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Original Research Article

Effects of Alpha-Tocopherol Supplementation on Adult Mices: Biochemichal Status, Histopathological Analysis and Review of Genes Modulated by Vitamin E

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Abstract: Vitamin E (VE) is an antioxydant defense system and a signaling molecule which has been the subject of various clinical trials in cancer chemoprevention or in adjuvant therapy after chemotherapy. In some circunstances it is indexed to act as a pro-oxidant inducing adverse effects such as progesssion of cancer metastasis or diabetes. The objective of this work is firstly to investigated the effect of VE (α-T) supplementation on mices, in way to evaluate the risk in developping diabetes and secondly to make review on vitamin E modulated genes. The study was performed on 32 adult albino mices in which alpha-tocopherol was administred at different doses. After, blood biochemical paramaters status has been analysed. Renal damages were researched by histopathological analysis. We have made review on VE modulated genes through indexed articles in genetic databases, PubMed Central and Google scholar. An inadequate status of blood biochemical paramaters especially, glucose level, hyperlipidemia and a hypercreatininemia has been observed. Renal damages with modifications in structures were noted. A list of genes modulated by VE, which could explain mechanisms by which α-T-induced diabetes could appear was highlighted. The study shows that high doses of α-T supplement resulted in disorder of biochemical parameters, with dysfunction of renal tissue and development of diabetes.

Keywords: Vitamin E, Alpha-tocopherol, Biochemical parameters, Diabetes, Genes expression.

INTRODUCTION

Vitamin E (VE) is micronutrient present in the cell membranes, in intracellular organelle membranes and in the matrix extracellular fibers (Anku *et al*., 2021, Poaty *et al*., 2021, Wang, *et al*., 1999). It interacts in various biological processes, for example, cell cycle and apoptosis, regulation of many genes expression via cell signaling pathways and acts as an potent antioxydant defense system (Kim *et al*., 2019, Luna *et al*., 2018, Borel *et al*., 2016). Indeed, it interacts with vitamin C to stabilize and protect cell membranes, proteins, lipids and DNA from oxydative damage (Sotomayor *et al.*, 2019). It inhibes in the cell menbranes the lipid peroxidation induced by reactive oxygen species (ROS) or nitrogen species (RNS) (Galmés *et al.*, 2018, Landrier, 2011).

VE is also considered to have anti-inflammatory, neuroprotection, reproduction and immune functions, anticancer and antidiabetic effects (Ferrero, 2021, Kim *et al*., 2019, Lloret *et al*., 2019, Lee *et al*., 2018). So, the micronutrient has been the subject of multiple clinical trials in diverse conditions such as infections, alzheimer and cardiovascular diseases, cancers and diabetes (Anku *et al*., 2021, Galmés *et al*., 2018, Morris *et al*., 2015). However, the results obtained are sometimes discordants and the beneficial effect of this antioxdant in vivo in humans is often questioned (Miller *et al*., 2005).

VE contains two natural members: tocopherols and tocotrienols divided each other in four variants: alpha (α), beta (β), gamma (γ) and delta (δ) (Lee *et al*., 2018, Rimbach *et al*., 2002). Alpha-tocopherol (α-T) is

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considered to be the most present in vegetable and it is known to be the main bioactive variant found in plasma (Anku *et al*., 2021, Morris *et al*., 2015).

VE is a liposoluble molecule with the metabolism which is comparable to lipid, and there has a correlation between VE and circulating blood parameters as cholesterol and triglycerides (Sotomayor *et al*., 2019).

In continuity with a previous study (Poaty *et al*., 2021, Moukobolo *et al*., 2021), the present work aims mainly at investigating directly the effects of α-T supplementation on blood biochemical parameters and in renal tissue of mices, in order to evaluate the risk in developing diabetes. Secondly, the study has been associated with a literature research of genes modulated by VE.

MATERIALS AND METHODS

The experimentation has been performed in National Research Institute on Health Sciences of Congo (IRSSA). Protocol was appproved by Medical Congo Ethic Commettee, the study number 048/MRSIT/IRSSA/CERSSA.

MATERIALS

Materials used for animal experimentation were: mices, drug and rich foods vitamin E intake.

Animal models

A total of 32 healty CD1 adult Albino mices (male and female) were selected, all aged of 9 weeks. They were randomly divided into seven groups (n = 4 in each group). The first consignment of mices was a control group. The animals were obtained from National Institute of Research on Health Sciences (IRSSA) of Brazzaville, where they were living in good conditions.

Drug

We used synthetic vitamin E: alphatocopherol acetate (α-T-acetate), liquid viscous capsules dosed to 500 mg, Pharma GDD Laboratory, France.

Rich dietary vitamin E intake

Diet was based on patties (approximative consommation of 35g daily) essentially made from a mixture of leafy vegetables, oil and eggs (Table-1). All the foodstuffs rich in α-T (Moukobolo *et al*., 2021, Gouollaly *et al*., 2020) were procured in the public markets of Brazzaville.

Methods

Alphatocophérol supplementation

Vitamin E was used in form of α-T-acetate capsules. It has not been combined with vitamin C. The content of capsule was dissolved in mineral water and it was given via oral gavage, 4 days per week during 12 weeks. Beginning with 150 mg, the dose supplementation of α-T-acetate was increased according the group. A maximal dose of 750 mg has been administered in the group 6 and 7. After 12 weeks, we evaluated the changes in the blood and in organism tissue (kidneys). The experiments were reproducted twice in the same conditions, in order to reevaluate the findings.

Weight parameter

In view of drug intake, body weight was measured daily.

Biochemestry analysis

Blood samples were collected and centrifuged in order to obtain serum and plasma. The parameters analysed the same day were plasmatic creatinine, glucose, uricemia, triglycerides, total cholesterol and the cholesterol fractions : high density liprotein (HDL), low density lipoprotein (LDL). Those biochemichal parameters were measured by spectrophotometer biochemical analyser (CyanSmart, ref cy009, version 20160902-(5.1), Belgium) in the Biochemical Laboratory at Teaching Hospital of Brazzaville. Normal control were considered according to parameters of our control mice and literature data (Table-2) (Zhao, *et al*., 2019, Bondonny, 2018).

Histopathological analysis

Mices were killed from 12 to 14 weeks later after α-T intake in order to preleve renal and hepatic tissues from each mice. The tissues were fixed in 10% of formaldehyde for three days, then conserved in paraffin embedded blocks. For histopathological analysis, tissue were stained in Haematoxylin-Eosin coloration (HE) counterstaining according to the usual protocol. Tissues in HE-stained, paraffin-embeed sections from kidneys α-T-acetate and control mice were visualized using Optika microcope, and pictures were acquired using camera logicial Micro Cam Labo II. Note that data for liver tissue are not reported in the present paper.

RESULTS AND DISCUSSION

The findings do not differ between male and female mice. Disorders in mass body, biochemical parameters and renal tissue were observed in mice groups at a certaine dose of α-T-acetate supplementation.

Obesity

Three months after experimentation, we noted progressive weight gain (Fig-1), predominant in the mice of groups 4 to 7. The study showed that the intake of synthetic α-T at high dose led to excess of the body weight with increased adipose tissue in the mices of groups 5 to 7, signing a real obesity. Unfortunately, obesity is known to be a risk factor for diabetes and several molecules in synergia with VE could originated that obesity (Luna *et al*., 2018).

According to review, α-tochopherol transfer protein is known to facilitate the transfer of the none bioactive α-T form into the liver and target tissues (Galmés *et al*., 2018). But, there are several other molecules which participate in the transport of VE from the cells. Among them:

CD36, NPC1, SR-B1, ABCA1, SCARB1, APOA1 (located in the apical or basolateral cells membranes), lipoproteins (using among others LDL, HDL cholesterol receptor) (Galmés *et al*., 2018, Borel *et al*., 2016).

The variations of above molecules could cause disorder in plasma lipids and lipoproteins and play a role in the pathogenesis of obesity (Galmés *et al*., 2018). Indeed, CD36 acts for LDL, and its excess induces obesity. α-T reduces lipoproteins and inhibes expression of CD36. SR-B1 coded by SCARB1 gene, acts for HDL and its deficiency improves obesity. ABCA1 acts in the circulation of lipophilic compounds as cholesterol, HDL and VE. ABCG1 acts in the repartition of VE, and its inactivation induced VE accumulation in tissues (Galmés *et al*., 2018).

Biochemical parameter variations

All the blood biochemical parameters (Table-3) showed an increased level concentration compared to the control group 1 and 2. The fat mass was predominant in the abdomen with one or two fatty nodules in group 7, from the dose of 400 mg of α-T-acetate. Indeed, an inadequate status of blood glucose level (Fig-2) urecemia and creatinine has been noted. An hyperlipidemia has been observed more pronounced with total cholesterol and triglycerides than with cholesterol fractions. LDL and especially HDL, were slightly increased.

Vitamin E contained in the most plants is supplied by the meal in the body in a bio-inactive form, and the digestion of vitamin E follows that of the lipids (Anku *et al.*, 2021, Landrier, 2011). It is incorporated into the chylomicrons to be absorbed in the duodénum. A part is exchanged with HDL lipoproteins and especially intestinal LDL and endothelial lipases to be distributed in the peripheral tissues. The remaining part is stocked in the liver (Landrier, 2011). α-T is incorporated into VLDL (Very low density lipoprotein) with the help of α-tocopherol transfer protein (α-TTP) for distribution to tissues (brain, heart, liver, muscles, kidney, skin). Kidney and liver are among the sites where VE is mainlly stocked and these organs play an important role in glucose homeostatsis (Galmés, 2018).

VE present in tissues is supposed to protect the cell membranes, proteins, lipids and DNA from oxydative damages (Sotomayor *et al*., 2019). But in some circumstances with increased oxidative stress, it has adverse effects and act as a pro-oxydant (Jansen *et al*., 2016, Rietjens *et al*., 2002).

Statistic analysis give mean values for each biochemical parameters in the different groups and some ones (4, 5, 6 and 7) largely differ from the control group.

Globally, values of the control group 1 and group 2 (no rich dietary vit E and intake of small dose of 150 mg α-T-acetate) do not show a very big difference. Thus, the adequate dose with any effects, not harmful, may be the low dose of 150 mg α-T. Control mices (group 1) suggests that in general, balanced diet procured adequate vit E by normal et diversified vegetable foods reported in many articles (Anku *et al*., 2021, Moukobolo *et al*., 2021, Gouollaly *et al*, 2020), without distubance in blood biochemical parameters.

Interestingly, group 2 (without rich dietary VE intake and only intake of 150 mg α-T-acetate) presented low levels concentrations in glucose and total cholesterol, suggesting that intake of small quantity alone of VE improves glycaemia (Table-3, Fig-2) and total cholesterol. In other words, VE consumption only at low doses has hypocholesterolemic property and it reduces plasma glucose; therefore, it could have beneficial effects in the management of type 2 diabetes mellitus. These results have been already reported in one experiment in vitro (Zappe *et al*., 2018).

The study also highlighted (per the groups 4 and 6, without rich dietary intake) that, the deleterious dose of α-T-acetate starts at the high dose of 400 mg daily, because we noted a real disorder in all biochemical parameters levels (elevated glycaemia and uricemia, cholesterol, triglyceridemia and creatininemia). In addition, groups 3, 5 and 7 (with rich dietary intake) indicate that a diet very rich in VE potentiates the effects of α-T supplement.

In opposite of low doses (150 mg), the high doses of the synthetic α-T increase plasma glucose level (Fig-2). These results are in accordance with some studies which have demonstrated that α-T influences glycaemia level and causes type 2 diabetes (Luna *et al*., 2018, Koyama *et al*., 2013).

In summary, as suggested in a previous study (Poaty *et al*., 2021), α-T supplementation at high dose do not provide beneficial effect. It affects blood parameters (Table-3) by inducing hyperglycaemia, hyperlipidemia and hyperuricemia. At high dose of α-T-acetate (beginning in our study at 400 mg) in groups 4 to 7, whatever the diet, we observed a clear disturbance in the glucose, protein and lipid metabolism with onset of renal diabetes induced. Those observations are in line with other studies (Koyama *et al*., 2013, Luna *et al*., 2018).

Renal damages

Concerning renal tissue, three elements caught our attention: adipose tissu auround the renal cortex, tubules and glomerular area.

Compared to the control group (Fig-3a, b), we noted in pathologic mice groups (4 to 7) a growth in number of adipocytes cells and in volume of adipocytes (Fig-3c). Proximal tubules of the pathologic groups decreased, dilated with wide light (Fig-3c, d). We also observed a decreased in area of glomeruli.

These damages as mentionned above, are associated with an increase concentration of serum level of : lipides (total cholesterol, tryglycerides, lipoproteins) (Table-3), creatinine, urecemia and glucose (Fig-2). Additionally, high-dose of vitamine E supplementation induced renal failures by decreasing proximal tubules and glomerular area in favor of induced-renal-diabetes. Deleterious renal tissues have already been reported in mice for the high doses of VE (Jansen *et al*., 2016).

Alphatocopherol and genes expression

We made review to understand how VE can induce the diabetes. According to published articles (Landrier, 2011, Azzi, *et al*., 2004a), α-T is known to be a signaling molecule, especially for signal transduction enzymes and transcription factors (Zingg, 2019, Kim *et al*., 2019, Luna *et al*., 2018, Borel *et al*., 2016). It regulates expression of several genes in multiple tissues and cells, via cell signaling pathways and nuclear receptors (Fig-4) as for instance : PXR (Pregnane X Receptor), PKC (Protein Kinase C), Cox (Cyclo-oxygenase), AP-1 (Activactor Protein 1) or NF-kB (Nuclear Factor Kappa B) (Lloret *et al*., 2019, Landrier, 2011, Azzi *et al*., 2004b, Rimbach *et al*., 2002). According some authors (Rimbach *et al*., 2002, Borel *et al*., 2016), its role of gene modulation could explain adverse effects observed with VE exogenous supplementation. Added to this, are the possibility of : tissue and cell-specific pathways in which VE acts, genetic variations of persons undergoing clinical trials, dietary patterns (nutritional value of meals consumed), lifestyle and environmental factors (Kim *et al*., 2019, Lloret *et al*., 2019, Jansen *et al*., 2016).

We note that Azzi *et al*., (2004a, 2004b), reported five groups of genes in which VE acts (Table-4). The variations of the group 2 (Table-4) genes including CD36 and SR-B1(mentioned above), involved in lipid uptake, could originate obesity, one of the main cause of type 2 diabetes mellitus (Galmés *et al*., 2018).

In addition, α-T also modulates the expression of adipogenesis marker genes including APO-1/ FAS ligand, CEBPα, Pref-1 and PPARγ (a transcription factor increased by α-T) (Landrier, 2011, Azzi *et al*., 2004b, Michalik *et al*., 2000). According to review, there is a link between increased adipocytes (and therefore obesity) and the disorder in serum parameter levels, leading to diabetes. Indeed, adipokines (cytokines) which include adiponectin and leptin (respectively regulated by PPARγ and CEBPα), are synthesized by the adipocytes, and they are involved in the regulation of glucose and lipids (Landrier, 2011, Koyama *et al*., 2013, Michalik *et al*., 2000).

Several studies reporte that, in mice and also in human individuals, adipocyte-derived factors are altered in obese subjects, resulting in β-cell dysfunction and insuline resistance which cause diabetes (Manning *et al*, 2014, Michalik *et al*., 2000).

Note also that α-T controls many microRNAs expression levels (also called miRNAs or miRs) (Ferrero *et al*., 2021, Fischer et al., 2019, Luna *et al*., 2018). A published study mentionned that dysregulation (in promoter regions) of two small RNAs controlled by α-T : miR-9-1(on chromosome 1) and miR-9-3 (on chromosome 15), are associated with obesity and diabetes (Luna *et al*., 2018). That dysregulation has impact on epigenetic regulation of DNA repair genes such as MLH1, one of genes of the MMR system involved in Lynch syndrome (Zappe *et al*., 2018, Poaty *et al*., 2017). miRNAs are small non-coding RNAs present in nuclear cells with a post-transcriptional regulator function (regulation of gene expression of several signal pathways) (Giulio Ferrero, 2021, Luna, 2018).

On view of all the literature data, dysregulation of the genes regulated by VE and cited above might be one mechanism by which diabetes could appear.

Unfortunately, hyperglycaemia status is associated with intense oxidative stress, leading to increased production of ROS and RNS (Ayeleso *et al*., 2016). The latter active the nuclear redox sensitive transcription factor kB which upregulates some genes as cytokines (TNF-α, IL-6), cell adhesion molecules (ICAM-1, VCAM-1) or endothelium 1, leading in increased lipid peroxidation, proteins and DNA disorders (Ayeleso *et al*., 2016, Rimbach *et al*., 2002), associated with organ tissues damages as observed in our study.

Table 1: Rich Foods vit E intake by mice groups

Categories	Aliments	Quantities consumed (g)
Oil	Unrefined oil palm	30
Plant	Spinach	50
Muts	Soybean	450
	Wheat	450
	Curcubita pepo	50
Fruit	avocado	50
Other	Eggs	1(of 50)

Table 2: Mice normal biochemical parameters values

Blood paramerters	Normal parameters values (controls mice)	Litterature values	References
Serum creatinine	0.46 mg/dl	0.42 ± 0.07 mg/dl	Zhao et *al.*, 2019
Uricemia	22.5 mg/l	25.9 ± 3.2 mg/dl	Zhao et *al.*, 2019
Glucose	89 mg/dl	112 ± 4.6 mg/dl	Zhao et *al.*, 2019, Bondonny et *al.*, 2018
Triglycerides	37 mg/dl	-	Our study, 2021
Cholesterol	81 mg/dl	-	Our study, 2021
HDL	0.28 (g/l)	-	Our study, 2021
LDL	0.19 (g/l)	-	Our study, 2021
Ratio HDL-Cholesterol	34 mg /dl	-	Our study, 2021

Table 3: Blood biochemical parameters levels of mice groups

Mice Groups (n=32)	**α-T (**mg/day) and **dietary Vit E intake**	**Glucose** (g/l)	**Total cholesterol** (g/l)	**Triglycerides** (g/l)	**HDL** (g/l)	**LDL** (g/l)	**Uricemia** (g/l)	**Serum creatinine** (mg/l)
Group 1 (Control group)	**No α-T** No rich dietary vit E intake	0.96 0.90 0.91 0.80	0.70 0.91 0.89 0.75	0.30 0.41 0.39 0.37	0.22 0.31 0.30 0.29	0.20 0.19 0.18 0.21	21 22 25 22	4.5 5.2 4.7 4.2
	Median value	**0.89**	**0.81**	**0.37**	**0.28**	**0.19**	**22.5**	**4.65**
Group 2	**α-T 150 mg,** No rich dietary vit E intake	0.31 0.22 0.30 0.48	0.52 0.82 0.70 0.80	0.41 0.62 0.44 0.55	0.33 0.50 0.39 0.41	0.25 0.33 0.34 0.38	25 29 26 24	5.2 4.9 5.9 3.7
	Mean value	**0.33**	**0.71**	**0.50**	**0.41**	**0.32**	**26**	**4.92**
Group 3	**α-T 150 mg,** and rich dietary vit E intake	1.00 1.10 1.08 0.99	0.90 0.89 0.98 0.87	1.01 1.10 1.20 1.28	0.42 0.30 0.40 0.29	0.41 0.44 0.49 0.50	80 78 62 75	7.1 7.9 6.9 5.9
	Mean value	**1.04**	**0.90**	**1.15**	**0.35**	**0.46**	**73.75**	**6.95**
Group 4	**α-T 400 mg** No rich dietary vit E intake	1.45 1.52 1.49 1.69	0.75 1.40 1.36 0.96	0.89 1.38 1.29 1.94	0.41 0.32 0.21 0.39	0.32 0.72 0.30 0.67	88 69 73 78	5.6 5.3 6.3 5.3
	Median value	**1.53**	**1.12**	**1.37**	**0.33**	**0.50**	**77**	**5.62**
Group 5	**α-T 400 mg** and rich dietary vit E intake	2.50 1.92 2.07 1.99	0.85 1.00 0.99 1.20	1.25 1.21 1.38 1.00	0.28 0.30 0.39 0.49	0.62 0.58 0.42 0.45	121 89 66 62	8.6 7.9 9.9 8.7
	Median value	**2.12**	**1.01**	**1.21**	**0.36**	**0.51**	**84.5**	**8.8**
Group 6	**α-T 750 mg** No rich dietary vit E intake	1. 40 2.80 2.00 1.67	2.05 2.01 2.41 1.00	1.45 1.59 1.62 0.98	0.40 0.68 0.49 0.45	0.38 0.45 0.52 0.40	78 69 72 60	9.7 9.9 9.0 8.9
	Median value	**1.97**	**1.07**	**1.41**	**0.50**	**0.43**	**50.25**	**12.13**
Group 7	**α-T 750 mg** and rich dietary vit E intake	2.70 2.12 2.19 2.68	0.92 2.49 1.90 2.18	1.30 1.43 1.40 1.66	0.30 0.42 0.38 0.22	0.39 0.58 0.50 0.61	135 79 72 70	7.8 9.2 7.6 6.9
	Median value	**2.42**	**1.87**	**1.45**	**0.33**	**0.52**	**89**	**7.9**

Table 4: Genes expression regulated by alpha tocopherol (Zingg *et al*., 2019, Azzi *et al*., 2004a, 2004b, Rimbach *et al*., 2002)

	Function	Genes
1	Genes which act in the uptake and degradation of α-T	α-TTP (α-tocopherol transfer protein), CYP3A (cytochrome P450), γ-glutamyl-cysteine synthetase heavy subunit, glutathione-S-transferase.
2	Genes involved in lipid uptake	CD36, SR-B1, SR-A1/2
3	Genes involved in the modulation of extracellular proteins	α-tropomyosin, Collagen-α-1, MMP-1, MMP-19, Connective tissue growth factor,
4	Genes involved in adhesion and inflammation	E-selectin, ICAM-1, VCAM-1 integrins, Glycoprotein IIb, IL-2, IL-4, IL-β, TGF-β, NF-kB
5	Genes implicated in cell signaling and cell cycle regulation	PPAR-γ, Cyclin D1, Cyclin D-E, Bcl2-L1, P16, P21, p27, Bcl2, pRb, CD95, P53, PKC, 5a-steroid reductase type 1

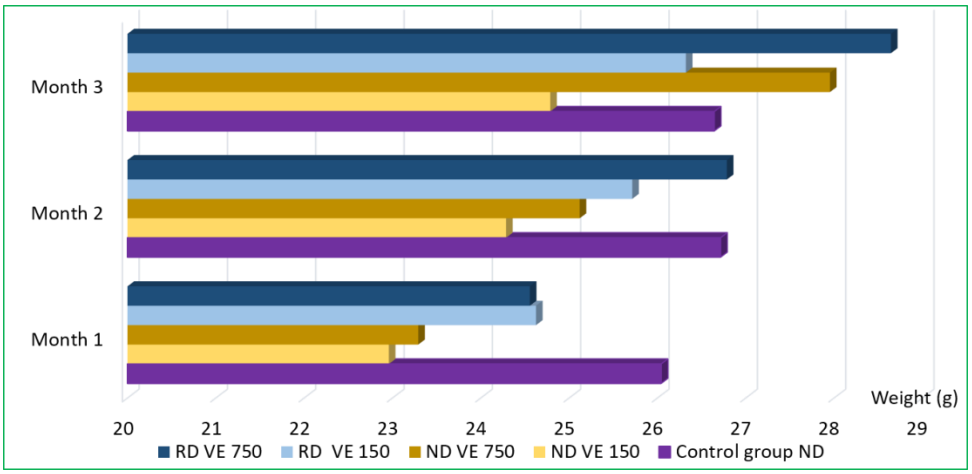

Fig-1: Curve of mice weight

Note a real progressive increased body weight for mices of group 3 (150 mg, RD VE), 6 and 7 (750 mg, RD VE/ND VE).

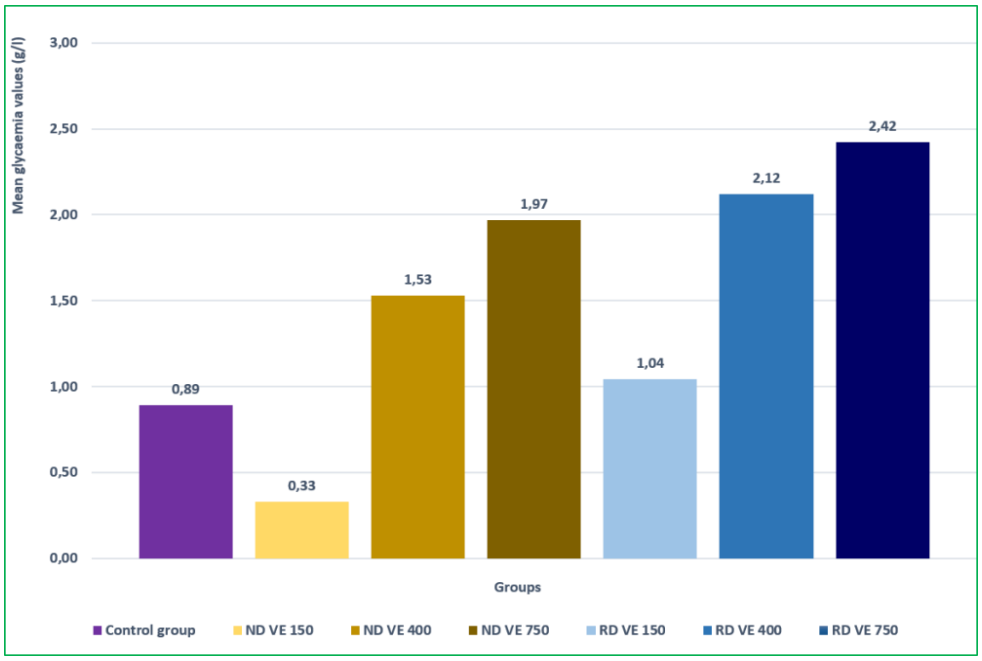

Fig-2: Variation of mean glycaemia values according the mice groups

(In purple, control group ; in variant yello, only VE supplementation with normal diet (ND VE). In variant blue, VE supplementation with rich dietary VE (RD VE). Note an increased glycaemia in group with high dose of VE (400 mg to 750 mg).

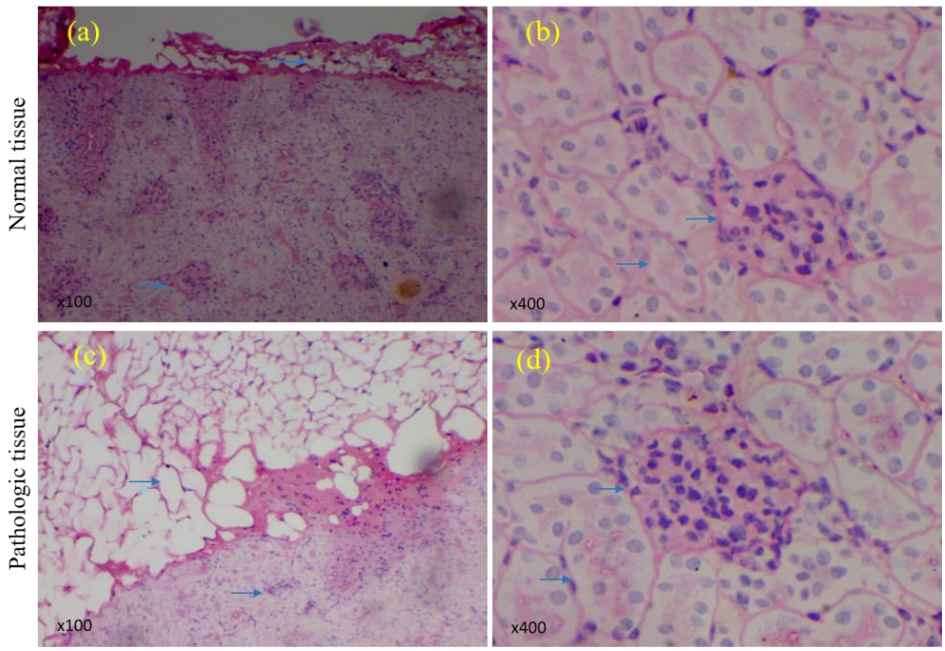

Fig 3: Kidney α-T mice histopathological images: (A) Normal kidney of group control: weak adipocyte tissue in cortical area, multiple glomeruli in corticomedular areas. (B) Normal kidney of group control showing nomal glomerili and multiples proximal tubules. (C) Pathological kidney of mice group 7: Excess of adipocytes tissue and decreased conjunctive fibers in area of glomeruli. (D) Pathological kidney of mice group 7 : reduced and dilated proximale tubules with increased epithelial cells in tubules and glomeruli

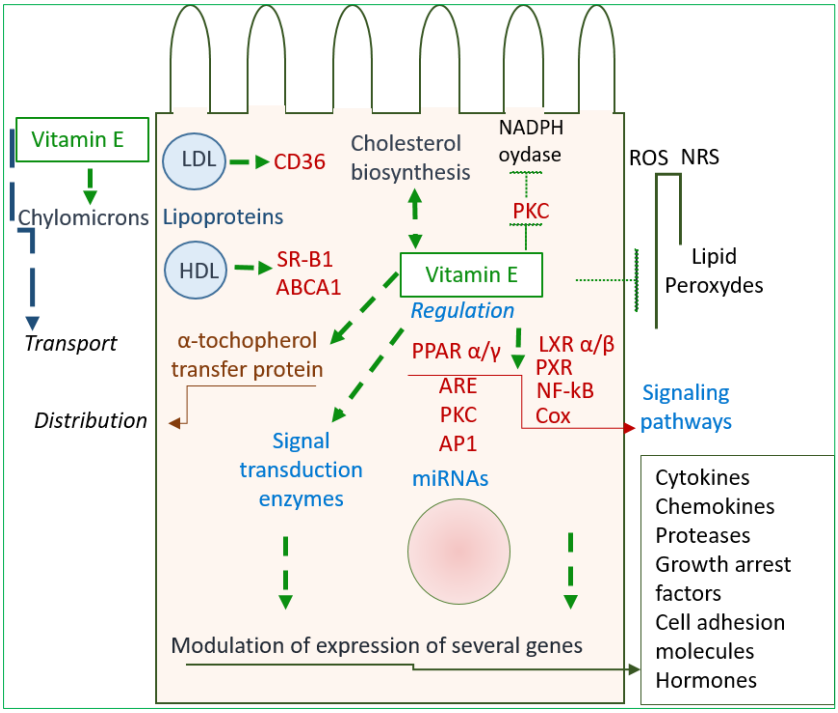

Fig 4: Genes modulated by vitamin E

Representation in enterocyte cell of some genes which expression is regulated by vitamin E. (Zingg *et al*., 2019, Azzi *et al*., 2004a, 2004b, Rimbach *et al*., 2002).

Study Limitations

The anomalies observed in our study are not induced by α-T alone. There is a synergy with other molecules (cited above) which are not studied in the present work.

To better understand the mechanism from which α-T- induced diabetes at high dose, it will be interessting to study key genes involved in lipid uptake and to analyse protein expression of some adipogenesis marker genes cited in this work.

SUMMARY AND CONCLUSION

The study showed that the intake of synthetic α-T at high dose led to excess of the body weight with increased adipose tissue in the mices, resulting in hyperplasia and hypertrophy of adipocytes cells.

All the blood biochemical parameters showed an increased level concentration compared to the control groups. α-T intake is strongly involved in glucose and lipids metabolism. The low dose of α-T supplementation decreased plasma glucose while we noted significant effects of high dose of α-T resulted in: obesity, hyperglycaemia, dyslipidemia associated with renal dysfunction. All these damages induced development of type 2 diabetes.

DECLARATION

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Author contributions: Conceived, designed the experiments and wrote the paper: HP. Performed the experiments FAMK and HP. Analyzed the data: FAMK, HP and EM.

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Data availability: All relevant data are in the manuscript.

Conflicts of interest: We declare no conflict of interest exists related to this paper.

HIGHLIGHTS

1. Animal experiment of alpha-tocopherol (vitamin E) with biochemical status, histopathological analyse and review of genes regulated by vitamin E.
2. The experiment indicates that vitamin E supplementation at high dose has harmful effects for mice organism, but interestingly low dose improve blood parameters, especially glycaemia and cholesterol.
3. This study procure a reproducible *in vivo* animal model of diabetes which can be used for an experimentation of medecinal plants.

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