Research Article

The changes of oxidative stress markers and vitamin E in patients with diabetes using SGLT2 inhibitors

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Abstract

Objectives: This study aimed to research the diversities of vitamin E and oxidative stress parameters related to sodium-glucose transport protein 2 (SGLT2) inhibitor use by type 2 diabetes mellitus (T2DM) patients.

Methods: This observational clinical study collected data from 67 T2DM patients (55.7±9.3 years, 46% female). Vitamin E, total oxidant status (TOS), total antioxidant status (TAS), total thiol, native thiol, myeloperoxidase, and catalase levels were evaluated. The TOS/TAS ratio was calculated as the oxidative stress index. Correlations of the parameters to each other and differences based on SGLT2 inhibitor use were recorded.

Results: The mean hemoglobin A1c was 7.1 (5.5–13.1). SGLT2 inhibitors (all combinations) were used by 25 patients (37.3%). The mean level of vitamin E was 6 (3.6–9.8) mg/L. There was a positive correlation between vitamin E and low-density lipoprotein cholesterol (p<0.001). While there was no significant correlation between vitamin E and all included oxidative stress parameters, the level of vitamin E was statistically lower in patients using pioglitazone (p=0.036) and statins (p<0.001). In patients using SGLT2 inhibitors, fasting glucose, triglycerides, alanine aminotransferase, and the spot urine protein/creatinine ratio were significantly lower, and the mean TAS was higher (p<0.05).

Conclusion: While no differences were observed in vitamin E and other oxidative parameters related to SGLT2 inhibitor use, the increase in TAS provides motivation for further research investigating the antioxidant properties of these inhibitors.

Keywords: Oxidative stress, sodium-glucose transport protein 2 inhibitors, type 2 diabetes, vitamin E

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Type 2 diabetes mellitus (T2DM) is a common disorder. According to the centers for disease control and prevention, 37.3 million people in the United States (US) have diabetes (11.3% of the US population) [1], and the incidence continues to increase because of obesity and a sedentary lifestyle. In Turkey, the incidence of T2DM was reported as 16.5% in 2013 [2]. Atherosclerotic cardiovascular disease, stroke, and diabetic kidney disease are problems highly associated with T2DM [3].

It is known that optimal glycemic control reduces the risk of chronic microvascular complications. Sodium-glucose transport protein 2 (SGLT2) inhibitors introduced between 2005 and 2013 (dapagliflozin empagliflozin, canagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, and tofogliflozin) have been used to regulate blood glucose [4]. SGLT2 is mainly expressed in the proximal tubules, and SGLT2 inhibitors reduce renal reabsorption of filtered glucose and ultimately increase urinary glucose excretion, resulting in a reduction in hemoglobin (Hb) A1c of 0.6–1.0% [5]. Other proven effects of SGLT2 inhibitors include favorable cardiovascular, hepatobiliary, renal, and neurovascular outcomes related to heart failure and hospitalization, cardiovascular death, non-fatal myocardial infarction, atrial fibrillation, non-alcoholic fatty liver, diabetic kidney disease,

chronic kidney disease, kidney failure, non-fatal stroke, and all-cause mortality [6]. In addition, reduced soluble dipeptidyl peptidase, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, interleukin-6 (IL-6), and positive effects on oxidative stress, including reduced hydrogen peroxide (H_2O_2), glutathione (GSH), and lipid peroxide, are remarkable [7].

Experimental and clinical studies have shown a strong relationship between oxidative stress and T2DM complications. Thus, oxidative stress markers have become the subject of important research. Total oxidant status (TOS), total antioxidant status (TAS), and oxidative stress index (OSI), i.e., percent ratio of TOS/TAS, were determined to be a sensitive means for identifying diabetic nephropathy in the early period [8]. Thiol/disulfide homeostasis is another method used to determine oxidative balance, and its sensitivity for diabetic retinopathy and neuropathy has been researched [9].

Research into the antioxidant properties of medications has increased in the recent years. The effects of vitamins C, D, and E on lipid parameters researched in a meta-analysis were found to provide beneficial effects that varied according to dosage, duration of treatment, and comorbidities [10]. Although an immuno-regulatory role of vitamin E has been suggested in preclinical studies, it has been difficult to confirm in all clinical studies [11, 12].

To investigate the possible antioxidant properties of SGLT2 inhibitors, we aimed to compare vitamin E and oxidative stress markers in T2DM patients based on SGLT2 inhibitor use.

Materials and Methods

Study design and population

This was an observational clinical study performed at Bezmialem Vakif University. The study was approved by the Bezmialem Vakif University Ethics Committee, numbered June 25, 2021-E.21421, and conducted in accordance with the Declaration of Helsinki.

T2DM patients who applied to Internal Medicine and Family Medicine outpatient clinics for routine disease control were recruited for the study using a voluntary consent form. Exclusion criteria included ischemic heart disease, active chronic obstructive pulmonary disease, chronic heart failure, autoimmune disorders, malignancy, active infection, and patients using vitamin supplements.

A total of 67 patients (31 female) were included in the study. The height and weight of all patients were recorded, and body mass index was calculated as kg/height (m^2). All medications in use were recorded, including oral antidiabetics, subcutaneous insulin, antihyperlipidemics, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers and acetylsalicylic acid. All of the cases using SGLT2 inhibitor were using this medication in different combinations with other antidiabetics. According to using or not using SGLT2 inhibitors, the patients were divided into two groups. The blood samples were taken at fasting in the morning and studied in serum sample. The parameters studied

at the time of blood sample taken are as follows: serum glucose (mg/dl), HbA1c, low-density lipoprotein (LDL) cholesterol (mg/dl), triglycerides (mg/dl), alanine aminotransferase (ALT) (U/L), aspartate aminotransferase (U/L), serum creatinine (mg/dl), spot urine protein/creatinine ratio (mg/g), and vitamin B12 (pg/ml).

At the same time, another serum sample was obtained from all study participants and stored at −80° before evaluation. At the end of the study, other parameters were anaylzed using these samples. TOS and TAS (μmol H_2O_2 equiv/L) tested and determined by the colorimetric method [13]. OSI was calculated as TOS/TAS. For thiol/disulfide homeostasis, total thiol and native thiol (μmol/L) were analyzed using DTNB (Ellman's reagent). Native thiol was subtracted from the total thiol, and half of the obtained difference provided the disulfide bond amount [14]. Myeloperoxidase (MPO) (IU/L)-colorimetric (o-dianisidine)- and catalase (IU/L)- colorimetric method- levels were determined. Vitamin B12 was analyzed using the CMIA Abbott i2000SR device, and vitamin E (mg/L) was analyzed using an HPLC Thermo-Fisher HPLC analyzer. All other analyses were performed using an Abbott Architect c16000 auto analyzer.

Statistical analysis

The relevancy of variables to normal distribution was evaluated with the Shapiro–Wilk test. A Mann-Whitney U-test was used in cases of normal distribution, and a Student's t-test was used when normal distribution could not be achieved. Descriptive statistics were expressed as mean±standard deviation in the case of normal distribution and median (minimum–maximum) values when the normal distribution was not observed. The relationships between the variables were analyzed using Pearson's correlation coefficient and Spearman's rank correlation coefficient. Categorical variables were expressed as n (%). Statistical analysis was accomplished with the IBM Statistical Package for the Social Sciences version 22.0 for Windows (IBM SPSS Corp., Armonk, NY, USA). Statistical significance was accepted as $p < 0.05$.

Results

A total of 67 patients with T2DM (31 female, 46.3%, mean age 55.7±9.3) were included in the study. The medications used and the mean results of evaluated parameters are presented in Table 1. No patients used SGLT2 inhibitors alone. 25 patients (37.3%) used an SGLT2 inhibitor, mostly in combination with metformin and different antidiabetic medications. The mean HbA1c was 7.1% (5.5–13.1). There was a significant reverse correlation between age ($p=0.039$) and glucose ($p=0.021$) with HbA1c levels, while HbA1c and ALT correlated in the same direction ($p=0.017$). Glucose positively correlated with HbA1c ($p<0.001$), LDL-cholesterol ($p=0.008$), and triglycerides ($p<0.001$). LDL-cholesterol and vitamin E positively correlated ($p<0.001$). No statistically significant relationship was found between vitamin E and TAS, TOS, OSI, total thiol, native thiol, and catalase with MPO levels ($p>0.05$). LDL-cholesterol ($p=0.003$) and vitamin E ($p=0.036$) were statistically lower in patients us-

Table 1. Descriptive properties, medication use, and mean laboratory and oxidative marker results

			n	%
Age (years)	55.7±9.3	Metformin*	54	80.6
HbA1c (%)	7.1 (5.5–13.1)	DPP4 inhibitors	36	53.7
LDL-cholesterol (mg/dl)	127.5±40.1	SGLT2 inhibitors	25	37.3
Triglyceride (mg/dl)	136 (42–860)	(empagliflozin or dapagliflozin)		
ALT (U/L)	19 (8–59)	Insulin	20	29.9
AST (U/L)	18 (12–41)	Sulfonylurea	13	19.4
Creatinine (mg/dl)	0.8±0.1	Pioglitazone	8	11.9
Spot urine protein/creatinine(mg/g)	16.7 (4.7–566.2)	Statin therapy	19	28.4
Vitamin B12 (pg/ml)	288 (149–615)	ACEI/ARB	27	40.3
Vitamin E (mg/L)	6 (3.6–9.8)	ASA	9	13.4
TOS (μmol H_2O_2 equiv/L)	17 (12–34)			
TAS (μmol H_2O_2 equiv/L)	1.3±0.1			
OSI	0.1 (0.1–0.3)			
Total thiol (μmol/L)	958.5 (769.3–1049.3)			
Native Thiol (μmol/L)	679.1±78.6			
Thiol-disulfide	139.5±35.6	*: All medications were used in combinations. LDL: low-density lipoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TOS: Total oxidant status; TAS: Total antioxidant status; OSI: Oxidative stress index; MPO: Myeloperoxidase; DPP4: Dipeptidyl peptidase 4; SGLT2: Sodium-glucose transport protein 2; ACEI/ARB: Angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers; ASA: acetylsalicylic acid; OSI.		
MPO (IU/L)	27 (3–170)			
Catalase (IU/L)	20 (6–88)			

ing pioglitazone. Glucose (p=0.014), LDL-cholesterol (p=0.001), triglycerides (p=0.034), and vitamin E (p<0.001) were statistically lower in patients using statins. Glucose, triglycerides, ALT, and the spot urine protein/creatinine ratio were found to be significantly lower (p<0.05), and TAS was higher (p=0.019) in patients using SGLT2 inhibitors. There was no significant difference in total thiol, native thiol, TOS, OSI, catalase, and MPO levels between of SGLT2 inhibitor user and non-user groups (p>0.05). Differences in all evaluated parameters according to combination of SGLT2 inhibitor use are presented in Table 2.

Discussion

The results of this study demonstrate that the most prescribed medication for T2DM is metformin, followed by dipeptidyl peptidase 4 inhibitors and SGLT2 inhibitors. The normal range of vitamin E is accepted as 5.5–18 mg/L. Our patients' mean vitamin E level was at the lower limit of 6 (3.6–9.8) mg/L. Patients with higher LDL-cholesterol had higher vitamin E levels. In patients using statins and pioglitazone, vitamin E was lower. No relationship was observed between serum vitamin E and oxidative markers. In patients using SGLT2 inhibitors, fasting glucose was statistically lower, but there was no difference in HbA1c. Only TAS was statistically higher for oxidative stress markers in patients using SGLT2 inhibitors.

SGLT2 inhibitors predominantly affect the proximal tubules and reduce renal the reabsorption of filtered glucose. In addition to their positive effects on HbA1c reduction, they also increase the sodium load along with glucose to the distal tubule, which is thought to reduce intraglomerular pressure. This activity may reduce cardiac preload and afterload and downregulation of sympathetic activity [5]. SGLT2 inhibitors

are not only approved as an antidiabetic medication, they also improve β-cell function and increase high-density lipoprotein cholesterol and apolipoprotein [15]. The clinical benefits of SGLT2 inhibitors for non-alcoholic fatty liver disease (NAFLD) have been reported, and a reduction in the risk for atrial fibrillation and heart failure has been confirmed [16–18] as well as favorable renal outcomes by reducing proteinuria [19]. Decreased all-cause mortality was also demonstrated with SGLT2 inhibitors compared to placebo [20]. This study found lower glucose, ALT, and triglyceride levels in patients using SGLT2 inhibitors. Although these results are encouraging, we could not analyze other NAFLD-related parameters.

The impact of SGLT2 inhibitors on oxidative stress has also been the subject of investigation. Empagliflozin was associated with a reduction in mTOR activity, control of the NF-kB pathway in isolated cardiomyocytes, and regulation of nuclear factor erythroid 2-related factor/heme oxygenase-1 (Nrf2/HO-1) [21, 22]. The cardiovascular risk reduction benefit of SGLT2 inhibitors has been demonstrated with glucagon-like peptide 1 receptor agonists. They are recommended as preferred medications in patients with established cardiovascular disease, kidney disease, and heart failure [23]. In this study, even though we excluded comorbidities that might influence the results, the patients using SGLT2 inhibitors had statistically higher TAS levels. While increased TAS may appear to be related to lower glucose values, there was no statistically significant difference in HbA1c between patients using SGLT2 inhibitors or not. Thus, the increased TAS seen in this study may not be associated with decreased glucose. We recognize the relatively small number of patients and the use of SGLT2 inhibitors in combination with other antidiabetics and medications as limitations of this study.

Table 2. Variations in biochemical parameters and oxidative stress markers based on SGLT2 inhibitor use

	No along with SGLT2 inhibitors (n=42)	Along with SGLT2 inhibitors*(n=27)	p
BMI	29.6±3.4	28.1±4.7	0.184
Glucose (mg/dl)	161 (84–481)	132 (60–216)	**0.012**
HbA1c (%)	7.0 (5.5–13.1)	7.2 (5.6–9.5)	1.000
LDL-cholesterol (mg/dl)	133.8±40.8	117.1±37.3	0.097
Triglycerides (mg/dl)	164 (42–860)	118 (50–441)	**0.016**
ALT (U/L)	21 (1–59)	16 (8–35)	**0.03**
AST (U/L)	18 (12–41)	18 (12–34)	0.309
Creatinine (mg/dl)	0.9±0.1	0.8±0.2	0.037
Spot urine protein/creatinine(mg/g)	23.8 (5.5–566.2)	12.3 (4.7–135.8)	**0.003**
Vitamin B12 (pg/ml)	288 (149–568)	290 (185–615)	0.755
Vitamin E (mg/L)	6.1±1.6	6.3±1.6	0.563
TOS (µmol H_2O_2 equiv/L)	17 (12–34)	17 (12–31)	0.820
TAS (µmol H_2O_2 equiv/L)	1.2 (1.1–1.5)	1.3 (1.2–1.6)	**0.019**
OSI	0.1 (0.1–0.3)	0.1 (0.1–0.2)	0.702
Total thiol (µmol/L)	960 (889–1049)	958 (769–1022)	0.795
Native thiol (µmol/L)	687.5 ±79.1	664.9±77.4	0.257
Thiol-disulfide	135.8±34.7	145.8±36.9	0.270
MPO (IU/L)	26 (3–170)	32 (3–140)	0.590
Catalase (IU/L)	20 (7–88)	23 (6–68)	0.712
Vitamin E (mg/L)	6.1±1.6	6.3±1.6	0.563

*: SGLT2 inhibitors use in combination, p<0.05 was accepted as the level of significance. SGLT2: Sodium-glucose transport protein 2; BMI: Body mass index; LDL: Low-density lipoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TOS: Total oxidant status; H_2O_2: Hydrogen peroxide; TAS: Total antioxidant status; OSI: Oxidative stress index; MPO: Myeloperoxidase.

The main effects of vitamin E in this study appear to be the clearance of reactive oxygen products and the reduction of oxidative stress [11]. However, in clinical studies, conflicting results have been presented. While reduced hypersensitivity and respiratory tract infections in the elderly were reported with vitamin E use, no benefit was seen for preventing malignancy, age-related cataracts, or dementia in epidemiological studies [12]. In this study, the mean vitamin E level was at the lower limit of the reference range and did not differ based on SGLT2 inhibitor use. However, vitamin E levels were statistically lower in patients using statins and pioglitazone. We did not detect any relationship between vitamin E level and TAS, TOS, OSI, thiol/disulfide homeostasis, MPO, or catalase.

The other parameters included in this analysis, TAS, TOS, and OSI, are studied from different perspectives for patients with T2DM. In many clinical studies, decreased TAS and increased TOS have been associated with the pathogenesis of glucose intolerance to diabetic nephropathy and end-stage renal disease [24, 25]. In a few clinical studies, TOS and TAS variability has been researched in patients using SGLT2 inhibitors. The empagliflozin-in-metformin combination was associated with increased TAS and superoxide dismutase [26]. In addition to oxidative stress, thiol-disulfide homeostasis is another parameter that, with increased knowledge, has been analyzed in different patient groups [27]. We did not encounter any study researching thiol-disulfide homeostasis associated with different serum vitamin E levels. While no relationship was observed in this study to elucidate the role of vitamin E in oxidative balance, thiol-disulfide homeostasis can be explored as a promising method.

We had the opportunity to analyze all patients' MPO and catalase levels. MPO is an oxidative enzyme whose major role is to contribute to the oxygen-dependent bactericidal activity of phagocytes. Increased MPO has been associated with many disorders characterized by acute and chronic inflammation. Along with SGLT2 inhibitors, decreased MPO levels have been reported in clinical studies [28]. Catalase is an antioxidant enzyme involved in the metabolism of H_2O_2 and reactive nitrogen species. Although no difference was observed in MPO and catalase levels based on SGLT2 inhibitor use in this study, in a prospective observational study, catalase levels, as well as GSH s-reductase and IL-10 levels reportedly increased after 24 weeks of empagliflozin treatment [29].

Conclusion

SGLT2 inhibitors are medications whose clinical efficacy continues to be investigated from different perspectives. This study evaluated their possible antioxidant properties along with oxidative stress markers. No difference was found in vitamin E and other parameters measured; however, increased TAS associated with these medications provides inspiration for further research.

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