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ORIGINAL ARTICALE

ALPHATOCOPHEROL AS A MARKER FOR PREDICTION OF FAMILIAL TYPE 2 DIABETES MELLITUS IN IRAQI APPRANETLY HEALTHY SUBJECTS

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ABSTRACT

Background: Diabetes mellitus is a chronic physiological disease characterized by increased levels of blood glucose and can lead to damage to the urinary system, circulatory system, eyes, and nervous system. It poses serious challenges to healthcare systems.

Objectives: This study was designed to investigate the role of serum levels of alpha-tocopherol, fasting blood glucose, glycated haemoglobin (HbA1c %), and fasting insulin in predicting type 2 diabetes mellitus (T2DM) in healthy subjects who are members of families affected by diabetes mellitus, compared to subjects from healthy families.

Materials and Methods: This case-control study was carried out at the Specialized Centre for Endocrinology and Diabetes, Baghdad, Iraq, during the period from March to September 2024. It included 190 subjects of both genders, classified into three subgroups:

Group 1 (G1; T2DM): 70 subjects with type 2 diabetes mellitus for more than five years and whose parents had T2DM

Group 2 (G2; Familial T2DM – FT2DM): 70 subjects who are members of the same family as G1 but do not have diabetes.

Group 3 (G3; Control): 50 apparently healthy subjects from different families without any history of diabetes.

Investigations included serum measurements of fasting glucose, insulin, and alpha-tocopherol, as well as blood HbA1c %.

Results: The mean (±SD) value of serum insulin in T2DM was significantly higher compared to FT2DM and controls ($p < 0.05$).The mean insulin value in FT2DM was also significantly higher than in controls ($p < 0.05$).

The mean alpha-tocopherol level was significantly lower in T2DM compared to FT2DM ($p < 0.05$) and controls ($p < 0.05$), and also lower in FT2DM than controls ($p < 0.05$).

Conclusion: The study indicated a decrease in alpha-tocopherol levels in healthy individuals with a family history of type 2 diabetes compared to controls with no family history of diabetes. This suggests that alpha-tocopherol could be considered an early marker for the development of type 2 diabetes in healthy individuals.

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Keywords*:* Diabetes, insulin, prediction, alpha tocopherol.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder, chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood glucose. Hyperglycemia, also called raised blood glucose or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the kidney.[1]

The term diabetes mellitus describes a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbance of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.[2]

Type 2 diabetes begins with insulin resistance, a condition in which cells fail to respond to insulin properly. It accounts for 85–90% of all cases worldwide and can often be prevented or delayed by maintaining a normal body weight, engaging in physical activity, and eating a healthy diet. A hallmark of type 2 diabetes is a decline in β-cell function, which begins as early as 10-15 years before diagnosis and continues throughout the disease process.[3] Pre-diabetes stage in the beginning, because of eating more food, the pancreas begins to secrete greater amounts of insulin than normal. This stage lasts for a few years, after which the B cells begin to lose its ability to produce large quantities of insulin because of some of them reaching the stage of dysfunction accompanied by an increase in insulin resistance by the cells of the body. This stage develops until the rate of dysfunction reaches 40%, then the patient becomes pre diabetes. These stages reach a period of approximately 10 years and are important and vital if they are identified and diagnosed strictly to avoid or delay.[4]

Alpha tocopherol

hydrophobic side chain that can cross biological membranes and hydrogen atom that can neutralize free radicals. Alpha-tocopherol (alpha-tocopherol) is a form of vitamin E that is absorbed and stored in the body at a higher rate than the others. There are eight distinct varieties of vitamin E—four tocopherols and four tocotrienols. All include a hydroxyl group that can give humans' chromane rings.[5].

Being lipid-soluble, vitamin E is found in many different types of tissues and is absorbed in many different ways. The most common type, -tocopherol, plays a role in molecular, cellular, and metabolic activities that are crucial to maintaining healthy levels of lipoproteins and lipids. The current state of knowledge is seen as "critical" for the modification of vitamin E homeostasis in a range of human disease states associated with oxidative stress. Malaria is an example of a disease where -tocopherol has a protective role by preventing the parasites from being damaged by the erythrocyte's high levels of reactive oxygen species.[6]

It has been known for some time in vitro that -tocopherol can serve as a pro-oxidant and promote the per oxidation of lipids.[7] Moreover, a rise in DNA damage due to -tocopherol has been reported after an insult leading to the production of reactive oxygen species (ROS) in cultured cells.[8] Upon encountering ROS, α-tocopherol within lipid becomes oxidised forming its own radical, which requires co-antioxidants (e.g ascorbic acid) in order for the α-tocopherol to be regenerated. If the tocopherol radical is not eliminated there is an increase in lipid peroxidation, a process known as tocopherol-mediated peroxidation(TMP) [9]. These lipid peroxides can generate reactive oxygen species (ROS) that can harm DNA. While TMP- and react with DNA-associated transition metals (Fe, Cu) to produce DNA-damaging hydroxyl radicals (•OH) via the Fenton reaction.[10] . When Cu,Zn-superoxide dismutase is oxidized, free copper is released, which can boost the production of•OH[11].

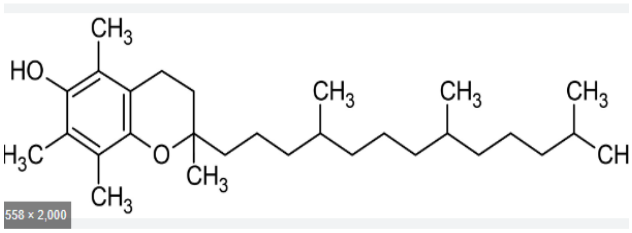


Figure 1. Structure of alpha tocopherol.

Subjects and Methods

This case control study was carried out at at Specialized Center for Endocrinology and diabetes, Baghdad, Iraq, during the period from march to September 2024. It included 190 subjects of both gender classified into sub groups: group 1(G1; T2DM) included 70 subjects with type 2 diabetes mellitus (T2DM) for more than five years and their parents had T2DM, group 2(G2; FamilailT2DM-FT2DM) involved 70 subjects who are member of the same family of G1 but who do not have DM, and group 3 (G3) included 50 apparently healthy subjects of different family without any history of DM who served as control group.

Body mass index was calculated using a global equation:

BMI (Kg/m^2)= weight (Kg)/ height (m ^{2})[8]

Waist circumference (WC) was measured using by inches measure around your middle at halfway between them and hip circumference (HC) was using measure by inches at the top of hip bone, than bring the tape measure away around your body [9].

Five milliliter (ml) of peripheral veinous blood was aspirated from each subject after 10-hous overnight fasting state, divided into two tubes;2.5 ml was placed in (EDTA) tube and it was processed within three hours for HbA1c measurement by high-performance liquid chromatography, using a L9100 automated ion exchange analyzer (Roche Company, USA)and

anthor2.5 ml was placed in a plain tube and left to clot for 15 minute, then centrifuged at 3000 rpm for 10 minutes to separate serum that used for measurements of fasting serum glucose byroxidase method, linear company Spain chemical. insulin by microparticle enzyme immunoassay with an automated analyzer (c 2022 f. Hoffmann-La Roche Ltd) and Alpha tocopherol by ELISA technique. The data was analyzed by the statistical package available from SPSS-26. Data were showed in simple measures of frequency, percentage, mean, standard deviation and range (minimum and maximum values).The significance of the difference for qualitative data was tested using the Pearson ANOVA and t- test. Statistical significance was taken into account when the P-value was equal to or less than 0.05.

RESULTS

Table 1 shows the gender distribution of the three groups without significant differences. The same table also shows the mean (±SD) values of age, BMI, WC, and HC of the three studied groups without significant differences among them.Whereas other study. in Western Finland showed that the family history of DM type 2 was associated with high BMI [8].

Table 1. distribution of gender and mean (±SD) values of age, Body mass index, waist circumference and hip circumference of three studied groups

Parameter	Control(n=50)	FT2DM (n=70)	T2DM (n=70)
Gender^{NS} M(F)	24(26)	32(38)	32(38)
Age^{NS} (years)	43.02 ± 7.63	42.93 ± 7.78	42.48 ± 6.65
BMI^{NS} (kg/m^2)	31.15 ± 2.10	30.97 ± 1.88	30.66 ± 2.22
Waist circumference ^{NS} (cm)	36.34 ± 2.87	36.40 ± 2.89	36.03 ± 3.01
hip circumference^{s}	38.24 2.65	38.27 ± 2.67	37.88 ± 2.85

NS: n± on-significant differences among groups

Table 2. Mean (±SD) values of fasting glucose, glycated hemoglobin, insulin and alpha tocopherol of three studied groups

Parameter	Control (n=50)	FT2DM (n=70)	T2DM (n=70)
Fasting serum glucose (mg/dl)	88.47 ± 8.13	90.0 ± 9.35^{NS}	204.71 ± 58.62$^{♠}$
HbA1c %	4.52 ± 0.59	4.81 ± 0.55^{NS}	8.62 ± 1.41^{o}
Insulin (µu/ml)	12.93 ± 6.13	28.94 ± 21.80*	39.97 ± 34.53*,**
Alpha tochopherol (µg/ml)	21.36 ± 3.27	8.91 ± 1.35**	9.85 ± 1.64$^{●}$

ANOVA and t-test reeval; ♠ significant increase in fasting glucose in T2DM thanFT2DM and controls (p=0.001), NS: non-significant difference between FT2DM and controls, ^{o}significant increase in HbA1c in T2DM than in FT2DM and controls (p=0.001), NS: non-significant difference between FT2DM and controls, * significant increase in insulin in T2DM and FT2DM than controls (p=0.001), ** significant increase in T2DM than FT2DM (p=0.001), ● significant

decrease in alphatocopherol in T2DM than in FT2DM and controls (p=0.001), ●● significant increase in FT2DM than controls (p=0.0

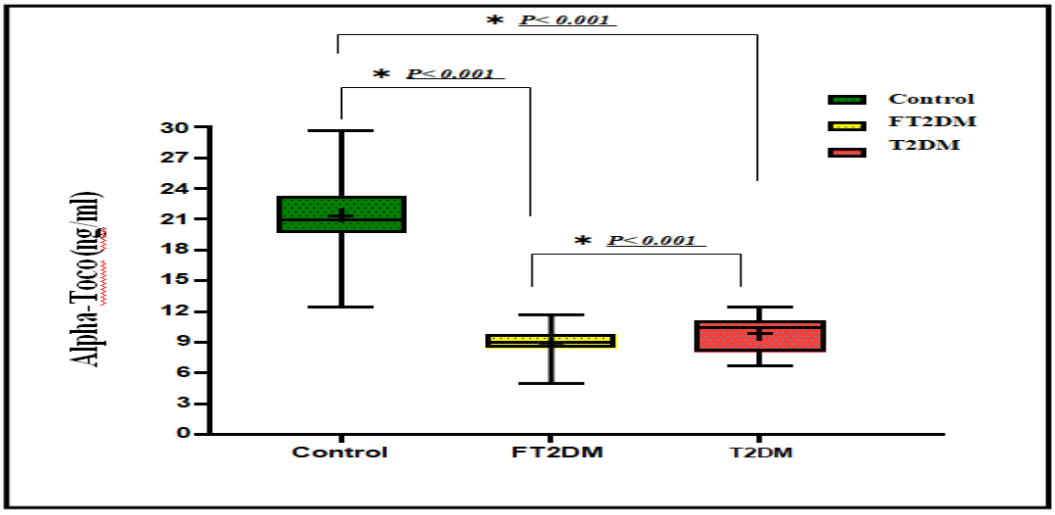
In T2DM, there was no any significant correlations among the studied parameters. The study found significant positive correlation between HbA1c values and alphatocopherol levels (r=0.133 , p 0.27) in FT2DM group. However, there was no other significant correlations in FT2DM, table 2

Table 3. The correlation coefficient(*r*) and (*P*-Value) FT2DM Parameters

	Insulin	FBS	HBA1c	Alphatoco
Insulin	1	0.132	**0.349****	0.179
P-value		0.278	**0.003**	0.142
FBS	0.132	1	0.162	-0.068
P-value	0.278		0.185	0.577
HBA1c	0.349**	0.162	1	**0.276***
P-value	0.003	0.185		**0.022**
Alphatoco	0.133	-0.008	0.05*	1
P-value	0.27	0.951	0.675	

**.Correlationi ssignificant at the 0.01 level (2-tailed).*.Correlationi significant at the 0.05level(2-tailed).

Table 4. The correlation coefficient(*r*)and(*P*-Value)T2DM parameters



ROC and AUC value 0.950 at cutoff value 5.23 unit with sensitivity98.6% and specificity83.7% Which is superior of that of insulin, fasting glucose and HbA1c (table 5). In T2DM patients group, HbA1c and fasting glucose are the best The present results showed that serum alphatocopherol is the best biochemical marker in prediction of T2DM in apparently healthy subjects when differentiated from FT2DM patients (FT2DM biochemical markers in differentiation of healthy individuals from established patients with T2DM (table 5). While, in prediction of T2DM in those subjects with risk of this disease (FT2DM group) when discriminated from documented T2DM, alphatocopherol is excellent one with ROC and AUC value0.675 at cutoff value 10.28 With sensitivity 58.6% and specificity 88.7% (table 5).

Table 5. FT2DM, T2DM from control Parameters ROC outcomes

Parameters	AUC	*P*-value	Cut-offvalue	Sensitivity	Specificity
Insulin	0.711	<0.001	22.05	49.3 %	95.9 %
FBS	0.680	0.001	108	52.2 %	100 %
HBA1c	0.637	0.011	4.45	82.6 %	38.3%
alphatocopherol	0.675	<0.001	10.28	58.6 %	88.7 %

*SignificantatP≤0.05, NS: Non-Significant

DISCSSION

This study was designed to included three study groups of T2DM, FT2DM, and healthy controls. Comparison among different groups regarding age, BMI, WC and HC the results refer no significant differences (table 1) which is stated in design of study in order to eliminated their effects on obtained results. The mean value of serum insulin was significantly increased in T2DM than FT2DM and controls as well as in FT2DM than controls (table2). These results are in agreement with Abdul-Ghanet et al. who found the insulin level is useful as a predictor of future development of type 2 diabetes [10]. Other researcher obtained different results for example, in study of Tullaya S. and Raweewan in Thailand who found that the higher HbA1c and higher fasting plasma glucose levels were associated with the risk of T2DM in the Thai population [18] In study on older adults with both IFG and elevated HbA_{1c} have a substantially increased odds of developing diabetes over 7 years. Combined screening with FPG and HbA_{1c} may identify older adults at very high risk for diabetes [19]. In research for Kyoko K. et al. 2009 during 4-year follow-up period, they confirmed 659 diabetes cases. In multivariate analysis, both FPG and A1C were independently associated with the risk of type 2 diabetes. The combined measurement of FPG and A1C was effective for predicting type 2 diabetes.
Healthy individual with a history of diabetes

(FT2DM) begin early in the stage of metabolic disorder, which results in increase in free fatty acid, an increase in free radicals, and a lack of antioxidants. This leads to entering the stage of insulin resistance, after which the pancreas works to increase insulin secretion to compensate for insulin resistance which interprets the significant increase in FT2DM when compared with healthy control group as well as in T2DM who have had a relatively short period of DM duration (table2).

Increase insulin level in the healthy individual is may be because the heritability of type 2 diabetes is high [11]. Insulin resistance is a risk factor for type 2 diabetes and cardiovascular disease progression. Current diagnostic tests, such as glycemic indicators, have limitations in the early detection of insulin resistant individuals [12]. Wolefgan et al.2022 report that the fasting and 2h-insulin are critical markers of future diabetes risk [17]. Our results are agreed with previous study for Tomoshige et al. they proved that the insulin level during OGTT (Oral Glucose tolerance test) have strong predictor of future type 2 diabetes. And they explained that as if insulin sensitivity reduces, insulin secretary must increase to keep normal glucose tolerance [21] The mean value of serum Alpha tocopherol was significantly increased in T2DM than FT2DM and controls as well as in FT2DM than controls Table (3-4).

In this study The cutoff of Alpha tocopherol in FT2DM group is (12.7 µg/ml)

and cut off of T2DM group is (12.4 µg/ml).

Alpha tocopherol is one of the most important antioxidants in the body. It is used by the body to get rid of free radicals. In group of F2DM the level of Alpha tocopherol decreases due to consumption by the body to get rid of free radicals.

The result of this study refer to alpha tocopherol level is a good biochemical marker for prediction diabetes in early stage in healthy individual with family history .

Arnalov et al. found serum concentrations of α-tocopherol independently predicted insulin resistance and type 2 diabetes incidence during 27 years of follow-up in a community-based study of men. This result supports the importance of impaneled antioxidant status for the development of insulin resistance and type 2 diabetes [12] .

Mayer et al. suggested that low serum concentrations or low dietary intake of antioxidants such as β-carotene and α-tocopherol play independent roles in the pathogenesis of type 2 diabetes [13].

Kataja et al. revealed in their study no independent association with these antioxidants and the development of type 2 diabetes [14] .

Gopaul et al. found Oxidative stress due to increased production of reactive oxygen species and decreased antioxidant status have been implicated in the pathogenesis of type 2 diabetes and its complications [15].

Bastet al. suggested from experimental studies that oxidative stress impaired pancreatic β-cell insulin secretion interfered with glucose disposal in peripheral tissues(Gopaul et al., 2001) and elicited systemic inflammation thereby accelerating the development and progression of type 2 diabetes. Vitamin E is a major lipid-soluble chain-breaking antioxidant with anti-inflammatory properties [16]

Tajiriet al. indicated that vitamin E may improve insulin action and insulin secretion by protecting peripheral tissues and β-cells from free radical–mediated damage, leading to the hypothesis that this vitamin may help delay the development of type 2 diabetes [17]

CONCLUSION

1. This study suggested that serum levels of Alpha tcopherol of less than (12.7µg/ml) are excellent biochemical markers in recognition of apparently healthy subjects who do not have any familial or familial T2DM history are at risk for progression of T2DM.
2. The study proposed that measurements of serum alpha-tocopherol of less than 10.20 µg/ml are clinically useful in predicting those subjects with familial history of T2DM.
3. Therfer the level of insulin increase in the group of healthy individual with family history of type 2 diabetes comper with control group healthy individual with no family history of type 2 diabetes this means level of fasting insulin level can be used for pridaction of type 2 diabetes in healty individual

DECLARATIONS

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Competing Interests

The authors have no competing interests to declare.

Ethical Approval

The study was approved by the appropriate ethics committee and conducted according to relevant guidelines and regulations.

Informed Consent

Not applicable.

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