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Original article

Vitamin A levels are decreased but not influenced by glucose- or lipid-lowering medications in subjects with type 2 diabetes

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ABSTRACT

Background and aim: Type 2 diabetes (T2D) is a complex polygenic disease with unclear mechanisms. Clinical studies on the association of vitamin A with T2D in humans are still controversial. Herein, we aimed to investigate the plasma levels of vitamin A, predictor factors, and its correlations with clinical phenotypes in Emirati population. The effect of glucose-and lipid-lowering medications on vitamin A levels was also studied.

Methods: A cross-sectional cohort comprised 158 T2D-subjects and 90 healthy controls were recruited from the United Arab Emirates National Diabetes Study (UAEDIAB). All anthropometric, clinical, and biomedical measurements were collected. Plasma levels of vitamin A were determined using ELISA assay.

Results: Levels of vitamin A were significantly lower in T2D-subjects compared to healthy control ($p < 0.01$). Vitamin A levels were unaffected by gender base and inversely correlated with age, fasting blood glucose (FBG), glycated hemoglobin (HbA1c), waist circumference, triglycerides, and body mass index (BMI). Regression analysis revealed that HbA1c and age are predictors for vitamin A. Intake of glucose- or lipid-lowering medications showed no effect on vitamin A levels.

Conclusion: HbA1c and age are predictors for low levels of vitamin A among Emirati-T2D subjects. No influence of glucose and lipid-lowering medications on the plasma levels of vitamin A.

1. Background

T2D is a global health burden affecting more than 425 million people worldwide (www.idf.org). Genetic and lifestyle factors, including diet, contribute significantly to the pathogenesis of the disease (Khan et al., 2015; Tremblay and Hamet, 2019). Over the past decades, diet composition has changed substantially, which is thought to contribute to increasing the incidence of T2D. Several studies have investigated the link of human dietary components such as carbohydrates, fats, and vitamins with T2D (Kaur and Henry, 2014; Khazrai et al., 2014). Among those, vitamin A or (Retinoic acid (RA)), which is a collection of dietary lipid-soluble metabolites obtained from animals as retinyl esters or plants as carotenoids (O'Byrne and Blaner, 2013). Normally, vitamin A is stored in the liver and then secreted into the blood bound to retinol-binding protein (RBP4) (Noa, 2000). Vitamin A is an essential molecule for ocular activity, cellular differentiation, immunity and is an important element of the defense system against oxidative stress (Roberts and Sporn, 1994; Beydoun et al., 2011; Gudas, 2012).

Epidemiological and clinical studies on the association of vitamin A with T2D in humans are still controversial. For example, several studies reported that serum vitamin A levels are elevated in individuals with T2D, obesity, or impaired glucose tolerance (Krempf et al., 1991; Tavridou et al., 1997). Other epidemiological studies showed contradictory findings on the relationship between vitamin A status and diabetes or its symptoms (Ylönen et al., 2003; Beydoun et al., 2011). Interestingly, intake of vitamin A or provita-

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min A carotenoids, such as β-carotene have been associated with reduced risk of T2D (Ylönen et al., 2003; Sluijs et al., 2015). A study from the National Health and Nutrition Examination Survey in USA performed on 1500 adults showed that total serum vitamin A (retinol and retinyl esters) is associated with a reduced risk of metabolic syndrome (Beydoun et al., 2011). In contrast, several other studies failed to reproduce any relationship between elevated risk of diabetes and vitamin A levels or intake of provitamin A (Reunanen et al., 1998; Abahusain et al., 1999; Liu et al., 1999; Kataja-Tuomola et al., 2008). However, the fact that all the malnourished diabetes patients suffered from vitamin A deficiency compared with the malnourished control population (Via, 2012). Another line of evidence showed that obesity and insulin resistance in mice and humans led to an elevation in serum levels of RBP4 (Yang et al., 2005; Graham et al., 2006), however, this finding was disputed by subsequent studies, which failed to detect this relationship (Cho et al., 2006). Importantly, there is substantial evidence that vitamin A restores insulin secretion in pancreatic β-cells in vitamin A-deficient rats (Chertow et al., 1987). Retinoic acid (RA) also has been shown to increases insulin production, glucokinase activity, and inhibits the proliferation in INS-1 cells (Fernandez-Mejia et al., 2004). Collectively, it remains to be established the association of vitamin A and the risk of diabetes as well as how it is involved in the pathogenesis of T2D. Recent reports showed a high prevalence of T2D in the UAE (Meo et al., 2017). Effective interventions are urgently needed to slow the diabetes epidemic and reduce diabetes-related complications (Lyons and Basu, 2012). Prevention is an ultimate goal in diabetes management and its complications long before overt disease development. To the best of our knowledge, there are no data exist on the levels of serum vitamin A in T2D-Emirati patients. Thus, we aimed in the current study to measure the levels of serum vitamin A levels among Emirati patients, analyze the correlation of vitamin A with age, HbA1C, BMI and finally to recognize the influence of glucose and lipids- lowering medications on the plasma levels of vitamin A.

2. Material and Methods

2.1. Subjects and data collection

In total, 248 individuals (158 with T2D and 90 age-sex matching healthy controls) were recruited from the United Arab Emirates National Diabetes Study (UAEDIAB), which is a cross-sectional study intended to study the prevalence of diabetes, obesity, and cardiovascular risk factors in the UAE population. Details of UAEDIAB are described elsewhere (Hamoudi et al., 2019; Mahmoud and Sulaiman, 2019). Personal interviews using a validated questionnaire, body measurements as well as blood tests were used to gather demographic and clinical data from all participants. Healthy controls were defined as subjects with no history of hyperglycemia, cardiovascular disorders, hypertension, or dyslipidemia. Diabetic subjects were defined as those known diabetics using glucose-lowering medications, and/or fasting serum glucose level ≥ 126 mg/dL or HbA1c ≥ 6.5% (Awadallah et al., 2020). Subjects with dyslipidemia were defined by medical history or by use of lipid-lowering medications, and/or by fasting levels of total cholesterol (TC) ≥ 200 mg/dL or triglyceride (TG) ≥ 150 mg/dL. Smoking habits, intake of glucose- and/or lipid-lowering medications were also recorded during personal interviews. All Anthropometric and metabolic characteristics of the recruited subjects are presented in Tables 1 and 2. The Ethics Review Board of the University of Sharjah and by the Research Ethics Committee of the Ministry of Health and Prevention (MOHAP/DXB/SUBC/No.14/2017) have approved the study protocol. All participants signed an informed consent form before blood sample collections and access to their medical record information. Measurements of body mass index (BMI), fasting blood glucose levels, and HbA1c were extracted from their medical records.

Table 1
Anthropometric and metabolic characteristics of the recruited subjects.

Variables (N)	Controls (90)	T2D (158)	p-value
Gender (Male/Female)	30/60	85/73	< 0.0001
Smokers, n (%)	5 (4.3)	18 (11.4)	< 0.0001
Age (Years)	41.7 ± 8.5	53.9 ± 11.9	< 0.0001
BMI (kg/m^2)	28.0 ± 4.7	30.9 ± 5.6	< 0.0001
Waist circumference	89.2 ± 12.1	104.2 ± 13.8	< 0.0001
SBP (mmHg)	117.3 ± 14.4	132.7 ± 21.6	< 0.0001
DBP (mmHg)	77.6 ± 9.3	83.1 ± 11.0	< 0.0001
Fasting Glucose (mg/dL)#	92.1 (86–99)	149.8 (126–205)	< 0.0001
HbA1c (%)	5.2 ± 0.5	7.7 ± 1.5	< 0.0001
HDL-Cholesterol (mg/dL)	52.7 ± 13.8	45.1 ± 15.0	< 0.0001
LDL-Cholesterol (mg/dL)	122.4 ± 34.4	111.3 ± 39.1	0.023
Triglycerides (mg/dL)#	88.1 (63–129)	132.7 (106–188)	< 0.0001

SBP; systolic blood pressure, DBP; diastolic blood pressure.
Data is presented as mean ± standard deviation for normal continuous variables, #non-Gaussian distribution presented Median (Ist quartile-3rd Quartile). Categorical variables are presented as frequencies (%).

Table 2
Anthropometric and metabolic characteristics of diabetic subjects only (n = 158).

Variable	Frequency
Sex, male/female	85/73
Age groups, n (%)	
< 50 years	51(32.3)
≥ 50 years	107 (67.7)
HbA1c, (%)	
< 7.0	61 (38.6)
≥ 7.0	97 (61.4)
Duration of Diabetes, n (%)	
Recently diagnosed (<5 years)	65 (41.1)
Previously diagnosed (≥5 years)	93 (58.9)
Glucose lowering medication, n (%)	
Not on medication	76 (48.1)
Oral medication only	45 (28.5)
Oral and insulin medication	37 (23.4)
BMI, n (%)	
< 30.0 kg/ m^2	78 (49.3)
≥ 30.0 kg/m^2	77 (50.7)
Normal lipid profile, n (%)	59 (37.3)
Abnormal lipid profile, n (%)	99 (62.7)
Not on lipid-lowering therapy	48 (48.4)
On lipid-lowering therapy	51 (51.6)
Smokers, n (%)	18 (11.4)
Normal Waist circumference, n (%)	52 (32.9)
Large waist circumference, n (%)	106 (67.1)
Males ≥ 102 cm	39 (36.8)
Females ≥ 88 cm	67 (63.2)
Normal lipid profile, n (%)	59 (37.3)
Abnormal lipid profile, n (%)	99 (62.7)
Not on lipid-lowering therapy	48 (48.4)
On lipid-lowering therapy	51 (51.6)

All the categorical variables are presented as frequencies (%).

2.2. Study size

The sample size needed in each of the two study groups was determined using the formula $n = [2(Z_{a/2} + Z_{\beta})^2 s^2] / (\mu 1\text{-}\mu 2)^2$ where n is the number of subjects needed per group. $Z_{a/2}$ reflects the level of statistical significance, Z_{β} represents the desired study power, s is the standard deviation of the outcome variable, and (μ1-μ2) is the effect size or the difference between the two population means. To calculate the sample size, the level of significance was

set at 5% and power at 90%. To detect an effect size of 121%, a minimum of 8 subjects were needed for each study group.

2.3. Anthropometric measurements

Measurements of Body weight, height, waist circumference, and blood pressure (systolic and diastolic) were performed according to international standards. The calculation of body mass index (BMI) was done by dividing body weight (Kg) by the square of height (M). Subjects with BMI values 18.5 to 24.9 kg/m^2 were considered a healthy weight (normal weight), BMI $\geq$ 25.0 to < 30.0 kg/m^2 was considered as overweight and BMI $\geq$ 30.0 kg/m^2 as obese (Alharbi et al., 2019). Central obesity was defined by waist circumference $\geq$ 102 cm for men and $\geq$ 88 cm for women according to the National Cholesterol Education Program (NCEP) guidelines (Zimmet et al., 2005).

2.4. Biochemical parameters

Blood samples (6 mL) were collected from all participants, and plasma was separated and stored at −80 °C until analyses. FBG, lipid profile (Triglycerides, LDL-cholesterol, and HDL-cholesterol) as well as HbA1c were determined by chemistry auto-analyzers in the clinical laboratory of Rashid Center for Diabetes and Research, Ajman, UAE. Serum levels of vitamin A were determined using commercially available ELISA assay (Elabscience, China).

2.5. Statistical analysis

All data analysis was conducted using the Statistical Package for Social Sciences version 26.0 (SPSS Inc., Chicago, IL). Independent sample *t*-test and ANOVA was used to compare the difference between the groups, while the Mann–Whitney *U* test was used for comparison of nonparametric variables. General Linear Model was used for adjusting potential covariates. Data are presented as mean ± standard deviation (SD) for variables following Gaussian distribution. Non-Gaussian variables are presented as median with interquartile range. Categorical variables were presented as frequencies (%). Partial correlation analysis was used for controlling the potential confounders and multiple linear regression analyses were conducted to evaluate the association between vitamin A and the relevant metabolic and glycemic variables of participants. All non-Gaussian variables were transformed prior to parametric testing. Statistical significance levels were set at $p < 0.05$.

3. Results

3.1. Anthropometrics and metabolic characterization of the study population

As shown in Table 1, most clinical and biomedical variables were significantly higher in T2D-subjects compared to non-diabetic healthy controls. However, levels of LDL and HDL-cholesterol were significantly decreased in T2D-subjects. Characteristics of T2D-subjects are shown in Table 2, the majority of them are greater than 50 years of age (67%) and nearly 50% had a BMI greater than 30.0 kg/m^2. Central obesity was observed in 67% of all recruited subjects. Almost, 41% of T2D-subjects had a duration of diabetes < 5 years, while 59% with more than 5 years. HbA1c values $\geq$ 7.0% were found in 62% of all subjects. Intake of oral glucose-lowering medications was seen in 30% of all subjects, 8% were on insulin therapy, 21.5% on combined intake of oral and insulin therapy, and 48% were on dietary treatment. The type, dose, and duration of the oral anti-diabetic medications were not documented. More, nearly 63% of T2D-subjects showed abnormal lipid profile, of them, 52% were on lipid-lowering therapy (statin) and 48% were not on any therapy. Dose and duration of statin intake were also not specified.

3.2. Measurements of vitamin a levels in T2D-subjects and healthy control

Measurements of plasma levels of vitamin A (adjusted to age, gender, glucose, and lipid-lowering medications) were found to be significantly lower (adj $p < 0.0001$) in T2D- subjects (1.18 ± 0.45 ng/ml) as compared to healthy control (2.61 ± 1.13 ng/ml) (greater than99% power at 5% alpha level). (Fig. 1A). More, hyperglycemic-subjects (HbA1c greater than 6%) showed a significantly lower (adj $p < 0.0001$) vitamin A levels compared to normoglycemic-subjects (HbA1c < 6%) (Fig. 1B). No difference in vitamin A levels were observed on a gender base (Fig. 1C). Subjects with hypertension had lower vitamin A levels compared to normotensive (adj $p = 0.008$) (Fig. 1D). Moreover, subjects with abnormal lipid profiles showed reduced vitamin A levels ($p < 0.05$) compared to normal profile, however, the difference was not significant ($p = 0.4$) after adjustment for age, gender, glucose, and lipid-lowering medications (Fig. 1E). Next, we correlated vitamin A levels with clinical variables of all recruited subjects. As shown in Fig. 2, vitamin A levels were inversely associated with age, FBG, HbA1c, waist circumference, triglycerides, and BMI (adjusted for age, gender, glucose, and lipid-lowering medication). No correlations were seen with cholesterol parameters (HDL and LDL) nor in T2D-subjects with disease duration greater than 5 years as compared to T2D-subjects with<5 years (not shown). Multiple linear regression analysis revealed that HbA1c and age were the best predictors for vitamin A (Table 3).

3.3. No effect of glucose- and lipid-lowering medications on plasma levels of vitamin a

To investigate whether glucose-lowering medications influence the levels of vitamin A in T2D-subjects, we stratified the patients into three different groups; no medications, oral only, or combined oral and insulin. As shown in Fig. 3A, no differences in plasma levels of vitamin A were observed among the studied groups after adjustment for sex, age, abnormal lipid profile, and lipid-lowering therapy. Likewise, stratification of T2D-subjects into three groups based on their lipid profile and lipid-lowering therapy showed a reduction of vitamin A in subjects with statin therapy ($p < 0.05$), however, the significant reduction was disappeared after adjustment for age, sex, glucose-lowering medication (Fig. 3B).

4. Discussion

Diabetes prevalence is growing faster than the rest of neighboring countries and is expected to double in number by 2040 (www.idf.org). The major driving factors of increased diabetes prevalence among UAE-local are obesity, sedentary lifestyle, less physical activity and unhealthy diet composition. To the best of our knowledge, this is the first study to investigate the plasma levels of vitamin A in a relatively-large representative sample of the local Emirati population. Our investigation was performed in a well-characterized cross-sectional study gathering clinical data such as body measurements, blood tests, demographic information from all participants. This enables us to analyze the relation between vitamin A levels with glycemic and metabolic phenotypes in Emirati population. Our data demonstrate that levels of vitamin A are significantly lower in T2D-subjects compared to non-diabetics control and that vitamin A levels were negatively correlated with age, FBG, HbA1c, waist circumference, triglycerides, and BMI. Impor-

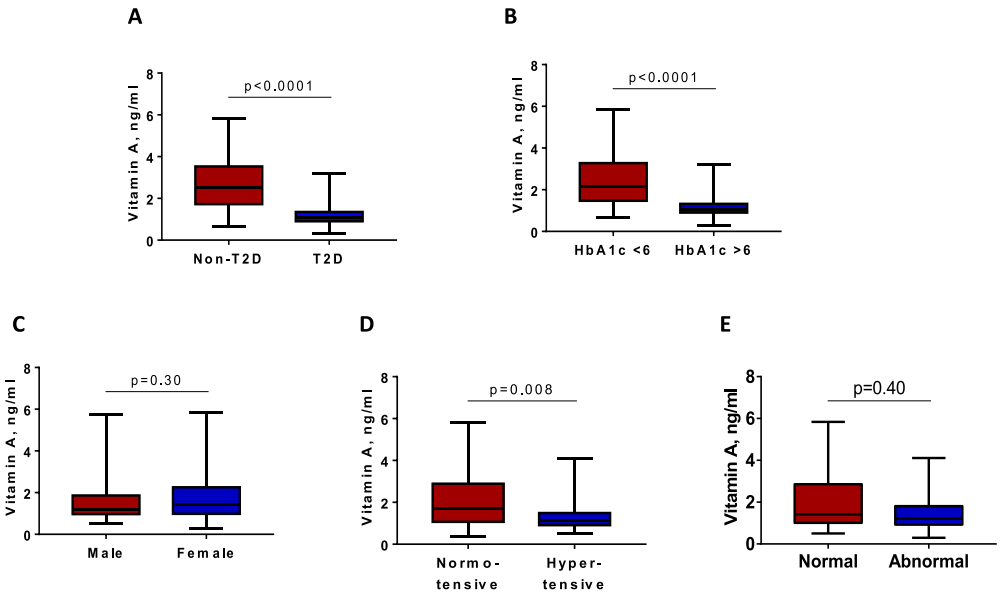

Fig. 1. Comparison of vitamin A levels in T2D-subjectes (n = 158) compared to healthy controls (n = 90) (A), hyperglycemic subjects (HbA1c greater than 7; n = 145) versus normoglycemic (HbA1c < 7; n = 103) (B), males (n = 115) versus females (n = 133), normotensive-subjects (n = 136) versus hypertensive (n = 99), subjects with normal lipid profile (n = 111) versus abnormal profile (n = 137). P-value denotes groups with significantly different levels of vitamin A.

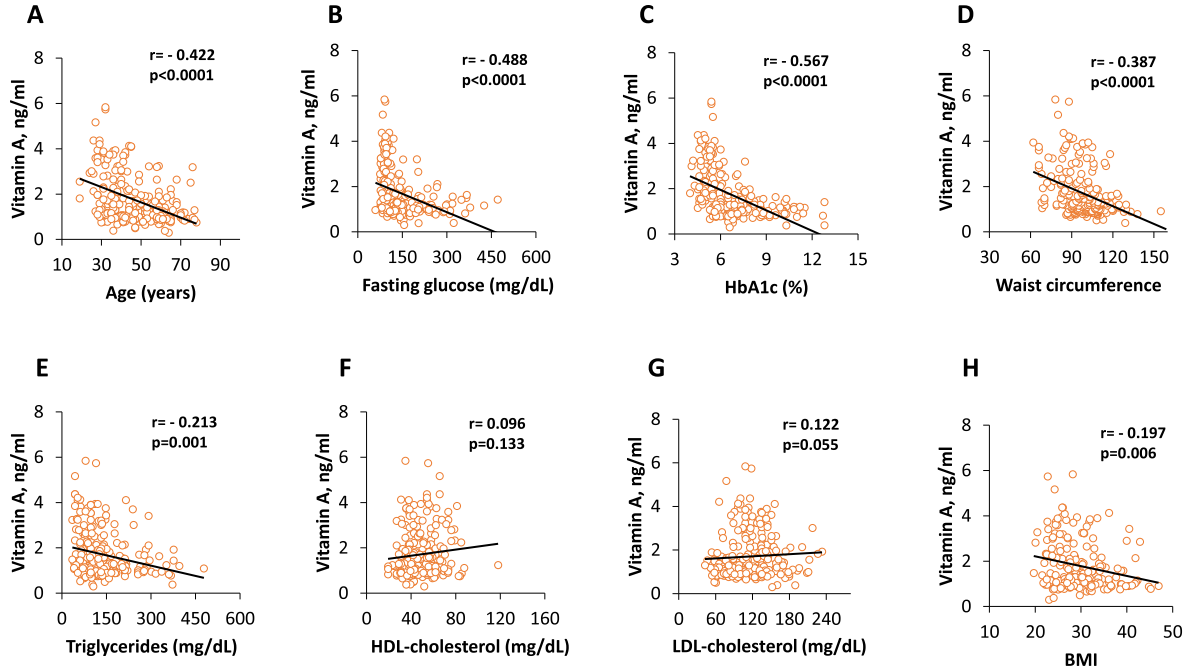

Fig. 2. Spearman's correlation of vitamin A levels with age (A), FBG (B), HbA1c (C), waist circumference (D), triglycerides (E), HDL-cholesterol (F), LDL-cholesterol (G), BMI (H) analyzed in 248 subjects. R and P values and are indicated in the respective graphs.

tantly, we could not observe that levels of vitamin A are influenced by glucose- and lipid-lowering medications taken by patients. To the best of our knowledge, this is the first study investigating vitamin A levels in T2D-subjects and the effect of glucose and lipid-lowering medication on the levels of vitamin A in Emirati population.

The underlying mechanism behind the lower levels of vitamin A in diabetes is not well established. However, several mechanisms have been suggested to explain the role of vitamin A in the pathogenesis of T2D (Berry and Noy, 2009; Amengual et al., 2010; Trasino et al., 2015). For example, Trasino et al, elegantly reported that mice fed dietary vitamin A deprivation exhibited hyperglycemia, increased β-cell apoptosis, increased α-cell mass, and hyperglucagonemia (Trasino et al., 2015). Reintroduction of dietary vitamin A improves glycemic control, restores islet size distributions, β-cell to α-cell mass ratios, and up-regulates the vitamin A receptors RARβ2 or RARγ2 transcript levels. Other studies showed that vitamin A metabolite "all-*trans*-retinoic acid" treatment of obese mice resulted in depletion of adipose lipid stores, weight loss, increase mitochondrial content in muscle cells, and improved

Table 3
Multiple linear regression analysis of serum vitamin A levels.

Variables	Standardized β ± SE	p-value
Age (Years)	**−0.24 ± 0.006**	**0.002**
BMI (kg/m^2)	0.016 ± 0.017	0.85
Waist circumference	−0.150 ± 0.007	0.12
SBP (mmHg)	0.19 ± 0.006	0.07
DBP (mmHg)	−0.145 ± 0.01	0.13
Fasting Glucose (mg/dL)	0.026 ± 0.001	0.78
HbA1c (%)	**−0.36 ± 0.063**	**0.001**
HDL-Cholesterol (mg/dL)	0.087 ± 0.013	0.65
LDL-Cholesterol (mg/dL)	0.64 ± 0.014	0.19
Triglycerides (mg/dL)	0.01 ± 0.002	0.93

For multiple regression analysis vitamin A was used as dependent variables. Data presented as beta coefficient ± standard error. P-value < 0.05 considered significant. All non-normal variables were square root or log transformed.

insulin responsiveness (Berry and Noy, 2009; Amengual et al., 2010). Together, these findings strongly suggest that vitamin A is a major player in maintaining the β-cell mass and function through the prevention of programmed cell death as well it has a functional role in regulating energy balance and suppressing obesity and insulin resistance.

Our findings that increased vitamin A levels were associated with lower FBG, HbA1c, waist circumference, triglycerides, and BMI (Fig. 1) are in agreement with previous reports showing that vitamin A insufficiency causes hyperglycemia and loss of pancreatic β-cell mass, while vitamin A treatment inhibits lipid biosynthesis capacities, improves insulin resistance and reduces body weight (Berry and Noy, 2009; Amengual et al., 2010; Trasino et al., 2015). More, our results revealed no significant gender effect on plasma vitamin A levels (retinol). This finding is consistent with a recent study showing no gender effect on plasma retinol in humans (Albahrani et al., 2020). Age has been reported to be an important factor in determining normal levels of vitamin A in humans (Lindblad et al., 1998). Our data reported a negative association between vitamin A with age. The latter finding might be attributed to the various physiological and pathological changes commonly associated with age.

Our data did not support any effect of glucose or lipid-lowering medications on vitamin A levels. Studies on the influence of glucose-lowering medication such as insulin and metformin or lipid-lowering medication such as statin on vitamin A are very limited. For example, it has been reported that metformin-treated T2D-patients had lower levels of vitamin B12 compared to untreated controls, however, vitamin D level was not affected by the treatment of these patients (Kos et al., 2012). In contrast, a combination of insulin with vitamin A was shown to be beneficial in treating diabetes and reducing peroxidative stress-induced cardiac injury (Zobalı et al., 2002). On the other hand, Simvastatin was demonstrated to interacts with the Retinoic acid signaling to potentiate the expression of the key protein, regulating the uptake of retinol (STRA6) and the expression of apoptosis-promoting CRABP2 (Sokalska et al., 2013). The combined therapy of statin with Retinoic acid was suggested for the treatment of women with endometriosis (Sokalska et al., 2013).

We acknowledge that this study has certain limitations. First, the sample size of T2D-subjects on combined intake of statin or insulin was limited. A larger number of subjects can provide robust evidence on the effect of both drugs on levels of vitamin A, however, in our opinion, the current investigation will serve as a significant pilot study. Second, our study has incomplete information about the type, dosage, and duration of intake of medication for hyperglycemia and/or dyslipidemia. Although insulin and statin intake was reported, oral medications such as metformin and fenofibrate were not available. Further investigations are needed to determine whether such incomplete information related to medication intake has an impact on our results. Third, we could not measure plasma levels of insulin to calculate HOMA/insulin resistance. Fourth, it will be great to assess other dietary factors that might interfere with vitamin metabolisms in T2D-subjects such as proteins and zinc (Chagas et al., 2016; Perignon et al., 2018) and subsequently β-cells function.

Statins and glucose-lower medications are largely prescribed drugs for diabetic patients. Thereby, understanding how both drugs affect vitamin A levels when used is directly relevant to the field of diabetes and its complications. Our findings support the necessity to recognize the role of vitamin A in pancreatic β-cell function and the development of diabetes. Our data also pave the way to utilize diet composition as an effective intervention or prevention strategy for diabetes management or its complications long before overt disease development. The public should be encouraged to shift to a healthier lifestyle and eat a healthy diet, such a strategy might be of a great socio-economic impact.

In conclusion, plasma levels of vitamin A are reduced in T2D-Emirati subjects. HbA1c and age are predictors of vitamin A levels in T2D patients. Glucose- and lipid-lowering medications commonly used by diabetics do not affect the plasma levels of vitamin A.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

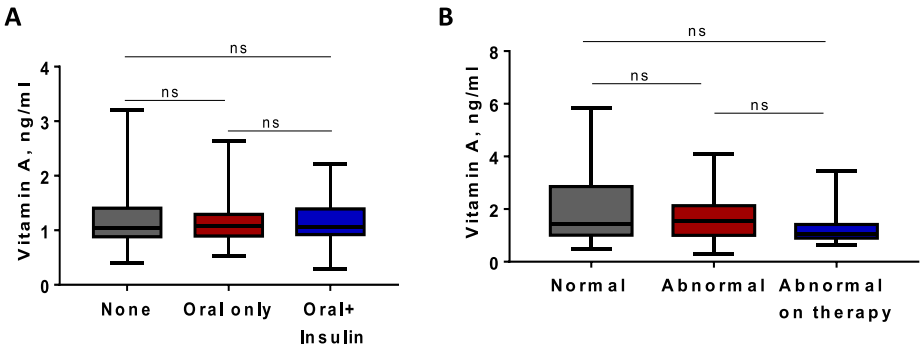

Fig. 3. Influence of glucose-lowering medications (subjects were stratified to none medication (n = 76), oral only (n = 45) or combined oral with insulin (n = 37) (A), lipid-lowering medications (subjects were stratified into normal lipid profile with no medication (n = 111), abnormal profile with no medication (n = 83) and abnormal profile with medication (n = 54)) (B) on the levels of vitamin A.

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Author Contributions

JT and NS; conceived and designed the experiments and JT wrote the manuscript, HU; performed all experimental work. NS; conceived and designed and led the UAEDIAB study and sample recruitment. JT, SA, AK analyzed the data, SA and NS edited the manuscript.

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