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Diabetes Mellitus type II has not affected α-tocopherollevels in sera of Iraqi Diabetic patients

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Abstract: Diabetes is a disease that described by worse glycemic control for which risk of the type IIDMprogresses with age. Anincrease in blood glucose levels causes elevated oxidative stress, which promotes the advancement of diabetes-associated complications.The aim of this research was to clarify the effects of the common oral antidiabetic drugs (glibenclamide or metformin) on α-tocopherol. The study includes 120 subjects with T2D and 60 healthy persons. The patients were under treatment with glibenclamide or metformin. Patients has non-significantly changed in serum α-tocopherol concentrations compared with the conrol group. The results indicated that metformin and glibenclamide cannot significantly change α-tocopherollevels in sera of diabetic patients compared with healthy control. In conclusion, serum α-tocopherol level cannot be used as an indicator for the choice of treatment in those diabetic patients.
Keywords: α-Tocopherol, Metformin, Glibenclamide, Type II Diabetes Mellitus.

Introduction:

Diabetes mellitus is a group of metabolic disorders described by hyperglycaemia subsequent from reduction of insulin secretion, defect of insulin action or both[1]. Type II diabetes arises from two principal metabolic defects: advanced pancreatic β-cell dysfunction and insulin resistance. β-Cell dysfunction cooperated with insulin resistance leads to hyperglycaemia and subsequently to type II diabetes[2].The treatment of type II was focused in the direction of restoring metabolic regularity by enhancing insulin secretion and decreasing insulin resistance. These aims are proficient through the use of oral hypoglycemic agents, precisely the sulfonylureas. The goal of oral hypoglycemic agents is to manage complications of diabetes, such as retinopathy, liver damage, nephropathy, neuropathy and other complications[3,4].

Oral antidiabetic drugs such as glibenclamide, are normally used to stimulate insulin secretion by blocking an ATP-dependent potassium channel on plasma membrane of pancreatic β-cells[5]. Despite the worldwide use of oral antidiabetic drugs, loss of β-cell mass and performance, and hypoglycemic episode have raised concern relating to its use[6]. Oral antidiabetic drugs may cause celldeath in β-cell lines and rodent islets, and its treatment failure is common in long-term usage[7]. However, some proof has recommended that chronic use of oral antidiabetic drugs may lead to the endoplasmic reticulum (ER) stress in β-cells, which finally causes exhaustion of β-cell operate[8], and the decline in β-cell perform causes the progressive deterioration of glycemic management. Glibenclamide acts to inhibit ATP-sensitive potassium channels in pancreatic beta cells and to amplify the release of insulin upto serum glucose level by activating an increase in intracellular calcium into the β cells of pancreaticgland[9,10].

Vitamin E (Tocopherol) is a fat-soluble vitamin, that is truly a family of compounds, the tocopherols, found in nature. Alpha-tocopherol is that the most typical and therefore the most active of the seven presently delineate forms-alpha, beta, gamma, delta, epsilon, and zeta. Specifically, D-alpha-tocopherol is that the most potent kind, additional active than the artificial DL-alpha-tocopherol[11]. Vitamin E is the main natural lipid-soluble antioxidant in human tissues and because of its hydrophobicity, transport must fundamentally takes place either through membrane associates, or through some specific proteins, principally with low density lipoproteins (LDL) [12,13].

Biochemical results recommend that α-tocopherol may decrease the possibility of diabetic complications in diabetic patients. However, the results that obtained from randomized clinical trials are inadequate. The aim of this study was to assess α-tocopherol status of patients with type II diabetes treated with metformin or glibenclamide. This was done as a cross-sectional monocentric cohort study employing a control group of unexposed patients.

Materials & methods

The patients were under treatment with glibenclamide or metformin. The participants classified into:

- Q_1: Healthy subjects (male).
- Q_2: Healthy subjects (female).
- R_1: Patients treated with glibenclamide (male).
- R_2: Patients treated with glibenclamide (female).
- S_1: Patients treated with metformin (male).
- S_2: Patients treated with metformin (female).

Materials and methods

Patients

An experimental study was performed in Al-Najaf Center for Diabetes and Endocrinology (Al-Najaf City, Iraq) during 2015. The inclusion criteria were clinical T2DM with duration of diabetes of a minimum of one year. Controls were selected from healthy adult volunteers with established levels of FBS<126 mg/dl. Patient characteristics and laboratory measurements are shown in Table 1.

A total of 120 subjects with T2DM and 60 healthy persons was included. The patients were under treatment with glibenclamide or metformin.

This study was completed in agreement with the ethical standards set by the Declaration of Helsinki. Also, it was approved by the local ethics committee.

Analytical methods

Estimation of α-tocopherol:

α-Tocopherol concentrations were calculated from a comparison of the sample fluorescence intensity with that of standard after correction had been made for blank.α –Tocopherol is mixed with ascorbic acid at alkaline medium to produce a fluorescence property at 290 nm as an excitation and 350 nm as the emission wavelength[14].

Statistical analysis

The results are expressed as mean ±SD.The hypothesis testing was performed using student's "t" taking $p \leq 0.05$ as the lowest limit of significance.

Results

Demographic data, clinical features and laboratory variables for the three groups are shown in table 1.

Vitamin E status

The data are presented in figure 1. Patients were treated with metformin or glibenclamide had non-significantly changed in serum α-tocopherol levels than the control group.

Table 1. Characteristics of the studied patients and controls; quantitative variables are expressed as mean ±SD

Group / Parameter	Healthy subjects		Patients treated with glibenclamide		Patients treated with metformin	
Gender	Male	Female	Male	Female	Male	Female
Number	30	30	30	30	30	30
Age (yrs)	45.4±5.2	45.5±8.7	46.5±9.2	48.2±9.7	48.6±8.8	47.7±9.3
BMI (kg/m^2)	24.7 ± 1.2	24.2 ± 1.5	24.3 ± 1.9 NS	25.6 ± 1.7 NS	25.4 ± 1.8 NS	25.6 ± 1.6 NS
HbA1c	5.11 ± 0.42	5.09 ± 0.61	8.53 ±0.57 *	8.71 ± 0.37 **	9.39 ± 0.31 *	9.41 ± 0.27 **

NS: non-significance versus healthy donors (male).
*: significance versus healthy donors (male).
**: significance versus healthy donors (female).
***: significance versus healthy donors (female).

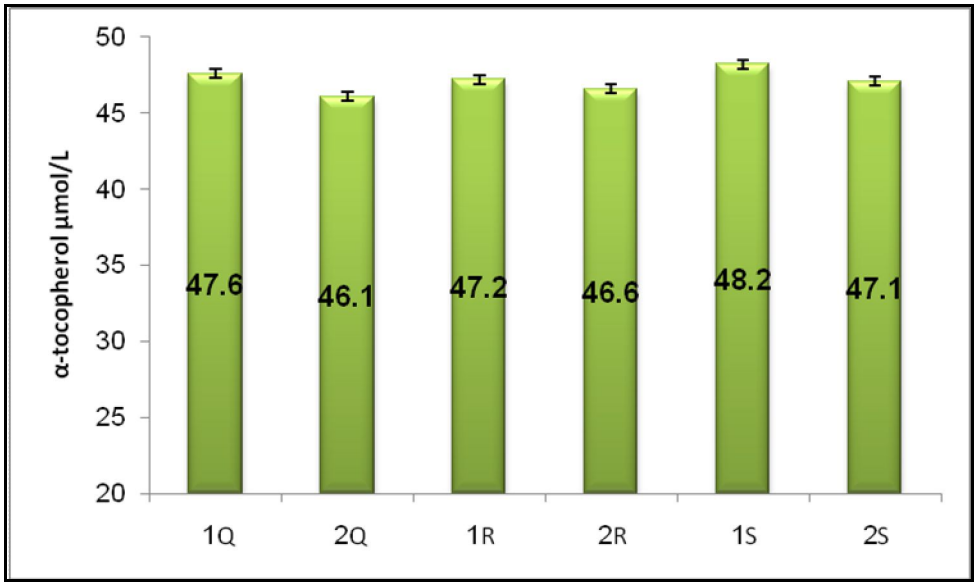

Figure 1: α-tocopherol µmol/L (Mean ± SD) in Serum of Diabetic patients and Healthy Donors Groups.

Discussion

Diabetes has taken place as one of the most significant diseases internationally, reaching epidemic proportions. Global approximates expect that the percentage of the adult population with diabetes will exceed 69% for the year 2030[15].Hyperglycemia in the sequence of diabetes frequently leads to the progress of microvascular complications. Diabetic patients are more disposed tobe raised atherosclerotic macrovascular disease. These complications reason for premature mortality and most of the social and economic problem in the long term of diabetes[16].Glucose can undergo auto-oxidation to produce hydroxyl radicals. Furthermore, glucose reacts with proteins in non-enzymatic pathway, called the Maillard reaction, and develops involved with proteins in sustained hyperglycaemia. Finally, advanced glycation end-products (AGEs) are produced. An increase in AGEs levels induces the deposition of material in the extracellular matrix and the production of reactive oxygen species (ROS)[17]. It has been assumed that α-tocopherol had an inhibitory effect on the glucose auto-oxidation progress, interrupting glycosylation at an initial step in the Maillard reaction[18]. Thus, ensued in the decrease in glycosylated haemoglobin. Other suggested mechanisms of α-tocopherol in improving glycaemic control contain protecting islet β-cell by decreasing the cytotoxicity intermediated by cytokines and their product and probably improving insulin action[19,20].Oxidative stress appears to show a pathogenic role in

metabolic syndrome involving insulin resistance and diabetes. Type 2 diabetes (T2D) is commonest, accounting for 90–95% of all diabetic patients[21].

The results of the present research appear non-significant change in serum α-tocopherol levels in diabetic patients that treated with metformin or glibenclamide compared with the healthy group. The different results were obtained depending upon the practical procedures, choice of individuals and geographical area.

Serum levels of vitamin Edepend on the liver function, which takes up the nutrient after the various forms are absorbed from the small intestine. The liver specially resecretes only α-tocopherol by the use of the hepatic alpha-tocopherol transfer protein[11]; the liver digests and excretes the other vitamin E kinds[22]. Consequently, blood and cellular levels of other forms of vitamin E are lesser than those of α-tocopherol and have been the topics of less investigation[23,24]. Antioxidants protect cells from the damaging effects of free radicals, which are molecules that comprise an unshared electron. Free radical damage cells and might participate in the progress of several types of diseases[25,26]. Unshared electrons have high energy and react quickly with oxygen to produce reactive oxygen species (ROS). Human body forms ROS endogenously when it metabolites food to energy, and antioxidants might protect cells from the damaging effects of ROS. The body is also exposed to ROS from environmental contacts, such as cigarette smoke, and air contamination.. α-Tocopherol is a fat-soluble antioxidant that inhibits the formation of ROS produced when fat undergoes peroxidation. Researchers are considering whether, by limiting free-radical formation and probably through other mechanisms, α-tocopherol might support prevent or delay the chronic diseases linkedto free radicals. Frank vitamin E deficiency is exceptional and overt deficiency symptoms have not been appearing in healthy subjects who obtain a little vitamin E from their diets[27].

α-Tocopherolhas been described to protect endothelial cells against hyperglycemia that prompted oxidative stress by regulating pro-oxidant and antioxidant enzyme activities[28]. A defensive effect of vitamin E supplementation on endothelial dysfunction has been shown in experimental models of diabetic's rats[29].

Correspondingly, a defensive role was shown in a mouse model[30] or in a 2-month rat diabetic model[31]. Depending upon the results of these researches, Kunisaki *et al.* [32] indicated in a rat model that diabetes led to improved protein kinase C translocation and enhanced diacylglycerol production, which both could be prevented by a two weeks α-tocopherol treatment in retinal vascular endothelial cells. In a different diabetes rat model, α-tocopherol reduced, but did not absolutely prevent, diabetes-induced endothelial dysfunction[33]. The treatment of diabetic rat for two-month with dietary α-tocopherol acts toreduce lipid peroxide levels[34]. It remains unclear, however, whether such progressive effects of α-tocopherol might be decreased in models with a longer period of the disease. In fact, diabetes is a chronic disease and most animal studies investigated a considerably short duration of diabetes (from 1 to 3 months). On the contrary, α-tocopherol supplementation does not prevent diabetic vascular dysfunction in long-term diabetes rat model of seven months duration, which is nearly a quarter of the normal life span of the rat[35].

Currently, a controversial explanation about the role played by vitamin E supplementation still exists, depended upon the different methodologies used, i.e. laboratory records or the results of clinical trials. Actually, while laboratory documents report great cellular and biochemical helpful actions, clinical trials fail to support them. Among clinical trials, disagreements have been attributed to differences in selection of subjects, dosage, chemical kinds of vitamin E, the period of treatment, stage of the disease and geographical area[36,37]. Because of these variables, it is still difficult to compare different studies. Additionally, many of the vitamin E trials look for an antiatherosclerotic effect, constructed on the potent properties of vitamin E, in inhibiting lipoperoxidation, and also for other effects such as anti-inflammatory action, inhibition of smooth muscle cell proliferation and platelet aggregation[38]. In conclusion, serum α-tocopherol level cannot be used as an indicator for the choice of treatment in those diabetic patients.

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Conflicts of interest

The authors declare that they have no competing interests.

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