Original Article

Vitamin E Prevented Hepatic and Renal Tissue Damage in Hypothyroid Rats

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Abstract

Background: Considering antioxidant effects of vitamin E (Vit E), in the present study, the effect of Vit E on liver and kidney functions and oxidative stress parameters in tissues of these organs of hypothyroid (Hypo) rats were reported.

Materials and Methods: The animals were included in three groups:(1) control, (2) hypo, and (3) hypo-hypo-Vit E. Hypothyroidism was induced in rats by giving 0.05% propylthiouracil (PTU) in drinking water. Besides PTU, the rats in group 3 were daily injected with Vit E (20 mg/kg) for 42 days. The animals were deeply anesthetized and sacrificed, and the serum of the rats was immediately removed to measure thyroxin level and subsequent analysis. The liver and kidney tissues were also immediately removed for biochemical oxidative stress criteria.

Results: PTU administration reduced serum thyroxin level and also thiol content, superoxide dismutase (SOD), and catalase (CAT) activities in the liver and kidney tissues while increasing malondialdehyde (MDA). Hypothyroidism also increased alanine aminotransferase (ALT), blood urea nitrogen (BUN), and creatinine while decreasing albumin. Vit E increased thiol, SOD, and CAT in the liver and kidney tissues while diminished MDA. Vit E also decreased ALT, BUN, and creatinine while increased albumin.

Conclusion: The results of this study showed that Vit E prevented liver and renal tissue damage in hypothyroid rats.

Keywords: Hypothyroidism, kidney, liver, vitamin E

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Introduction

Propylthiouracil (PTU) is a drug that commonly prescribed to people of stricken with hyperthyroidism. It has also been frequently used to induce hypothyroidism in animal models. Some investigations have represented that aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values in animals of hypothyroid (Hypo) were higher than control.[1] It has been observed that inducing of hypothyroidism by PTU leads to increase of peroxidation of lipids in liver tissues as well as decrease in the antioxidants index including glutathione (GSH), catalase (CAT), and superoxide dismutase (SOD).[2]

It has been distinct that hormones of thyroid gland stimulate resting metabolic rate and are regarded as major controller of mitochondrial energy metabolism and activity, oxygen consumption, and reactive oxygen species (ROS) metabolism.[3,4] It is not a surprise that thyroid dysfunctions are connected with different pathological conditions in liver diseases.[5] In fact, thyroxin serum content has been observed

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as follows: normal and incidental or increased or decreased in different hepatic-related disorders.[6] These changes represent biochemical irregularities due to liver dysfunction and pathological changes associated with end-organ damage.[7] In addition, some clinical studies have reported that administration PTU in patients results in adverse effects on liver and kidney function.[8,9] For example, previous studies have demonstrated that hypothyroidism had negative effects on liver function in alcoholic liver disease and children.[10,11] Other clinical studies have demonstrated that administration PTU had negative effect on renal function.[9]

Indeed, different studies have also affirmed an oxidative stress status followed by hypothyroidism.[12,13] It has been well documented that experimentally induced hypothyroidism leads to an imbalance of production ROS by mitochondria and oxidant enzymes and, scavenging of ROS by the antioxidant system in tissues like the liver interrupted.[14] Furthermore, it was shown that acute liver failure is connected with enhanced blood endotoxins and pro-inflammatory cytokines and chemokines that are followed by dysfunction of the thyroid gland.[15] It has also been reported that there is a correlation between hypothyroidism and the progression of the stage of cirrhosis.[16] A change in thyroid hormone normal status is regularly connected with the interference of metabolism and homeostasis of lipids in the liver.[17] It has also been shown that hypothyroidism is more common in nonalcoholic fatty liver patients than in the control group,[6,18] which shows that thyroid hormones perform a pivotal role in the function of the liver by many complex mechanisms; more research is needed on these mechanisms' decoding. Some studies have reported that thyroid dysfunctions can lead to a raised blood ALT level.[19] Hypothyroidism has also been represented to be accompanied by reduction of glomerular filtration rate, renal metabolism, kidney function, kidney blood flow, and renin–angiotensin–aldosterone system activity.[20] Other studies have observed oxidative damage in the kidney in hypothyroidism conditions.[14,21]

In recent years, many studies have shown that natural antioxidants, like vitamin E (Vit E), are efficacious in inhibiting ROS-induced liver pathologies.[22,23] A variety range of Vit E has been administrated due to its therapeutic and antioxidant characteristics on the liver and kidney.[22,24] In a study, the hepatic damages induced by ethanol were confirmed by a significant elevation in ALT, AST, conjugated dienes (CD), and triglycerides in plasma, while a decreased level of total free radical-trapping antioxidant potential. Vit E supplementation improved radical-trapping antioxidant potential and decreased levels of AST and CD in alcohol-fed rats.[25] It has also been observed that Vit E protected kidney tissue against oxidative damage.[26,27]

So far, many studies have focused on hepatotoxicity. But the significance of our work is exploring the hepato-renal toxicity induced by hypothyroidism during juvenile growth. Therefore, the administration of Vit E may protect the rats against the hepato-renal toxicity associated with PTU-induced hypothyroidism. The changes in the animal tissue oxidative stress damage parameters alongside the liver and kidney function tests were examined.

Material and Methods

Animals

Twenty-eight male Wistar rats (21 days of age, weighing between 55 and 65 g) were kept in standard cages under 12 h: 12 h light: dark cycle, respectively, in a room at around 22°C. Experimental procedures were conducted under institutional ethics guidelines (ethical code: IR.MUMS.fm.REC.1396.476). The animals were randomly assigned to three groups: (1) control, (2) hypo, and (3) hypo-Vit E. Rats in groups 2–3 received drinking water containing PTU (0.05% during 42 days). Vit E was injected (20 mg/kg) intraperitoneally and daily to animals in group 3.

Blood collection

At the end of experiment, when the PTU and Vit E treatment were terminated, total blood was collected from apical heart of urethane-anesthetized rats. In separating blood serum, the tubes containing 2 ml of collecting blood were centrifuged at a speed of 3000 rpm (8–10 min).

Biochemical assessment

Animals' livers and kidneys were dissected and used for biochemical tests including total thiol (SH) content, MDA concentration, CAT, and SOD. ALT, albumin (Hitachi 902), blood urea nitrogen (BUN), and creatinine (Pars Azmoon Company, Iran) serum levels were measured by the commercial kits. In measuring MDA levels, 1 ml of tissue homogenates and 2 ml of thiobarbituric acid (TBA) reagent solution (trichloroacetic acid + hydrochloric acid) were incubated by heating in a boiling water bath for 40 min. A red-colored complex (peak absorbance: 535 nm) produced a result in the reaction of tissue MDA with TBA reagent. The MDA content was determined as follows:[28,29] MDA content (m) = absorbance/(1.65×10^5).

Content of total thiol was measured by DTNB (2,2′-dinitro-5,5′-dithiodibenzoic acid) using a reagent that reacts with the sulfonyl groups and makes an orange-colored complex which has a peak identification absorbance at 412 nm. One millimeter tris–EDTA buffer (pH = 8.6) was mixed with 50 µl of tissue homogenates and the absorbance was perused at the wavelength of 412 nm. In the next stage, 20 µl of DTNB was added to a prior mixture including tissue homogenates and tris-EDTA, and after incubation of 15 min at 37°C, absorbance of the second solution was perused again.

The activity of SOD was analyzed concerning the enzyme function production. Generation of superoxide by pyrogallol auto-oxidation and the suppression of superoxide (O^-)-dependent reduction of the tetrazolium dye, MTT (3-(4,5-dimethylthiazol-2-yl) 2,5-diphenyltetrazolium bromide) to its formazan by SOD was analyzed at 570 nm.

The principle of the measurement of CAT is based on Aebi method as estimation of the rate constant, *k* (dimension: s^{-1}, k), of hydrogen peroxide (H_2O_2) decomposition. By determining the decline in absorbance at 240 nm/min, the rate constant of the enzyme was estimated. Activities were expressed ask (rate constant) per liter.[12-14]

Statistical analysis

All data were expressed as means at each point (±SEM). All data were analyzed by one-way ANOVA followed by Tukey's post-hoc comparisons test. $P < 0.05$ would mean that differences between groups are statistically significant.

Results

Our result showed that adding PTU to the drinking water of male rats resulted in a significant reduction of thyroxin levels in serum in comparison with healthy male rats ($P < 0.001$). Interestingly, our result also revealed that injection of Vit E leads to elevation of thyroxin concentration in the serum of the Hypo-Vit E group in comparison with the hypo group, but the thyroxin level in the Hypo-Vit E group was still lower than that in the control group [$P < 0.05$, Table 1].

The biochemical assessment also showed that exposure to hypothyroidism conditions induced by PTU influenced liver performance which was presented by increasing ALT ($P < 0.01$). Moreover, injection of Vit E to hypothyroid rats resulted in a decrease in the serum ALT compared to the Hypo group [$P < 0.05$, Table 1]. The results of our study also revealed that hypothyroidism status lowered the serum concentration of albumin compared to the control group [$P < 0.05$, Table 1]. Additionally, the serum albumin concentration in the rats treated with Vit E was higher than that of the Hypo group [$P < 0.01$, Table 1].

Table 1 shows that treatment of male rats with PTU resulted in an increase in MDA level of liver tissue in comparison with the control group ($P < 0.001$). The results also revealed that treatment of hypothyroid juvenile male rats with 20 mg/kg Vit E for 6 weeks led to a decrease in MDA levels of hepatic tissue in comparison with hypothyroid rats which did not receive Vit E ($P < 0.01$ compared to Hypo group). In contrast to MDA, induced hypothyroidism by PTU attenuated the liver tissue thiol levels in rats ($P < 0.01$). Vit E administration restored the thiol levels of the liver tissues ($P < 0.05$ compared to the Hypo group). A comparison of SOD concentration in the liver tissues of the Hypo and control groups showed a statistically significant difference between the two compared groups ($P < 0.001$). The SOD activity in the liver tissues of Hypo-Vit E group was higher than that in the Hypo group ($P < 0.05$). The results were interesting when the effects of hypothyroidism on CAT activity of the liver tissues were observed and the Hypo group had significantly lower CAT activity in liver tissue compared to that in the control group ($P < 0.001$). The findings also showed that CAT activity was significantly lower in the Hypo-Vit E group compared to the control group ($P < 0.01$) [Table 1].

The results also showed that hypothyroidism due to PTU administration affected the kidney function presented by an increase in BUN and creatinine ($P < 0.001$). Table 2 shows Vit E supplementation attenuated BUN in the serum of the Hypo-Vit E group compared to the Hypo group ($P < 0.001$). Interestingly, it was found that injections of Vit E to the Hypo-Vit E group resulted in a significant decrease in serum creatinine levels compared to the Hypo group ($P < 0.001$). Additionally, Vit E attenuated oxidative damage status in the renal tissues. Our results also revealed that the Hypo group had a higher level of MDA compared to the control group in the renal tissue ($P < 0.001$), while the thiol level in the Hypo group was lower than that in the control group ($P < 0.001$). Injection of Vit E attenuated the MDA while enhancing thiols in the kidney tissues of the Hypo-Vit E group compared to the Hypo group ($P < 0.001$ for both). Additionally, hypothyroidism was accompanied by decreased levels of SOD and CAT in the renal tissues ($P < 0.001$ for both). The results also showed that administration of Vit E prevented a decrease in SOD and CAT due to hypothyroidism in the kidney tissues ($P < 0.001$ for both compared to the Hypo group) [Table 2].

Discussion

In this study, we attempted to determine how Vit E can improve renal and liver damage caused by hypothyroidism in juvenile male rats. Hypothyroidism induced in juvenile male rats for

Table 1: The effects of Vit E on serum thyroxin as an indicator of thyroid gland function, on the concentration of ALT and albumin in the serum as indicators of liver function, and MDA, thiol, SOD, and CAT in the liver tissues as indicators of oxidative stress status

Parameters	Control	Hypo	Hypo-Vit E
Serum thyroxin	4.94±029	2.22±0.17***	3.12±0.23^{+}
Serum ALT (U/l)	11.83±1.55	22.83±3.88**	14.57±2.37^{+}
Serum albumin (g/dl)	4.00±0.00	3.34±0.17*	3.82±0.15^{++}
Liver tissue MDA (nmol/g tissue)	7.08±0.42	17.45±2.09***	11.54±0.97^{++}
Liver tissue thiol (µmol/g tissue)	5.85±0.41	3.65±0.11**	4.63±0.50
Liver tissue SOD (U/g tissue)	13.45±1.15	6.23±0.51***	8.03±0.62
Liver tissue CAT (U/g tissue)	0.87±0.26	0.36±0.24***	0.73±0.68^{++}

*$P<0.05$, **$P<0.01$, and ***$P<0.001$ compared to the control group, $^{+}P<0.05$ and $^{++}P<0.01$ compared to Hypo group. The data are presented as mean±SEM (n=8 in each group)

Table 2: The effects of Vit E on concentration of creatinine and BUN in the serum as indicators of kidney function and MDA, thiol, CAT, and SOD in the kidney tissues as indicators of oxidative stress status

Parameters	Control	Hypo	Hypo-Vit E
BUN (mg/dl)	13.28±1.39	42.71±3.86*	12.71±1.56^{+}
Creatinine (mg/dl)	3.00±0.00	7.00±0.03*	0.44±0.04^{+}
Kidney tissue MDA (nmol/g tissue)	9.78±0.79	36.38±0.88*	27.57±0.67^{+}
Kidney tissue Thiol (µmol/g tissue)	20.00±035	7.87±0.24*	13.22±0.18^{+}
Kidney tissue SOD (U/g tissue)	19.44±0.56	7.49±0.30*	13.52±1.08^{+}
Kidney tissue CAT (U/g tissue)	1.31±0.03	0.49±0.05*	0.78±0.01^{+}

*P<0.001 compared to the control group, ^{+}P<0.01 compared to Hypo group. The data are presented as mean±SEM (n=8 in each group)

6 weeks results in a reduction of antioxidant markers such as CAT and SOD activity, and thiol level and enhancement of the MDA, which is an important oxidative stress indicator, in the renal and liver tissue. In the current study, we also found that oxidative stress induced by hypothyroidism results in enhanced creatinine and BUN levels in serum which indicates that oxidative stress affected the function of the kidneys. Our results also revealed that induced hypothyroidism leads to an increase in serum ALT (liver enzymes) and a decrease in serum albumin which indicates that oxidative stress induced by hypothyroidism affected the function of the liver. Furthermore, our findings revealed that administration of Vit E (20 mg/kg) normalized the antioxidant markers like CAT and SOD activity, and thiols levels as well as MDA levels in renal or hepatic tissue. Furthermore, we also found that administration of Vit E (20 mg/kg) improved liver or kidney function which is reflected in marker such as ALT, albumin, BUN, and creatinine serum levels. Based on the results of present study, it can be concluded that Vit E may mitigate oxidative damage in liver and kidney tissues by reducing oxidative stress in hypothyroid juvenile male rats.

Similar to our results, several studies have previously reported that hypothyroidism induces oxidative stress in liver and kidney tissues.[14,21] Other studies also showed that hypothyroidism induces oxidative stress in cardiovascular,[30] brain,[31] and reproductive tissues.[32] Oxidative stress caused by the PTU administration does not seem to be induced by the direct pharmacological effect on liver and kidney tissues, since studies showed that levothyroxine treatment reversed the oxidative effects of hypothyroidism to similar values of the control group.[33,34] It has been revealed that thyroid hormones play a crucial role in reducing oxidative stress by decreasing the formation and by scavenging of ROS.[35] For instance, in patients with hypothyroidism, MDA levels were observed to decrease in response to thyroxine treatment.[36] It is also reported that ROS production is connected to the effects of thyroid hormones on mitochondria. In this regard, it has been reported that hypothyroidism leads to elevate unpaired electrons in the mitochondria matrix which finally leads to overgeneration in ROS[37]

The serum ALT enzyme level is mainly monitored as a signal for the evaluation of liver destruction. Although this enzyme is not very specific, an enhancement in its activity reflects liver damage.[38] It is suggested that ALT for the diagnosis of liver damage is more precise and is elevated before other liver dysfunction markers.[39] Previous observations have frequently suggested that hypothyroidism is connected with enhanced levels of liver enzymes.[14,40] ALT as a sensitive serological indicator of liver toxicity has been shown to have a negative correlation with serum T4 levels.[14,40,41] It has been reported that hypothyroidism elevates the activity of this enzyme.[14] ALT level was significantly increased in the present study which is in agreement with the result of previous studies.[14,40,42] In addition, it has been shown that the globulin, albumin, and total proteins in the serum of hypothyroid rats were decreased.[14] Furthermore, serum albumin always assays the excretory and synthetic performance of the liver.[43] In the current study, we illustrated that the serum albumin of Hypo rats was lower than the control group.

Moreover, the Hypo rats exhibited significant biochemical markers of the kidney as indicated by the increased BUN and creatinine. The results of our study are in line with the findings of previous studies that reported hypothyroidism may have harmful effects on the kidney.[44,45] For instance, we recently observed that the PTU exposure in the juvenile period impairs kidney function in rats.[21]

It has been suggested that Vit E protects hepatic and renal tissues against various toxic agents *in vivo*.[23,26,46] Vit E was also reported to attenuate hepatic and renal injury induced by cyclophosphamide,[47] cypermethrin,[48] cisplatin,[27] and water immersion-restraint stress.[24] In the current research, an increased ALT level due to hepatotoxicity was decreased, when Hypo group was given with Vit E. Serum albumin level was also improved by Vit E. Similar to our results, Abdel-Daim *et al*.[49] have reported that Vit E administration leads to decreased oxidative damage in hepatic tissues induced by fipronil.

Furthermore, the present study showed that Vit E administration decreased MDA levels in Hypo-Vit E group compared to Hypo group which showed that Vit E had an antioxidant effect. The results of the present study are consistent with the results of Sarandöl *et al*.[50] which examined the effects of Vit E on oxidative stress markers in renal and hepatic tissues of adult hypothyroid rats. However, our study was more comprehensive than Sarandöl *et al.* study.[50] Indeed, in addition to oxidative damage markers, we also examined liver and kidney function

with determining compounds such as ALT, BUN, creatinine, and serum albumin. Many studies also have reported that hypothyroidism has severe adverse effects during the growth period.[11,51,52] In this study, one of the reasons of the severe adverse impact of hypothyroidism on kidney and liver function of juvenile rats maybe is due to the age of the rats in our study.

Increased thiol levels in hepatic and renal tissues after Vit E supplementation are likely to play a role in decreasing oxidative stress in these tissues. Inconsistent with our results, it has been observed that there is a negative correlation between liver GSH and oxidative damage.[53] It seems that Vit E may either act as an antioxidant or restore activities or levels of antioxidant molecules such as thiol.

It has been well documented that reactive radicals and oxidants are harmful to cells and tissues.[54] It has been reported that O_2 produces peroxyl radicals that extract H atoms through exposed near polyunsaturated fatty acids (PUFAs) to trigger a chain reaction. In fact, it has been demonstrated that Vit E provides an H atom to damaged PUFAs, reproducing stable lipids. In addition, it has also been reported that Vit E scavenges peroxyl radicals. Thus, it seems these effects of Vit E eventually lead to protecting them from oxidative stress injury by increasing antioxidant or anti-apoptosis compounds.[30,49,55,56] In point of fact, tocopherols diminish oxidative damage mainly because of their capability to clean up lipid peroxyl radicals more rapidly than such radicals' reaction with fatty-acid side chains or proteins.[57] Studies also have shown that administration of Vit E results in reduce oxidative stress and inflammation in intestinal mucositis induced by 5-fluorouracil administration.[58]

In this study, Vit E also restored SOD and CAT activity in Hypo-Vit E group compared to Hypo group. In confirming our results, previous studies have reported that Vit E administration leads to protecting the rat liver against hepatic reperfusion injury and modulated biochemical indexes like CAT and SOD.[46] Antioxidant enzymes such as CAT and SOD collect active oxygen species including H_2O_2 and O_2^-, respectively.[59] Glutathione peroxidase scavenges H_2O_2 and also lipid hydroperoxides, which results in the generation of oxidized glutathione (GSSG). Glutathione reductase acts to restore levels of reduced GSH via the reduction of GSSG by consumption of NADPH.[59] It was also previously reported that IP injection of Vit E (500 IU/kg) once a week significantly increased level of reduced GSH in kidney and liver of PTU-induced hypothyroid rats.[50] It was also suggested that enhanced GSH levels by Vit E may be followed by increased level of T3, since GSH acts as a cofactor in the conversion of T4 to T3 in peripheral tissues[50] that may play a role in the results of the current study, although further research is needed.

Finally, Vit E improved serum thyroxin level slightly in the current research but the effect was not significant. Considering these results, it seems that the beneficial effects of Vit E which were seen in the present study are not due to its protective effect against direct effect of PTU on thyroid glands; nevertheless, more research needs to be conducted. Furthermore, a comparison between the effects of Vit E and thyroxin administration is suggested to be evaluated in future studies.

In conclusion, the result of present study indicated that administration of Vit E may modulate harmful effects of hypothyroidism on liver and kidney during juvenile growth. Protection against hepatic and renal tissues' oxidative stress probably provides beneficial effects of Vit E.

Limitations

The primary limitation of this study was that serum level of Vit E was not measured. However, many studies evaluated the effect of Vit E on different tissues without measuring serum levels of Vit E.[50,60] But the result would be more reliable if serum levels of Vit E were measured. A second limitation was a group as a normal control treated by Vit E was not included. Thus, we suggest that these limitations need to be taken into consideration in future studies.

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Conflicts of interest

There are no conflicts of interest.

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