Assessment of formation of the glyoxal and methylglyoxal levels in various sugar-free or sweetened products under *in vitro* gastrointestinal digestive system

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ABSTRACT Sweeteners and sugar-free products are commonly used substitutes for caloric sugars for weight management or maintaining normal blood sugar. However, α-dicarbonyl compounds (α-DCs) of these products have limited studies. Present study aimed to determine the formation of α-DCs such as glyoxal (GO) and methylglyoxal (MGO) in various sweetener-containing products under gastrointestinal digestion system conditions. The GO and MGO content were determined by High-Performance Liquid Chromatography using pre-column derivatization. Initial GO and MGO values ranged between 21.1-234.4 µg/100 g and 109.7-3164.5 µg/100 g for GO and MGO, respectively. After gastrointestinal digestion, the formation of GO and MGO increased up to 2546 % and 607.9 %, respectively. The results revealed that sweetener-containing products had high GO and MGO content. Also, it was found that *in vitro* digestive system conditions may increase the formation of α-DCs. Further studies should focus on the aspects of α-DCs formation in sweetener-containing products with different types of sugar.

KEYWORDS Advanced glycation end products; Dicarbonyl compounds; Digestion; HPLC; Diabetic products

1. Introduction

The prevalence of obesity is increasing, a significant risk factor contributing to chronic diseases, including hypertension, dyslipidemia, and diabetes (Schiano et al., 2020). Diabetes is a chronic condition characterized by hyperglycemia (Daher et al., 2019). Approximately, 350 million people worldwide have diabetes, which is expected to increase due to a sedentary lifestyle and obesity (Mirghani et al., 2021). Type 2 diabetes is the most common form of diabetes, and most diabetic individuals are overweight or obese (Daher et al., 2019). Because obesity and diabetes are related to many chronic diseases, people are looking for new prevention strategies. In this manner, sweeteners are commonly consumed products to reduce energy intake, control body weight, and maintain blood glucose levels (Rosales-Gómez et al., 2018).

Artificial sweeteners are food additives that provide a sweet taste without high calories like sugar (Sanyaolu et al., 2018). Non-nutritive sweeteners are considered healthy substitutes because they have no calorie or glycemic effects (Pepino, 2015). However, it is claimed that some sweeteners may be associated with diabetogenicity, mutagenic, glycosylation, and Advanced Glycation end Products (AGEs) formation due to the products released from their breakdown (Deo et al., 2020). AGEs are diverse groups of highly oxidant compounds that have pathogenic importance in diabetes and in several other chronic diseases. AGEs are formed during the Maillard or browning reaction, which is a non-enzymatic reaction between reducing sugars and free amino groups of proteins, lipids, or nucleic acids (Uribarri et al., 2010). N-carboxylethyl lysine, methylglyoxal-lysine dimers, pyrraline, and pentosidine are well-known AGEs (Uribarri et al., 2010; Goldberg et al., 2004). AGEs precursors, such as GO and MGO, can be derived from the Maillard reaction, caramelization, sugar autooxidation, and lipid peroxidation (Ede Çintesun et al., 2021b). Heat treatment, pH, moisture, storage conditions, and shelf-life may affect the AGEs formation in foods (Uribarri et al., 2010). It is reported that about 10 % of dietary AGE is absorbed. In animal models with diabetes and atherosclerosis, it was found that restriction of dietary AGE intake decreased in disease progression and circulating AGEs (Goldberg et al., 2004).

Today, artificial sweeteners are consumed by diabetic people as to manage blood glucose levels. Additionally, the interest towards healthy eating trends has raised the consumption of these products to reduce calorie intake, limit sugar, or control weight (Daher et al., 2022). It is known that AGEs can be easily formed in sugar-rich products through Maillard Reaction or sugar autooxidation (Uribarri et al., 2010; Maasen et al., 2021); however, in the literature, the AGEs formation in artificial or low-calorie sweeteners has been poorly studied. Besides, digestive system conditions such as enzymes, metallic ions, or pH may also affect the formation of α-dicarbonyl compounds (α-DCs) (Papetti et al., 2014; Yaman et al., 2022). In this aspect, the present study aimed to investigate the GO and MGO formation in sugar-free or sweetened products under *in vitro* gastrointestinal digestive system conditions.

2. Methods

2.1 Sampling

In this research, seven different diabetic jams, one sugar-free wafer, one sugar-free biscuit, one diabetic halvah, one

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sugar-free chocolate, and one sugar-free candy (mixture of lemon, orange, berries), samples were collected from supermarkets in Istanbul, Turkey. All of these products were sweetened products. The ingredients of the products are presented in Table 2.

2.2 Materials

Glyoxal (40 %), methylglyoxal (40 %), methanol, glucose, fructose, saccharose, sodium acetate, 4-nitro-1.2-phenylenediamine, acetonitrile, KCl, NaCl, $CaCl_2{\cdot}2H_2O$, $NaHCO_3$, pepsin (p. gastric mucosa, $\geq$ 250 units/mg solid), alpha-amylase (A. oryzae, 1.5 U/mg), pancreatin (p.pancreas, eight $\times$ USP), lipase (p. pancreas, 100-500 units/mg protein), bovine serum albumin, urea, bile salts, uric acid, mucin were obtained from Sigma Aldrich (St. Louis, MO, U.S.A).

2.3 Extraction and derivatization of GO and MGO

First, the test samples were homogenized with a blender. Then, 5 g of sample was added into 50 mL falcon tubes dissolved in 5 mL methanol, then mixed with Ultra-Turrax at 10000 rpm for 2 min (IK-22000 rpm). After that, the sample was centrifuged at 8000 rpm for 5 minutes. One mL of supernatant was poured into a 10 mL glass tube, and then 1 mL of 0.1 M CH_3COONa buffer (pH 3) was added. After that, 1 mL of derivatization solution (4-nitro-1,2-phenylenediamine (4-NPD) in methanol (1 %) was added, and then the mixture was left at 70 °C for 20 minutes in a water bath. The derivatized solution was filtered through 0.45 µm cellulose acetate filter. Finally, samples were injected into HPLC (Cengiz et al., 2020).

2.4 Determination of GO and MGO

High-performance liquid chromatography (HPLC) was used to analyze derivatized GO and MGO compounds using with UV/VIS detector. In this study, the method used by Cengiz et al. (2020) was applied to determine the GO and MGO amounts. The HPLC system consisting of a Shimadzu LC 20AT pump with a Shimadzu SPD-20A UV/VIS detector (Shimadzu Corporation, Kyoto, Japan) was used. The mobile phase was prepared as follows methanol: water: acetonitrile (42:56:2, v/v/v). The derivatized GO and MGO compounds were separated using an Inertsil ODS-3, 250 $\times$ 4.6 mm, 5 µm column. The flow rate was 1 mL/min, and the column oven temperature was 30 °C. The wavelength was set to 254 nm.

2.5 *In vitro* digestion of GO and MGO

The *in vitro* digestion system was simulated by using saliva, gastric, and duodenal juices described by (Yaman et al., 2019). Saliva juice was prepared as 1.7 mL of NaCl (175.3 g/L), 8 mL of urea (25 g/L), 15 g of uric acid, 280 mg α-amylase, and 25 mg mucin; then the final volume was completed 500 mL with deionized water. Gastric juice was prepared to mix 6.5 mL of HCl (37 g/L), 18 mL of $CaCl_2{\cdot}H_2O$ (22 g/L), 1 g of bovine serum albumin, 2.5 g of pepsin, and 3 g mucin with the pH 1.5 $\pm$ 0.02, and final volume was completed to 500 mL with deionized water. Duodenal juice consisted of 6.3 mL of KCl (89.6 g/L), 9 mL of $CaCl_2{\cdot}2H_2O$ (22.2 g/L) with a pH of around 8.0 $\pm$ 0.2, 2 g of bovine serum albumin, 1 g of pancreatin, and 1.5 g of lipase, and then, completed to 500 mL with deionized water.

First, 5 g of the test sample was dissolved with 5 mL saliva juice and incubated for 5 min at 37 °C in a shaking water bath. After, the mixture was mixed with 12 mL of gastric juice and left for 2 h at 37 °C in a shaking water bath. For intestinal conditions, 5 mL of bile solution was added, the pH was adjusted to 7. Then, 10 mL of duodenal juice was added. The mixtures were incubated for 2 h at 37 °C. After that, the volumes of the mixtures were completed to 50 mL with deionized water and centrifuged for 10 min at 10000 rpm. After the filtration of the centrifuged samples with 0.45 µm cellulose acetate filter, the samples were injected into the HPLC device.

2.6 Method validation

Linearity was determined between 0.4 and 4.0 µg/mL for GO and MGO using five levels of calibration. The limit of detection (LOD) and limit of quantitation (LOQ) were determined based on the signal-to-noise (S/N) ratio by 3 and 10, respectively. The repeatability and reproducibility were studied by analyzing one of the test samples (1) 16 times, respectively. In addition, 1 µg/mL of GO and MGO standards were spiked to the test sample to check the recovery of the method. Method validation parameters are showen in Table 1. All analyses were performed in triplicate ($n = 3$).

2.7 Statistical analysis

Significant differences between the results were shown by the analysis of variance (ANOVA) ($p < 0.05$, Tukey's test). Multi-variate statistical analyses were conducted to associate the ingredients and the formation of GO and MGO. All statistical analyses were performed using JMP PRO 16.

3. Results and discussion

In this study, 12 sugar-free or diabetic products were examined. The HPLC chromatogram of GO and MGO in the diabetic strawberry jam sample (sample 1) was shown in Figure 1.

The method validation results of the GO and MGO are shown in Table 1. As presented in the table, recovery values for GO and MGO ranged from 98.30 to 99.20 % and from 99.10 to 100.20 %, respectively.

The main ingredients of products are summarized in Table 2. The GO and MGO values, at initial and after *in vitro* digestion, obtained from HPLC analysis were presented in Table 3.

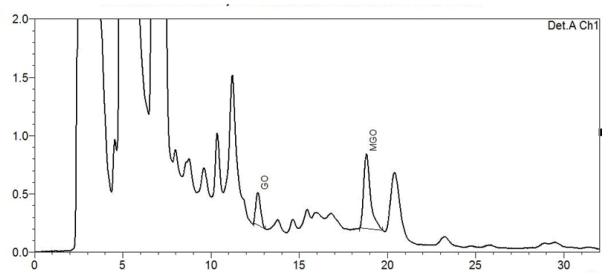

Figure 1: The HPLC chromatogram of GO and MGO in diabetic strawberry jam sample.

Table 1: Validation parameters of glyoxal and methylglyoxal.

Analytical parameters	Glyoxal	Methylglyoxal
Linear range (µg/mL)	0.4-4	0.4-4
Correlation coefficient ($r2$)	0.997	0.998
LOD (µg/100 g)	1.10	1.20
LOQ (µg/100 g)	3.70	4.00
Repeatability limit (r)	0.06	0.07
Reproducibility limit (R)	0.11	0.14
Recovery (%)	98.30 – 99.20	99.10 – 100.20

As presented in Table 3, the initial GO and MGO values were ranged between 21.1 to 234.4 µg/100 g, and 109.7 to 3164.5 µg/100, respectively. Regarding the initial values, biscuit (S9) had the highest GO and MGO values. Biscuit is a widely consumed snack that contains flour, oil, or fat and sugar as the main ingredients. High heat treatment during food processing, low moisture content, pH, lipid peroxidation, and long shelf-life may be influencing factors for AGEs formation (Uribarri et al., 2010; Van der Lugt et al., 2020). GO and MGO values of biscuits were found between 35-224 µg/100 g and 32-1573 µg/100 g respectively (Ede Çintesun et al., 2021a). In another study, initial GO and MGO values of biscuits were found between 81-169 µg/100 g and 55-607 µg/100 g, respectively (Yaman, 2021). Despite, the present study carried out with sugar-free sweetened type of biscuit, the present results were similar to normal biscuits (Ede Çintesun et al., 2021b).

Diabetic halvah, candy, wafer, and chocolate samples had high initial MGO values ranging from 193.7-505.9 µg/100 g, whereas initial GO values were between 44.7-85.2 µg/100 g. As shown in Table 2, diabetic halvah, wafer, and chocolate have high fat content, which can contribute to AGEs formation via lipid peroxidation. Additionally, high heat treatment may also increase the formation of α-DCs (Wang, 2019). Despite candy sample did not contain any sugar and fat, the high AGEs precursor values may be attributed to polyol content. The polyol pathway promotes glycation processes. Fructose metabolites can be formed in the polyol pathway, which are converted into α-oxaldehydes. α-oxaldehydes and can form AGEs with monoacid interactions (Van der Lugt et al., 2020).

The initial GO and MGO values in diabetic jams ranged between 21.1 µg/100 g to 125.0 µg/100 g and 109.7 µg/100 g to 976.1 µg/100 g, respectively. Jams are sugar rich products with intermediate moisture content (Shinwari and Rao, 2018). However, few studies evaluated the AGEs formation in jams. Degen et al. detected 3-deoxyglucosone (3-DG) and MGO content between 1.7-1061 mg/L and 0-13 mg/L, respectively, in jams (Degen et al., 2012). Maasen et al., reported MGO, GO, and 3-DG with high concentrations in the strawberry jam (∼50 mg/kg) (Maasen et al., 2021). Although, limited studies evaluated AGEs content of jams, no study focuses on diabetic types. The results showed that, diabetic jams have high GO and MGO content.

Diabetic products containing non-calorie sweeteners or sugar alcohols are commonly consumed by diabetic individuals to maintain normal blood sugar levels (Farid et al., 2020). However, AGEs can be formed in sugar free or sweetened 'diabetic' products through the Maillard reaction, lipid peroxidation, or polyol pathway (Aleksandra Twarda-Clapa et al., 2022). In addition to these, gastrointestinal digestive conditions such as low pH, metallic ions or the presence of oxygen incorporated into food during mastication could decrease or enormously increase free α-DCs depending on food content or reactions occurring during digestion (Hamzalıoğlu and Gökmen, 2020). The effects of gastrointestinal digestion on AGEs formation in sweetened products remain unclear. In this context, it is important to evaluate the effects of digestion on diabetic products. For that purpose, present study evaluated the effects of *in vitro* digestion on GO and MGO formation. After *in vitro* digestion, the formation rates of GO ranged between 138.0 % and 2546.4 %, whereas the formation rates of MGO ranged between 56.5 % and 607.9 %.

As expected, high formation rates were observed after digestion in wafer, biscuit, halvah, candy, and chocolate samples, which are high heated processed snacks with high fat and low moisture content (Wang, 2019). Van der Lugt et al. found that gastrointestinal digestion increased AGEs formation more than 400 % in biscuits (Van der Lugt et al., 2020). Yaman et al. determined *in vitro* digestion increased GO and MGO formation in cookies up to 645 % and 698 %, respectively (Yaman et al., 2022). Present results demonstrated that *in vitro* digestion may increase α-DCs formation in sweetened snack products despite low or zero sugar content.

In diabetic jam samples, it was observed that *in vitro* digestion strongly increased the GO formation up to 607.4 %. It was reported that digestive system conditions such as pH, minerals, and temperature might increase α-DCs formation through Maillard reaction or lipid oxidation (Hamzalıoğlu and Gökmen, 2016). The increased MGO content may be attributed to these reactions in digestion. Also, it was seen that MGO formation in diabetic jams decreased up to 56.5 %. α-DCs are highly reactive molecules that can bind with proteins; it is conceivable that the decrease in MGO concentrations occurred due to the reaction between enzymatic proteins (Papetti et al., 2013). Interestingly in sample 5, MGO content increased 118.7 % after digestion, this difference may be related to sugar content. As seen in Table 2, sample 5 had the highest sugar value among jam samples. Yaman et al. indicated that sugar content may increase the α-DCs formation under *in vitro* digestional system (Yaman et al., 2022). The effects of gastrointestinal conditions on AGEs formation have not been fully elucidated yet. Some studies indicate that *in vitro* digestion decreases free α-DCs in balsamic vinegar, coffee, and biscuits may related to interactions between reactive carbonyls and amino acids during digestion (Papetti et al., 2013, 2014; Hamzalıoğlu and Gökmen, 2016). Other studies reporting that gastrointestinal conditions strongly increase AGEs precursors in barley, soy sauce, biscuits, and cookies (Papetti et al., 2014; Van der Lugt et al., 2020; Yaman et al., 2022). Interestingly, in

Table 2: Declared amount of energy and nutrient contents.

Sample	Product	Sugar Substitute	Energy (100 g/kcal)	Protein (g/100 g)	Fat (g/100 g)	Saturated Fat (g/100 g)	CHO (g/100 g)	Sugar (g/100 g)	Polyol	Salt (g/100 g)
S1	Diabetic strawberry jam	Sorbitol, Acesulfame-K, aspartame	173	0.4	0	0	12.2	3.3		
S2	Diabetic orange peel jam	Sorbitol, Acesulfame-K, aspartame	176	0.3	0	0	14.6	0		
S3	Diabetic plum jam	Sorbitol, Acesulfame-K, aspartame	186	0.3	0	0	17.6	5.1		
S4	Diabetic mix berry jam	Sorbitol, Acesulfame-K, aspartame	172	0.6	0	0	13.4	3.6		
S5	Diabetic blueberry jam	Sorbitol, Acesulfame-K, aspartame	176	0.3	0	0	15.1	5.4		
S6	Diabetic apricot jam	Sorbitol, Acesulfame-K, aspartame	146	0.3	0	0	65.4	4.1		
S7	Diabetic cherry jam	Sorbitol, isomalt, maltitol	157	0.3	0	0	60.1	4.8	54	0.8
S9	Biscuit	Maltitol	431	6.1	17	1.7	65	<0.5	9.3	
S10	Diabetic halvah	Maltitol, isomalt, sorbitol	495	14.6	35.3	7	42,9	1.7	38	5.7
S11	Candy (sugar free)	Isomalt, maltitol, Acesulfame-K	239	0	0	0	98	0	98	0
S12	Chocholate	Isomalt, sucrolase	435	8.5	33.1	13	49.5	<0.5		1.2

Table 3: GO and MGO values of samples at initial and after *in vitro* digestion and formation rate.

Sample Number	Product	Sugar substitute	Initial Value µg/100 g		After Digestion µg/100 g		Formation of %	
			GO	MGO	GO	MGO	GO	MGO
S1	Diabetic strawberry jam	Sorbitol, Acesulfame-K, aspartame	125.0±5.7 Ba	347.6±15.7 EFa	172.1±7.8 FGb	275.2±12.5 EFb	138.0±11.1 F	79.3±6.4 DE
S2	Diabetic orange peel jam	Sorbitol, Acesulfame-K, aspartame	112.8±5.1 Ba	444.7±20.1 DEa	262.2±11.9 DEb	370.6±16.8 DEb	232.9±18.7 EF	83.5±6.7 DE
S3	Diabetic plum jam	Sorbitol, Acesulfame-K, aspartame	121.7±5.5 Ba	976.1±44.2 Ba	231.3±10.5 EFb	818.7±37.0 Bb	190.5±15.3 F	84.0±6.7 DE
S4	Diabetic mix berrr jam	Sorbitol, Acesulfame-K, aspartame	79.6±3.6 CDa	434.6±19.7 DEa	206.4±9.3 EFb	340.4±15.4 Eb	259.7±20.9 EF	78.5±6.3 DE
S5	Diabetic blueberry jam	Sorbitol, Acesulfame-K, aspartame	70.1±3.2 DEa	109.7±5.0 Ha	209.0±9.5 EFb	130.0±5.9 Fb	298.9±24.0 DEF	118.7±9.5 D
S6	Diabetic apricot jam	Sorbitol, Acesulfame-K, aspartame	21.1±1.0 Ga	446.9±20.2 DEa	128.1±5.8 Gb	252.1±11.4 EFb	607.4±48.8 C	56.5±4.5 E
S7	Diabetic cherry jam	Sorbitol, isomalt maltitol	78.3±3.5 CDa	689.9±31.2 Ca	329.0±14.9 CDb	586.7±26.5 Cb	420.9±33.8 CDE	85.2±6.8 DE
S8	Wafer	Maltitol, isomalt	44.7±2.0 Fa	125.0±5.7 Ha	1134.6±51.3 Ab	758.2±34.3 Bb	2546.4±204.4 A	607.9±48.8A
S9	Biscuit	Maltitol	234.4±10.6 Aa	3164.5±143.2 Aa	1144.0±51.8 Ab	3500.5±158.4 Ab	489.0±39.3 CD	110.8±8.9 D
S10	Diabetic halvah	Maltitol, isomalt sorbitol	85.2±3.9 Ca	505.9±22.9 Da	336.0±15.2 Cb	583.5±26.4 Cb	395.1±31.7 DE	115.6±9.3 D
S11	Candy (sugar free)	Isomalt, maltitol Acesulfame-K	77.4±3.5 CDa	294.4±13.3 FGa	261.3±11.8 DEb	517.4±23.4 CDb	338.2±27.1 DEF	176.1±14.1C
S12	Chocholate	Isomalt, sucralose	62.4±2.8 Ea	193.7±8.8 GHa	567.9±25.7 Bb	576.8±26.1 Cb	912.1±73.2 B	298.5±24.0 B

While the uppercase letters show the statistical difference between each sample, lowercase letters show the statistical differences in the same sample before and after digestion ($p < 0.05$). GO; Glyoxal, MGO; Methylglyoxal.

present study *in vitro* digestion strongly increased GO and slightly decreased MGO. Studies focused on the effects of *in vitro* digestion on AGEs formation are limited. In existing literature, no study evaluated the AGEs formation under digestive system conditions in diabetic products. These results revealed that sugar-free and sweetened products contain AGEs precursors, and may increase with gastrointestinal digestion. To have a better understanding, AGEs formation in diabetic sugar-free or sweetened products, further research should focus on the effects of different sugar types on AGEs formation under *in vitro* digestion.

Nowadays, a considerable increase is seen in the number of food products that contain non-calorie sweeteners to get through the health problems related to obesity and diabetes (Farid et al., 2020). The use of non-nutritive sweeteners can reduce energy and carbohydrate intake. It is reported that, replacing sugar with non-nutritive sugar in the diet positively affects body weight and glycemic control (Ley et al., 2014). AGEs from food sources are absorbed, thereby increasing the level of circulating AGEs which can disrupt endocrine functions (Ravichandran et al., 2019). It has been reported that dietary AGEs are associated with many diseases, as well as the development of insulin resistance and diabetes (Yılmaz and Karabudak, 2018). Similar to sugars, sweeteners may also be risky in terms of AGEs exposure due to interactions between reactive groups and amino acids that increases glycation processes. (Ali and Devrukhkar, 2016).

4. Conclusions

Sweetened or sugar free diabetic products are commonly consumed to reduce energy intake and maintain blood sugar levels. However, the AGEs content of these products had been poorly studied. In this study, it was observed that sugar-free or sweetened products, including wafer, biscuit, candy, halvah, and chocolate contain high AGEs precursors such as GO and MGO. Besides, it was determined that the AGEs formation may increase after *in vitro* gastrointestinal digestion. Interestingly *in vitro* digestion strongly increased GO formation, whereas slightly decreased MGO formation in diabetic jams. The AGEs formation may occur through the Maillard reaction, lipid peroxidation, and polyol pathway in these types of foods. Moreover, to have a better understanding AGEs formation in sugar free or sweetened products under gastrointestinal digestion, further research should evaluate the results with different sugar types.

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