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Sub-acute Exposure to Sodium Selenite-induced Dyslipidemia, ATPase-independent Electrolytes Disruption and Tissue Damage in Male Wistar Rats

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ABSTRACT: Selenium (Se) is a trace element required for many cellular functions in most organisms although also known to be toxic, has a narrow range separating chronic conditions of deficiency and toxicity. This study investigated the effects of exposure to different doses of Se as sodium selenite on some biochemical markers in male albino rats. Twenty-four rats grouped into four with six animals each were used. One of the groups served as control given distilled water and the other three groups were respectively given 16, 32, and 64 ppm Se orally in their drinking water for 4 weeks. Animals were sacrificed thereafter, blood and tissues were collected, and biochemical parameters carried out using spectrophotometric method. In the plasma of exposed animals, activities of both aspartate and alanine transaminases (AST and ALT) were significantly increased while significant decrease in albumin and direct bilirubin levels were observed when compared to control. Exposure to Se also resulted in decreased levels of HDL triacylglycerol (TAG) and cholesterol (Chol), while increasing those of VLDL + LDL. In the tissues, TAG levels were decreased while hepatic Chol level increased. Furthermore, Se disrupted electrolyte homeostasis in the different compartments studied independent of the ATPases. These results thus point out some of the cellular alterations caused by sodium selenite exposure and may proffer biochemical basis for some of the clinical manifestations of selenium toxicity.

Keywords: Sodium selenite, Selenium, Selenosis, Lipid profile, Tissue damage, Electrolytes

Introduction

Selenium (Se) is a trace element that exists as organic and/or inorganic forms in living cells and earth crust. Selenomethionine (Semet) and selenocysteine (Secys) are the primary organic forms, whereas selenite (SeO_3^{-2}), selenide (Se^{2-}), selenate (SeO_4^{-2}) and selenium element (Se) are the inorganic states (Mehdi, 2013). Selenium as an element or metallic selenide (Se^{2-}) is less toxic compared to selenates (SeVI) and selenites (SeIII) that behave like oxidants. The low toxicity of elemental or metallic selenide has been adduced to its low bioavailability (Mehdi, 2013). Furthermore, Se a constituent of the uncommon amino acids selenocysteine and selenomethionine can be obtained from staple food such as meat, grains, vegetables, and nuts (MacFarquhar *et al.*, 2010). Also. Se, in the form of sodium selenite, when given as a solitary or repetitive dose to humans or animals is well assimilated from the gastrointestinal tract and transported in the blood as selenoprotein P, it binds to globulins (α and β), low density lipoprotein (LDL) and very low density lipoprotein (VLDL) (Meschy, 2010). Although distribution of Se is throughout the body, the highest amounts are present in liver, kidneys, and muscle tissues (Zachara, 2001). As a cofactor of several selenoproteins, Se performs key roles in various cellular activities, like protection against oxidative damage, synthesis of DNA and thyroid

hormones as well as involvement in reproduction and fertility. Selenium, alongside vitamin E, helps in the normal functioning of muscle by enhancing stamina and recovery and has also been shown to slow aging process (Suttle, 2010). Despite these benefits, there have been reported cases of individuals who consumed food crops grown in selenium-rich stony coal (carbonaceous shale) who suffered from selenosis because of high selenium content in foods (Yang and Xia, 1995; Li *et al.,* 2012; Razmi *et al.,* 2017; Senthilkumaran *et al*., 2012).Selenosis may also ensue from exposure to low level but chronic Se in drinking water (Vincet*i et al.,* 2013). Symptoms of Selenosis include cirrhosis of the liver, pulmonary edema, reduced sperm motility and increased incidence of some forms of cancer or can even result in death (Hawkes and Turek, 2001, Rayman, 2012; Nuttall, 2006; Vinceti *et al.,* 2013). It is known that Se intake varies across countries (NIH, 2018; Stoffaneller and Morse, 2015; Wasowicz *et al.*, 2003; Jabłońska *et al.*, 2013). Similar to every other essential trace element, Se, is required in little quantities for cellular functions and at high quantities presents toxic side effects (Mehdi, 2013). However, WHO recommends a low Se intake of 26 and 34 µg/day for adult females and males, respectively (Jabłońska andVinceti, 2015).

The espial of the essentiality of selenium, acknowledgment of selenocysteine as an amino acid and insertion into mammalian proteins (Mehta *et al*., 2004), coupled with the involvement of selenoproteins in the pathogenesis of cardiovascular diseases and cancer (Davis *et al*., 2012; Tanguy *et al*., 2012), have engendered considerable scientific attention. Over the years, the importance of Se has been disseminated via media to the public, repeatedly encouraging increased consumption of selenium supplementation. Unfortunately, the range between chronic conditions of deficiency and toxicity is thin, and distinguishing toxic from non-toxic elevations is a more frequent and challenging issue (Nuttall, 2006; Zhang *et al.*, 2014; Wang *et al*., 2017). Also, most researches into selenium toxicity have focused on the clinical manifestations, resulting in paucity of information on its effects on cellular and biochemical events. Therefore, we aim to determine the effects of different doses of Se administered as sodium selenite on lipids and electrolytes homeostases as well as to assess its reno-hepatic implications in male albino rats.

Materials and methods

Chemicals and reagents: Sodium selenite (Na_2SeO_3) was obtained from Sigma-Aldrich, Missouri, USA. All other reagents used were obtained commercially and were of analytical grade.

Experimental animals: The approval of the departmental animal ethical committee was obtained prior to the experiment. The rats were handled with care in line with the guide required for the care and use of laboratory animals (National Research Council, 2010). Twenty four male rats of weight between 150 - 170 g were purchased from the Zoology Department University of Ibadan and housed in plastic cages. The animals were acclimatized for two weeks, kept at ambient temperature (25 ± 2 ºC) and allowed free access to food and water.

Experimental design: Animals were divided into four groups of six rats each and administered varying doses of Se as sodium selenite. Group I served as control while groups II, III and IV were exposed to 16, 32, and 64 ppm Se orally respectively for 28 days. After exposure, animals were fasted overnight and sacrificed under light anesthesia using diethyl ether. Blood samples were collected into clean heparinized tubes. Tissues (kidney and liver) were also excised, rinsed in cold saline and processed for biochemical analysis.

Preparation of samples: Plasma was obtained from blood collected by centrifugation at 3000 rpm for ten minutes. Tissue homogenate (10 % w/v) was prepared using 0.25 M sucrose solution. The supernatant (obtained from the centrifuged homogenate) and the plasma were used for biochemical evaluation and enzyme assays.

Biochemical Parameters

Hepatic and renal function tests: Activities and levels of hepatic and renal biomarkers were assessed in the plasma. Activities of both alanine transaminase (ALT) and aspartate transaminase (AST) as well as levels of direct bilirubin (DBil), total bilirubin (TBil), creatinine (Cr) and urea were assayed using standard kits from Cypress diagnostics (USA). Also, the level of albumin in the plasma was determined using Randox diagnostic kit, Crumlin, UK. The assays were carried out according to methods described in the diagnostic kits.

Isolation and determination of lipids: Isolation of high-density lipoproteins (HDL) and very low-density lipoproteins + low-density lipoproteins (VLDL + LDL) fractions from plasma and extraction of lipids from tissues were done as described by Ugbaja *et al.* (2016). Levels of triacylglycerol (TAG), cholesterol (Chol) and phospholipids (Phol) were determined in the plasma, lipoproteins fractions and tissue homogenates using standard laboratory kits.

Determination of electrolytes homeostasis: The levels of some electrolytes (Na^+, K^+, Ca^{2+}, Mg^{2+}) were determined using standard kits obtained from Cypress diagnostics (USA). The activities of Na^+/K^+ and Ca^{2+}/Mg^{2+} ATPases were also assayed in the liver and kidney homogenates, according to the methods of Tsakiris and Deliconstantinos (1984) and Hanahan and Ekholm (1978) respectively.

Statistical analysis: Values on analysis are expressed as mean ± standard error of means (SEM). The level of homogeneity among the results of groups was tested using one-way Analysis of Variance (ANOVA), with $p < 0.05$ considered significant. Where heterogeneity occurred, groups were separated using Duncan Multiple Range Test (DMRT). All analyses were done using Statistical Package for the Social Sciences (SPSS) version 20.0.

Results

Results of hepatic and renal function markers observed in the plasma are presented in Table 1. Activities of ALT and AST significantly increased in selenite-treated groups compared to the control. ALT activity was increased in a dose-dependent manner, by 1.4, 2.3 and 2.8 fold in rats exposed to 16, 32 and 64 ppm, respectively while activity of AST peaked in rats exposed to 32 ppm Se. Levels of albumin and direct bilirubin significantly reduced in all Se-exposed rats compared to the control. However, there was no significance in the levels of urea and TBil in exposed animals compared to the control group.

Table 1: Effect of selenite on plasma concentrations of some biochemical parameters of experimental animals

Biochemical	**Treatment**			
Parameters	**Control**	**16 ppm Se**	**32 ppm Se**	**64 ppm Se**
ALB (g/L)	4.12 ± 0.06^{c}	3.48 ± 0.15^{b}	3.46 ± 0.16^{b}	2.90 ± 0.18^{a}
Urea (mg/dL)	57.87 ± 2.11^{a}	55.92 ± 4.02^{a}	57.35 ± 5.91^{a}	53.53 ± 5.43^{a}
CR (mg/dL)	1.52 ± 0.14^{a}	1.84 ± 0.06^{a}	0.92 ± 0.08^{b}	1.02 ± 0.02^{b}
DBil (mg/dL)	0.07 ± 0.02^{b}	0.03 ± 0.01^{a}	0.02 ± 0.01^{a}	0.02 ± 0.02^{a}
TBil (mg/dL)	0.01 ± 0.005^{a}	0.02 ± 0.006^{a}	0.006 ± 0.001^{a}	0.018 ± 0.01^{a}
ALT (U/L)	39.94 ± 9.21^{a}	54.01 ± 8.10^{a}	90.04 ± 6.62^{b}	110.32 ± 9.23^{b}
AST (U/L)	88.47 ± 4.63^{a}	95.64 ± 3.73^{ab}	154.72 ± 14.16^{c}	119.90 ± 8.71^{b}

Values are expressed as mean ± S.E.M (n=6). Values with different letters across the row, are significantly different at $p<0.05$.

Both lipotoxic and non-lipotoxic perturbations were observed in plasma, kidney and liver of all exposed rats (Table 2). Lipotoxic effect in the plasma resulted in increased TAG level by 24, 19.4 and 109 % in animals exposed to 16, 32 and 64 ppm Se, respectively while significant decrease ranging between 44 and 66 % in plasma Chol level characterized the non-lipotoxic effect. Similarly, decrease ranging between 12 and 15 % in HDL-TAG level were observed in all exposed rats, while that of HDL-Chol ranged between 13 and 17 % compared to the control. In contrast, both VLDL+LDL-TAG and VLDL+LDL-Chol concentrations significantly increased in Se-exposed groups.

In the hepatic tissue, while TAG level significantly reduced consistently with increasing doses of Se, Chol level increased in a dose-dependent manner. Non dose-dependent decrease of 31, 50 and 30 %, respectively were observed in hepatic Phol levels in groups exposed to varying doses of Se compared to the control.

Also dose-dependent decrease in renal TAG level was observed on exposure to 16, 32 and 64 ppm Se compared to the control group. Renal Chol level increased and peaked at 9.22±1.83 mg/g in group exposed to 32 ppm. A hormetic response was observed in renal Chol level such that exposure to 16 ppm Se resulted in a 16 % decrease in the level, on doubling the dose, a 40 % increase was observed on further doubling to 64 ppm, effect observed was similar to that of the control (Table 2).

Table 2: Lipid profile of plasma, lipoproteins, liver and kidney of experimental animals

	Biochemical	**Treatment**			
Compartment	**parameter**	**Control**	**16 ppm Se**	**32 ppm Se**	**64 ppm Se**
Plasma	TAG (mg/dL)	88.54 ± 7.48^{a}	109.77 ± 5.20^{a}	105.68 ± 11.67^{a}	185.05 ± 15.77^{b}
	Chol (mg/dL)	176.26 ± 7.55^{c}	99.93 ± 4.51^{b}	60.25 ± 5.47^{a}	64.93 ± 7.85^{a}
Plasma HDL	TAG (mg/dL)	94.96 ± 2.87^{b}	83.62 ± 3.16^{a}	80.86 ± 1.02^{a}	80.02 ± 1.14^{a}
	Chol (mg/dL)	110.76 ± 3.43^{b}	91.07 ± 5.02^{a}	97.23 ± 6.39^{ab}	95.20 ± 3.94^{a}
VLDL +LDL	TAG (mg/dL)	41.91 ± 1.03^{a}	231.53 ± 3.18^{c}	182.25 ± 5.78^{b}	197.05 ± 4.14^{b}
	Chol (mg/dL)	88.88 ± 7.20^{a}	119.08 ± 6.55^{b}	203.41 ± 6.52^{c}	209.55 ± 7.87^{c}
Liver	TAG (mg/g)	14.10 ± 1.57^{b}	13.85 ± 0.94^{b}	7.89 ± 0.43^{a}	6.97 ± 0.55^{a}
	Chol (mg/g)	3.18 ± 0.81^{a}	5.29 ± 0.58^{b}	6.26 ± 0.78^{b}	8.37 ± 0.61^{c}
	Phol (mg/g)	272.93 ± 9.50^{c}	187.11 ± 12.64^{b}	135.73 ± 6.84^{a}	190.12 ± 16.49^{b}
Kidney	TAG (mg/g)	18.98 ± 1.02^{d}	14.19 ± 1.07^{c}	6.87 ± 1.22^{b}	3.10 ± 0.31^{a}
	Chol (mg/g)	4.89 ± 1.31^{a}	6.31 ± 0.70^{a}	9.22 ± 1.83^{b}	5.23 ± 0.24^{a}
	Phol (mg/g)	172.91 ± 6.78^{b}	144.09 ± 10.78^{a}	242.36 ± 7.88^{c}	174.81 ± 8.93^{b}

Values are expressed as mean ± S.E.M (n=6). Values with different letters across the row, are significantly different at $p<0.05$.

Table 3 represents the effects of different doses of Se on some electrolytes and ion pumps studied. In the hepatic tissue, while exposure to Se significantly caused between 2.4 and 3.6 fold increase in K^+ level, Na^+ level was not significantly altered on exposure to Se. Similarly, there was no significant difference in activity of hepatic Na^+-K^+ ATPase on

exposure to Se. Hepatic Ca^{2+} level increased significantly in animals exposed to 16, 32 and 64 ppm by 2.5, 4.6 and 3.9 fold respectively. In contrast, no significant change was observed in the level of hepatic Mg^{2+} and activity of the pump (Ca^{2+}-Mg^{2+} ATPase) involved in their translocation.

In the renal tissue of exposed animals, both Na^+ and K^+ levels decreased; however, Na^+ decreased dose-dependently. A hormetic response was observed with renal $Ca^{2+}$and Mg^{2+} levels. While rats exposed to 16 and 32 ppm Se had hypocalcemia, those treated with 64 ppm had hypercalcemia. Also higher doses (32 and 64 ppm) caused reduction in plasma Mg^{2+} while 16 ppm Se exposure increased Mg^{2+} level by 82 %. Renal Ca^{2+}-Mg^{2+} ATPase activity was not altered on exposure to Se.

Level of plasma K^+ was increased on exposure to all doses of Se but peaked at 10.40±0.43 mEq/L in animals exposed to 32 ppm Se. In contrast, observed differences in Na^+ level was of no significance statistically. Plasma Ca^{2+}level decreased with the different doses while Mg^{2+} level decreased in groups exposed to higher Se concentrations (32 and 64 ppm).

Table 3: Effects of selenite on electrolytes and ion pumps levels of experimental animals

Biochemical parameters	**Compartment**	**Treatment**			
		Control	**16 ppm Se**	**32 ppm Se**	**64 ppm Se**
K^+ (mEq/L)	Liver	2.85±0.59^a	6.77±1.36^b	6.27±0.63^b	10.11±1.68^c
	Kidney	8.62±0.85^b	6.14±0.54^a	6.65±0.42^a	6.85±0.91^{ab}
	Plasma	3.53±0.15^a	5.14±0.38^b	10.40±0.43^d	6.72±0.19^c
Na^+ (mEq/L)	Liver	48.83±5.55^a	49.25±3.69^a	48.98±6.92^a	52.73±5.40^a
	Kidney	38.59±3.97^b	33.35±3.08^b	23.74±3.18^a	21.84±3.77^a
	Plasma	1.31±0.27^a	1.36±0.82^a	1.38±0.45^a	1.10±0.97^a
Ca^{2+} (mEq/L)	Liver	0.33±0.08^a	0.83±0.04^b	1.51±0.57^b	1.29±0.24^b
	Kidney	4.40±0.22^b	4.19±0.81^{ab}	3.32±0.33^a	4.77±0.76^b
	Plasma	6.47±0.28^c	5.49±0.14^b	1.65±0.16^a	1.88±0.32^a
Mg^{2+} (mEq/L)	Liver	2.01±0.11^a	2.01±0.05^a	2.01±0.05^a	1.96±0.03^a
	Kidney	2.11±0.11^b	3.84±0.04^c	1.98±0.02^b	1.59±0.12^a
	Plasma	2.71±0.24^{bc}	2.77±0.07^c	2.56±0.08^b	1.98±0.07^a
Na^+-K^+ATPase	Liver	0.05±0.02^a	0.04±0.01^a	0.03±0.02^a	0.09±0.05^a
(µmol Pi/g organ/hr)	Kidney	0.01±0.001^a	0.01±0.001^a	0.01±0.001^a	0.01±0.001^a
Ca^{2+}-Mg^{2+} ATPase	Liver	0.30±0.04^a	0.28±0.04^a	0.34±0.04^a	0.30±0.02^a
(µmol Pi/g organ/hr)	Kidney	0.38±0.06^a	0.31±0.03^a	0.34±0.03^a	0.35±0.02^a

Values are expressed as mean ± S.E.M (n=6). Values with different letters across the row, are significantly different at $p<0.05$.

Discussion

Sodium selenite has been shown to enter the animals and human cells passively (Sun *et al*., 2014), and metabolized to selenide (Se^{2-}) (Spallholz, 1994). In the cells it is used either for selenoprotein biosynthesis or biomethylation (Gailer, 2002). The synthesis of selenoproteins depends on available Se and the tissue involved (Hesketh and Meplan, 2011). The liver and kidney have been reported to be the major organs involved in the metabolism of Se *in vivo* (Jäger *et al.*, 2015). After absorption, Se may undergo first pass effect in the liver and possibly incorporated into selenoproteins (Hesketh and Meplan, 2011). The kidney is also involved in its subsequent elimination from the body (Jäger *et al.*, 2015). ALT and AST are cellular enzymes involved in transamination but normally found in small amounts in the blood, probably because of organ growth and repair. However, if both transaminases are elevated in the plasma, it is an indication of impaired liver function and/or loss of membrane integrity (Priti *et al.*, 2012). Our results showed a gradual increase in the biomarkers of liver damage expressed by an increase in plasma ALT and AST activities in Se-exposed animals. This may result from leakage from the liver or other extrahepatic tissues such as the muscle (Sankaran *et al*., 2010), the latter leading to tiredness, which interestingly is one of the symptoms of Se poisoning (Nuttall, 2006). Although Se may not affect membrane integrity directly, it has been implicated in the generation of reactive oxygen species (ROS) (Shen *et al.,* 2000; Stewart *et al.,* 1999; Sun *et al.,* 2014) which in turn have the potential to disrupt membrane integrity.

Results also revealed a dose-dependent decrease in the level of plasma albumin. Albumin, a plasma protein, has vital binding and transport roles and mechanistic researches have demonstrated that albumin is the main transport protein for Se (Haratake *et al.,* 2008). Albumin, used in clinical diagnosis of liver dysfunction, makes up about 60% of total plasma protein, and being a major binding protein, toxic effects could develop from the accumulation of unbound substances. In conditions where the albumin concentration is considerably reduced,

the plasma osmotic pressure is not enough to pull water from the tissue spaces back into the plasma, leading to the build-up of extracellular fluid termed edema (Thapa and Walia, 2007). Low serum albumin is implicated in liver diseases, protein energy malnutrition, disorders of water balance, nephrotic syndrome, and protein-losing gastrointestinal diseases (Cheesbrough, 2006). Albumin and most other plasma proteins are produced in the liver, and thus, the observed decreased levels from our results may further indicate liver disease (Thapa and Walia, 2007), such as cirrhosis, which has been reported earlier as one of the symptoms of selenium toxicity (Nuttall, 2006).

Exposure to different doses of Se resulted in both lipotoxic and non-lipotoxic alterations in lipids homeostasis in the plasma, tissues and lipoprotein fractions (Table 2). When compared to the control animals, lipotoxcity is characterized by hepatic cholesterogenesis, hypertriglyceridemia and hypercholesterolemia in VLDL+LDL fraction. Decrease in hepatic phospholipids, renal triacylglycerol and also depletion of plasma cholesterol, HDL cholesterol and HDL triacylglycerol in circulation were the hallmark of the observed non-lipotoxic effects caused by Se. Generally, tissues obtain lipids either from circulating free fatty acids associated with albumin and lipoproteins or by *de-novo* synthesis (Afolabi *et al*., 2015, Goldberg*et al*., 2012). Tissues such as liver, heart and brain involved in *de novo* synthesis secrete excess lipids in lipoproteins (Postle, 2009; Walters *et al.*, 2012). Since fatty acids are transported by albumin, decreased plasma albumin as shown by our data could also mean lowered free fatty acid concentration and subsequently decreased TAG levels both in the hepatic and renal tissues as observed. A major function of free fatty acids is to serve as an immediate substrate for TAG synthesis (Afolabi *et al.,* 2015; Donnelly *et al*., 2005). Reduction in the *de novo* synthesis of tissue TAG is thus evident by observed decreased TAG and ultimately lipid homeostasis further indicating possible liver injury on exposure to Se In contrast, increased hepatic cholesterogenesis in Se-exposed groups may be due to activation of 3-hydroxy-3-methylglutaryl Coenzyme A (HMG CoA) reductase - the rate limiting enzyme for cholesterol biosynthesis (Sawada *et al*., 2005) or inhibition of cholesterol-7α-hydroxylase, a cytochrome P450 enzyme located in the endoplasmic reticulum involved in the synthesis of bile acids- which is a major route used in the elimination of cholesterol from the body (Kojima *et al*., 2004). The lipoprotein- HDL may protect against atherosclerosis via the up-regulation of reverse cholesterol transport and thus low levels of HDL cholesterol are concomitant with a higher risk of atherosclerosis (Olofsson and Borèn, 2005). The liver has limited capacity to store lipids hence, the excess cholesterol and triglycerides are packaged into VLDL particles and secreted into circulation (Afolabi *et al.,* 2015). Consistent with this is enrichment of the fraction of VLDL+LDL with cholesterol and triglycerides observed from this study. These lipoproteins (VLDL+LDL) have been implicated in the progression of atherosclerosis (Olofsson and Boren, 2005). These lipoproteins, apart from transporting of lipids, are also involved in the transport of apoproteins such as Apo B which bind to LDL receptor thereby facilitating the interaction between LDL and the arterial wall thus instigating the progression of atherosclerosis by initiating plaque formation and development in the blood vessels (Olofsson and Boren, 2005). This may also be one of the underlying mechanisms involved in Se-induced atherosclerosis.

Selenite exposure altered the levels of some electrolytes studied. This may partly be as a consequence of edema that resulted from hypoalbuminemia observed in our results and earlier reported by Thapa and Walia, (2007) or by other unclear mechanisms. Edema might affect electrolyte balance, by either dilution or bulk flow. Electrolytes are extensively involved in the maintenance of body homeostasis, as they help to regulate heart and neurological function, fluid balance, oxygen delivery, acid–base balance and much more (Liamis *et al.,* 2013). The most consequential electrolyte disturbances involve abnormalities in the levels of sodium, potassium or calcium. Other electrolyte imbalances are less common, and often occur in conjunction with major electrolyte changes and may lead to muscle spasm, weakness, twitching, convulsions, irregular heartbeat, confusion, blood pressure changes, nervous system or bone disorders (Guyton and Hall, 2006), which correlate with some of the symptoms reported for selenium toxicity (Nuttall, 2006). However, no significant difference was observed for tissue ATPases, suggesting that the disruption of electrolyte balance by selenite was not by direct inhibition of the pumps, which could have otherwise affected these integral ATPases, it may be due to other underlying factors.

Conclusion

Although exposure to the different doses of Se used in this study produced different effects, the hallmark of selenite poisoning as identified in our study are increased plasma transaminases, reduced plasma ALB and lowered tissue TAG level. These effects and other individual perturbations induced might mediate some of the clinical manifestations previously reported in cases of selenite poisoning.

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