilirubin in line with **Hoffman et al. (1991)** who reported increased liver hemosiderin pigmentation in mallard ducks exposed to 32ppm selenium as selenomethionine for 14 weeks, reflecting an increase in bilirubin concentration and a decrease in both hemoglobin and iron concentrations secondary to the increased damage of RBCs.

In this study we recorded increase IL 1β value after 2 months, this result in line with **Johnson et al., (2000)** who recorded increase level of IL 1β in mice exposed to sodium selenite in drinking water. They said that the in-

crease in IL 1β may be attributed to the increased production of ROS following Se supplementation which result in increase production of IL 1β. The proinflammatory cytokine expression is controlled by the NF kapan B nuclear transcription factor and reactive oxygen species are pow-erful activators of NF kapan B mediated transcription **(Kaul and Forman 1996)**. After 3 months we reported decrease in the level of IL 1β this result matches **Wang et al., (2005)** who reported decrease in IL 1β after initial increase, they said that selenium poisoning slightly increase IL 1β in the early stage and showed a significant decrease in the later stage. The reason could be due to the overdose of selenium that caused the injury of the immune organ (such as spleen). Decreased serum IL1 β has been reported in heavy metals toxicity and could be due to decrease production of IL1 β from macrophages **(Maria et al., 2000)**. Disagreement with these results, **Kiremidjian-Schumacher et al., (1990)** who indicated that the amounts of IL-2 and IL-1 produced by lymphocytes and macrophages, respectively, remo-ved from Se-deficient or Se-supplemented animals did not differ significantly from the amo-unts of IL-2 and IL-1 produced by cells removed from animals maintained on the control diet.

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الملخص العربي

دراسات باثولوجية إكلينيكية تجريبية على التسمم بالسيلينيوم فى الفئران

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استهدف هذا البحث دراسة تأثيرات السيلنيوم على خصائص الدم و المؤشرات البيوكيميائية بالإضافة إلى الاختلافات في المؤشرات المناعية و الباثولوجية التي تحدث نتيجة تركيزات غذائية مختلفة من السيلنيوم في الفئران. أجريت هذه الدراسة على عدد خمسة وسبعون من ذكور الفئران البيضاء. تم تقسيم الحيوانات إلى 3مجموعات متساوية (تشمل كل منها خمسة وعشرون فأر). المجموعة الأولى الضابطة:استخدمت هذه المجموعة كضابطة و لم تعطى اى دواء. المجموعة الثانية : تم إعطاء السيلنيوم لهذه المجموعة بجرعة 2 جزء من المليون في مياه الشرب لمدة 3 أشهر على هيئة صوديوم سيلنيت. المجموعة الثالثة :تم إعطاء السيلنيوم لهذه المجموعة بجرعة 4 جزء من المليون على هيئة صوديوم سيلنيت في مياه الشرب لمدة 3 أشهر. تم تجميع عينات الدم و فصل السيرم و تجميع عينات من الكبد و الكلى و الطحال و الأمعاء و السيمس و القلب و البنكرياس عند نهاية الشهر الأول و الثاني و الثالث. أدى إعطاء السيلنيوم بجرعة عالية إلى حدوث أنيميا مع تقليل للعد الخلوي الأبيض العام مع حدوث نقص معنوي في الخلايا المتعادلة. تم حدوث زيادة انزيمات الكبد و حمض البوليك والكرياتينين والصفراء. على النقيض من هذا تم حدوث انخفاض ملحوظ في مستوي البروتين الكلى و الزلال. كان من الملاحظ أيضا حدوث زيادة فى الانترلوكين 1 بيتا عند شهرين ثم تبع بنقص معنوي عند 3 أشهر. كما اظهر الفحص المجهري للانسجه عن وجود إصابات باثولوجية شديدة في الكبد والكلي و الطحال و الأمعاء و السيمس.