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Ozlem Soyluk Selçukbiricik * , Fulya Calikoglu , Cemile İdiz , Gulay Dura , Gokmen Sir , Onder Yuksel Eryigit , Isik Kulaksiz , Mustafa Hakan Yilmazturk , Ayse Kubat Uzum , Kubilay Karsidag , Ilhan Satman

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Effects of *Cephalaria Syriaca*-Added Bread on Glucose Metabolism and Appetite Regulating Hormones in Healthy Individuals, Patients with Obesity and Patients with Diabetes: A Pilot Study

Ozlem Soyluk Selcukbiricik [1,*], Fulya Calikoglu [1], Cemile İdiz [1], Gulay Dura [2], Gokmen Sir [3], Onder Yuksel Eryigit [3], Isik Kulaksiz [2], Mustafa Hakan Yilmazturk [3], Ayse Kubat Uzum [1], Kubilay Karsidag [1] and Ilhan Satman [1]

[1] Istanbul University, Istanbul Faculty of Medicine, Department of Internal Medicine, Division of Endocrinology and Metabolism, Istanbul, Türkiye
[2] Istanbul Metropolitan Municipality, Medical Laboratory, Istanbul, Türkiye
[3] Istanbul Metropolitan Municipality, Istanbul, Türkiye
* Correspondence: drozlem76@hotmail.com

Abstract

Background: Improving nutritional quality of widely consumed foods such as bread with natural additives is a rational approach for community nutrition and management of non-communicable diseases (e.g., diabetes, obesity). Pelemir (*Cephalaria syriaca L.*), an annual weed growing in wheat fields, improves the quality of bread when added to wheat flour and is expected to reduce the glycemic index due to its high protein, fiber and polyphenol contents. We aimed to investigate the effects of pelemir-added bread on glucose metabolism and appetite-regulating hormones. **Materials and Methods:** Study population consisted of three groups (healthy control, obesity, and diabetes; each n=20). The participants ingested two test meals (bread with and without pelemir) with one-week interval. Blood samples for glucose, insulin, C-peptide, GLP-1, leptin, ghrelin, and PYY were obtained at 0, 30, 60, 90, 120 minutes. The effect on appetite was evaluated subjectively by visual analog scales. **Results:** Area under curve (AUC)-Insulin and AUC-C-peptide were higher with pelemir-added bread in total group (p=0.044). In healthy group, AUC-GLP-1 was higher with pelemir-added bread (p=0.021). Additionally, pelemir-added bread resulted in an increased trend in AUC-C-peptide and AUC-PYY in healthy group; AUC-Insulin, AUC-C-peptide and AUC-Ghrelin in diabetes group; and a decreased trend in AUC-Leptin and AUC-PYY in obesity group. AUC for progressive food consumption was lower with pelemir bread in obesity group (p=0.006). **Conclusion:** The preliminary findings of this pilot study suggested that pelemir may possess beneficial effects on regulating glucose metabolism and hormonal responses. However, long-term, large-scale studies are needed to further clarify these effects.

Keywords: pelemir; *Cephalaria syriaca*; bread; diabetes; obesity; insulin resistance

1. Introduction

Non-communicable diseases (NCD) are considered the most important public health problems whose prevalence increased rapidly over the last 50 years. Obesity is a complex, multifactorial NCD, characterized with excessive fat accumulation in the body secondary to high energy intake and insufficient physical activity, and increases the risk of diabetes. Another NCD, diabetes is a chronic, broad-spectrum metabolic disorder that requires continuous medical care, in which the organism cannot adequately benefit from carbohydrates (CHO), fats and proteins due to insulin deficiency and/or defects in or resistance to insulin action.

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Nutrition is the essential step in the treatment and management of obesity, diabetes, and accompanying diseases [1]. Consumption of low glycemic index (GI) and high fiber foods is one of the primary approaches in medical nutrition therapy to facilitate weight loss and glycemic control and ensure long-term satiety in patients with obesity as well as those with diabetes. Bread is an important source of CHO in nutrition and is widely consumed in Türkiye so that the annual bread consumption is much higher than the world average being mean 272.3 g/day according to the Turkey Nutrition and Health Survey-2017 data (328 g/day for men, 217 g/day for women) [2,3]. Although approximately 85% of bread consumed in Türkiye consists of white bread, the production of different types of bread and whole wheat flour products has been predominant in recent years [4]. Epidemiological studies have shown that consumption of whole wheat bread is inversely related to the incidence of type 2 diabetes mellitus (T2DM) and cardiovascular disease [5]. In contrast, some clinical studies have shown that whole wheat bread consumption improves glycemic control and has positive effects on postprandial glucose, insulin and incretin hormone responses [6,7]. Therefore, reducing the GI value of bread is worth in both prevention and management of obesity and diabetes.

Pelemir *(Cephalaria syriaca L.)* is an annual weed found in the family *Dipsacaceae*, which grows mostly in wheat fields [8]. This species is widely distributed especially in Anatolia as well as in other Mediterranean regions like southern France, southern Spain and in northern Africa. It is chilling resistant and can grow in infertile soils [9]. Different species of this genus contain plenty of triterpenes, flavonoids, glycosides and alkaloids, which are extensively used in traditional medicine as well as cosmetic and pharmaceutical industry [10–12]. Methanol and water extracts of *Cephalaria tchihatchewii Boiss* have various biological activities, including antioxidant activity and α-glycosidase, acetylcholinesterase, carbonic anhydrase -II enzyme inhibition effect [13]. The root water and leaf ethanol extracts of *Cephalaria gigantea* displayed the most potent inhibition of α-amylase and α-glucosidase. This suggested that these extracts have antioxidant and antidiabetic potentials [14]. *Cephalaria syriaca* is rich in vitamins and minerals, and contains protein (14-21%), dietary fiber (9-30%), and polyphenols which is responsible for its antioxidant properties [11,15]. Dietary polyphenols exhibit antidiabetic activities via lowering the GI of foods and increasing glucose entry into the cells [16]. *Cephalaria syriaca* is also considered an oilseed with high oil content (21-26%) [10]. The fatty acid composition of pelemir is 36.9% linoleic, 23.0% oleic, 19.5% myristic, 9.4% palmitic, 2% stearic, and 1.5% lauric acid [17–19]. Addition of pelemir products (whole or degreased flours) substantially changed the rheological properties of dough and improved the quality of bread. In Kayseri and Erzican regions of Türkiye, pelemir is specifically grown for its seeds, which are added to wheat to ameliorate its baking value and to delay staling [18,20]. Flour and oil obtained from pelemir seeds are mixed with wheat flour at low levels (0.5-3.0%) for delaying the staleness of the bread and making the dough rise better [15,21]. Considering the seed's less exacting character, the Turkish Ministry of Agriculture made some field trials with pelemir to replace wheat in the arid and less productive areas of southeastern Türkiye [17,22–25].

The dietary fiber, fat, and protein contents in foods and their polyphenol constituents lower their GI. Therefore, *Cephalaria syriaca* added to bread flour is expected to reduce the GI of bread. In our country, bread made up pelemir-added flour is produced with the brand name "Akdeniz Bread™". The content of CHO in pelemir-added bread flour is same as the white bread without pelemir but the fat and protein contents of pelemir-added bread are higher.

Although there are few *in vitro* studies regarding the effects of several *Cephalaria species* on glucose metabolism in the literature, no clinical studies with published results have been found on glucose metabolism and gut hormones [26]. Therefore, this study is planned to investigate the effects of adding *Cephalaria syriaca* flour to wheat flour on glucose metabolism, gut hormones, and appetite in individuals with obesity and diabetes, and healthy volunteers.

2. Materials and Methods

This study was carried out between 05 April 2022 and 01 February 2023 at Istanbul University, Istanbul Faculty of Medicine, Dept. Internal Medicine, Div. Endocrinology and Metabolism. The

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study was approved by the Local Ethical Review Board (Istanbul Faculty of Medicine, Clinical Research Ethics Committee) (05.04.2022-834721). The study was conducted with good clinical practice in accordance with the Declaration of Helsinki latest criteria [27]. Written informed consent was obtained from all participants. This study was registered in the 'ClinicalTrials.gov' (NCT05687812).

Participants were gathered in three groups categorized as healthy control, obesity, and diabetes (T2DM) groups. The sample size was calculated using G*Power software (version 3.1.9.7; Heinrich-Heine-Universität, Düsseldorf, Germany), with 0.05 type 1 error and 80% power. A total of 60 individuals over the age of 18 were included. The first group consisted of healthy individuals (n=20) with a normal body mass index (BMI: 18.5-24.9 kg/m^2), with no known chronic disease (diabetes, hypertension, etc.), not smoking and not using alcohol, not on any regular medication (antihypertensive, antilipidemic, antidepressant, etc.) and not using food supplements. The second group included individuals with obesity (BMI ≥30 kg/m^2) but no diabetes (n=20), and the third group consisted of individuals with a diagnosis of T2DM who were using only oral antidiabetic drugs (n=20). Individuals in healthy control and obesity groups underwent a 2-hour OGTT with 75 g glucose after 10-12 hours of fasting and confirmed to have normal glucose tolerance. Exclusion criteria were pregnancy, breastfeeding, presence of chronic diseases (chronic kidney disease, chronic obstructive pulmonary disease, malignancy etc.), regular use of food supplements, use of DPP-4 inhibitors for diabetes and glucagon-like peptide-1 (GLP-1) receptor analogues for the treatment of diabetes or obesity and engaging excessive physical activity.

All participants ingested two test meals with one-week interval, first bread produced by wheat flour (called “regular bread” throughout the article), then followed by a bread produced by pelemir-added wheat flour (called “pelemir bread” throughout the article). The breads used in this study were produced by “Istanbul Halk Ekmek Co.”. Pelemir used in the study was supplied by “Ziya Organik Tarım İşletmeleri A.Ş”. A serving of both types of bread contained 50 g CHO. The weight of the pelemir bread (added 0.3% pelemir) was 100 g and that of regular bread was 95 g. Other ingredients are shown in Table 1.

Table 1. Ingredients of the test breads.

Ingredient	Regular bread	Pelemir bread
Wheat flour (g)	95	100
CHO (g)	50	50
Energy (kcal)	291.5	285.4
Dietary fiber (%)	3.40	3.12
Fat (%)	2.25	2.64
Saturated FA (%)	0.52	0.80
Protein (%)	9.20	10.10
Pelemir flour (%)	0	0.3
NaCl (%)	0.71	0.70

CHO, carbohydrate; FA, fatty acid; NaCl, sodium chlorine.

The body composition of the participants was measured with bioelectrical impedance analyzer (TANITA BC 420 MA) before the test. Height was measured using a stadiometer. BMI was calculated by weight in kilograms (kg) divided by the square of height in meters (m^2). BMI is classified normal if 18.5-24.9 kg/m^2, overweight if 25.0-29.9 kg/m^2 and obesity if ≥30.0 kg/m^2 according to the World Health Organization [28].

Participants were asked not to restrict CHO and not make any changes in their diet during the day before the tests. First, they were fed with regular bread containing 50 g CHO with 250 ml water for breakfast (following 10-12 hours of fasting). After one week, they were fed with pelemir bread (including 0.3% *Cephalaria syriaca* added flour) containing 50 g of CHO with 250 ml water. Participants were asked to consume the bread within 10 minutes. During the test, venous blood samples were taken at 0, 30, 60, 90, and 120 minutes from the time of bread ingestion via an indwelling cannula

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placed in the antecubital fossa for measurement of glucose, insulin, C-peptide, triglycerides (TG), glucagon-like peptide 1 (GLP-1), polypeptide YY (PYY), leptin, ghrelin, and interleukin-6 (IL-6). The samples were transferred to the laboratory and analyzed within half an hour. Abbott Architect CI 8200 Integrated System device was used for analyses of glucose (hexokinase/G-6-PDH method), TG (glycerol phosphate oxidase method), insulin (Chemiluminescent microparticle immunoassay method-CMIA) and C-peptide (CMIA). Peptide YY (E-EL-H1237, Elabscience, USA), ghrelin (E-EL-H1919, Elabscience, USA), IL-6 (E-EL-H0102, Elabscience, USA), leptin (E-EL-H6017, Elabscience, USA), and GLP-1 (E-EL-H6025, Elabscience, USA) were analyzed by ELISA. The homeostasis model of assessment insulin resistance (HOMA-IR) was calculated using the formula: *'Fasting Glucose (mg/dl) × Fasting Insulin (μU/ml)] / 405'* [29]. The quantitative insulin sensitivity check index (QUICKI) was calculated using the formula: '*QIUCKI = 1 / (log[Fasting Insulin (μU/ml)] + log[Fasting Glucose (mg/dl)])* [30]. Glycemic index (GI) is defined as the ratio of area under the curve (AUC) for 0-2 hour blood glucose after the ingestion of a given amount of test food (usually containing 50 g CHO) to the AUC for 0-2 hour blood glucose after the ingestion of a reference food (containing the same amount of white bread or glucose) [31]. The GI of pelemir is calculated using the formula *'GI = AUC-Glucose-Pelemir / AUC-Glucose-Regular x 100'*. If the GI value of the regular (white) bread taken as reference is accepted as 100, the reference ranges of foods with low, moderate and high GI are ≤55, 56-69 and ≥70, respectively [32]. Subjective appetite was assessed with visual analog scales (VAS) [33]. It is a measurement tool for subjective characteristics or attitudes that cannot be measured directly. VAS was used to measure satiety (S), hunger (H), fullness (F), and prospective food consumption (PFC) scores immediately before consumption of test meal and at 30, 60, 90 and 120 min later. The VAS was a 100-mm straight line, and the patients were asked to make a vertical mark across this line corresponding to their concurrent feelings from 0 (not at all) to 100 (very) measuring S, H, F, and PFC.

Statistical analysis: Statistical analysis was performed with SPSS software version 21. The normality of the variables was tested with visual (histogram) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test), and an analysis of the distribution was made. Comparisons of the parameters in groups composed of patients with diabetes and obesity, and healthy individuals after consuming pelemir bread and regular bread were determined by Wilcoxon signed-rank test. Kruskal-Wallis and Mann-Whitney U tests were used to compare the parameters between groups. Pearson and Spearman tests were used to test correlations between variables. A p value less than 0.05 was considered statistically significant. Additionally, a p value between 0.05 and 0.10 was considered as a potential trend. AUC for glucose, insulin, C-peptide, TG, GLP-1, PYY, leptin, ghrelin, and IL-6, during the meal tests were calculated with the trapezoidal method. End point changes from baseline were assessed using ANOVA.

3. Results

The general characteristics of the study group are presented in Table 2. The proportion of female participants was numerically higher in all groups except the obesity group. The only significant difference was between healthy and obesity groups (p=0.001). The healthy group had significantly lower BMI than both diabetes and obesity groups. Weight, fat mass and fat-free mass were notably different between the groups, obesity group having the highest (p<0.001 for all).

Table 2. General characteristics of the study groups.

	Total participants (n=60)	Healthy control group (n=20)	Obesity group (n=20)	Diabetes group (n=20)	p (intra-groups)
Women/Men (n)	38/22	18/2	7/13	13/7	0.001
Age (year)	43.40±10.01	38.10±7.58	39.45±6.53	52.65±8.66	<0.001
BMI (kg/m²)	29.67±7.71	22.45±2.13	35.09±4.57	31.47±8.38	<0.001
Weight (kg)	80.36±20.38	61.62±6.19	99.41±15.10	80.05±16.49	<0.001
Height (cm)	165.51±7.80	165.80±6.50	168.10±8.18	162.65±8.01	0.084

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Fat mass (%)	31.17±7.77	26.41±6.27	34.33±7.81	32.78±7.06	0.002
Fat mass (kg)	25.60±10.49	16.46±4.99	34.06±9.47	26.29±7.97	<0.001
FFM (kg)	**54.70±13.25**	**45.16±4.51**	**65.19±12.88**	**53.76±12.12**	**<0.001**

BMI, body mass index; FFM, fat free mass.

The AUC of the biochemical parameters, HOMA-IR and QUICKI calculated for regular bread and pelemir bread meals of the whole group and subgroups are shown in Table 3.

Table 3. Comparison of the biochemical parameters after consuming regular bread and pelemir bread in the study groups. Data are given as 'median (range)'.

Median (range)	Total (n=60)			Healthy control group (n=20)			Obesity group (n=20)			Diabetes group (n=20)			p (inter-groups)	
	Regular bread	Pelemir bread	p	Regular bread	Pelemir bread	p	Regular bread	Pelemir bread	p	Regular bread	Pelemir bread	p	Regular bread	Pelemir bread
AUC-Glucose (mg*min/dL)	684.75 (585.68-585.68)	670,25 (568.75-924.00)	0.483	579.63 (493.19-617.50)	574.75 (528.75-628.13)	0.823	659.50 (591.63-727.25)	659,13 (514.69-755.81)	0.126	1109.88 (818.69-1281.00)	1127.00 (821.50-1348.75)	0.717	**<0.001**	**<0.001**
AUC-Insulin (µU*min/mL)	163.66 (105.80-225.04)	183.70 (109.06-318.03)	**0.044**	124.79 (89.53-155.57)	132.55 (84.88-168.00)	0.615	167.88 (109.85-299.76)	192.24 (129.64-327.25)	0.313	219.25 (132.89-366.21)	277.70 (199.95-403.35)	**0.053**	**0.006**	**0.008**
AUC-C-peptide (ng*min/mL)	31.82 (24.38-40.80)	34.82 (24.69-46.32)	**0.004**	25.31 (17.64-30.11)	28.26 (22.78-36.39)	**0.070**	33.99 (27.13-42.57)	33.48 (26.77-46.28)	0.351	37.89 (31.14-54.80)	39.16 (34.76-60.95)	**0.064**	**<0.001**	0.374
AUC-TG (mg*min/dL)	632.63 (423.56-1132.25)	567.25 (412.31-1195.81)	0.917	412.50 (318.75-509.88)	407.25 (331.25-493.25)	0.936	747.63 (497.44-1367.44)	591.00 (470.38-1475.00)	0.823	1079.88 (647.00-1372.75)	921.75 (694.75-1601.50)	0.809	**<0.001**	**<0.001**
AUC-Leptin (pg*min/mL)	7010.13 (2493.63-16342.13)	5968.75 (2633.00-16020.00)	0.464	2265.63 (1673.19-7038.31)	2507.00 (1644.75-6432.69)	0.601	12155.63 (3507.25-24742.38)	7940.63 (4045.81-15807.69)	**0.073**	8818.50 (5056.88-21236.19)	8887.50 (3720.00-22728.50)	0.748	**0.002**	**0.004**
AUC-PYY (pg*min/mL)	406.9 (265.73-598.28)	347.5 (212.67-537.37)	0.895	429.33 (257.05-686.79)	450.02 (319.65-842.84)	**0.073**	362.45 (196.69-571.27)	311.44 (169.04-439.34)	**0.067**	402.38 (292.79-657.53)	339.05 (180.83-583.48)	0.546	0.181	**0.018**
AUC-GLP-1 (pg*min/mL)	74.38 (66.08-431.81)	77.00 (62.60-1204.65)	0.192	641.46 (69.09-1257.53)	1355.06 (204.26-1745.84)	**0.021**	72.28 (65.20-89.42)	70.11 (59.87-93.13)	0.940	73.01 (66.12-80.57)	71.75 (60.89-79.08)	0.243	**0.066**	**0.002**
AUC-Ghrelin (ng*min/mL)	5.18 (2.59-11.07)	5.90 (3.55-16.48)	0.129	13.98 (5.56-22.44)	14.51 (5.97-25.95)	0.737	3.51 (2.02-5.64)	4.08 (2.04-8.53)	0.370	3.67 (2.35-6.92)	5.25 (3.55-10.21)	**0.091**	**<0.001**	**0.001**
AUC-IL-6 (pg*min/mL)	14.96 (9.04-41.56)	19.82 (9.09-64.69)	0.476	20.57 (7.11-89.83)	52.77 (24.09-142.35)	**0.097**	13.95 (10.57-33.81)	13.96 (9.56-36.57)	0.654	11.93 (8.36-31.43)	11.67 (5.10-24.60)	0.147	0.262	0.961
HOMA-IR	1.56 (0.96-2.87)	1.66 (0.97-2.46)	0.596	1.06 (0.68-1.30)	1.06 (0.81-1.26)	0.778	1.79 (1.16-3.19)	2.15 (0.97-2.47)	0.575	2.77 (1.45-3.75)	2.19 (1.69-3.67)	0.872	**<0.001**	**0.001**
OUICKI	**0.36 (0.33-0.38)**	**0.36 (0.33-0.39)**	**0.795**	**0.38 (0.37-0.41)**	**0.38 (0.37-0.40)**	**0.494**	**0.35 (0.32-0.37)**	**0.34 (0.33-0.40)**	**0.391**	**0.33 (0.31-0.36)**	**0.34 (0.31-0.35)**	**0.872**	**0.104**	**0.030**

AUC, area under the curve; TG, triglyceride; PYY, polypeptide Y; GLP-1, glucagon like peptide-1; IL-6, interleukin-6; HOMA-IR, homeostasis model of assessment insulin resistance; OUICKI, quantitative insulin sensitivity check index.

Comparison of healthy control, obesity and diabetes groups: Glycemic index (GI): The GI of pelemir bread was similar in all groups (healthy: 99.2, obesity: 99.2, diabetes: 101.5).

AUC-Glucose: With both regular and pelemir breads, AUC-Glucose was lowest in healthy group and highest in diabetes group (p<0.001 for both).

AUC-Insulin: With both regular and pelemir breads, AUC-Insulin was lowest in healthy group and highest in diabetes group (regular bread: p=0.006, pelemir bread: p=0.008).

AUC-C-peptide: With regular bread, AUC-C-peptide was lowest in healthy group and highest in diabetes group (p<0.001). In contrast, with pelemir bread, AUC-C-peptide was numerically lowest in healthy group and highest in diabetes group.

AUC-TG: With both regular and pelemir breads, AUC-TG was lowest in healthy group and highest in diabetes group (p<0.001 for both).

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AUC-Leptin: With regular bread, AUC-Leptin was lowest in healthy group and highest in obesity group (p=0.002). In contrast, with pelemir bread, AUC-Leptin was lowest in healthy group and highest in diabetes group (p=0.004).

AUC-PYY: With regular bread, AUC-PYY was numerically highest in healthy group and lowest in obesity group, while with pelemir bread, AUC-PYY was highest in healthy group and lowest in obesity group (p=0.018).

AUC-GLP-1: With both regular and pelemir breads, AUC-GLP-1 was highest in healthy group, and similar in-obesity and diabetes groups (regular bread: p=0.066, pelemir bread: p=0.002).

AUC-Ghrelin: With both regular and pelemir breads, AUC-Ghrelin was highest in healthy group, and similar in obesity and diabetes groups (regular bread: p<0.001, pelemir bread: p=0.001).

AUC-IL-6: With both regular and pelemir breads AUC-IL-6 was highest in healthy group, and similar in obesity and diabetes groups.

HOMA-IR calculated before regular and pelemir breads, was lowest in healthy group, and highest in diabetes group (regular bread: p<0.001, pelemir bread: p=0.001).

QUICKI calculated before regular and pelemir breads, was highest in healthy group, and similar in diabetes and obesity groups (regular bread: p=0.104, pelemir bread: p=0.030).

Comparison of the regular bread and pelemir bread in the groups: In the whole study population, AUC-Insulin and AUC-C-peptide were significantly higher with pelemir bread (p=0.044, p=0.004; Table 3, Figure 1a,b). No significant difference was obtained in AUC-glucose, AUC-TG, AUC-Leptin, AUC-PYY, AUC-GLP-1, AUC-Ghrelin, and AUC-IL-6. Likewise, there was no statistical difference of HOMA-IR and QUICKI between pelemir bread and regular bread. However, AUC-TG was numerically lower and AUC-Ghrelin higher with pelemir bread.

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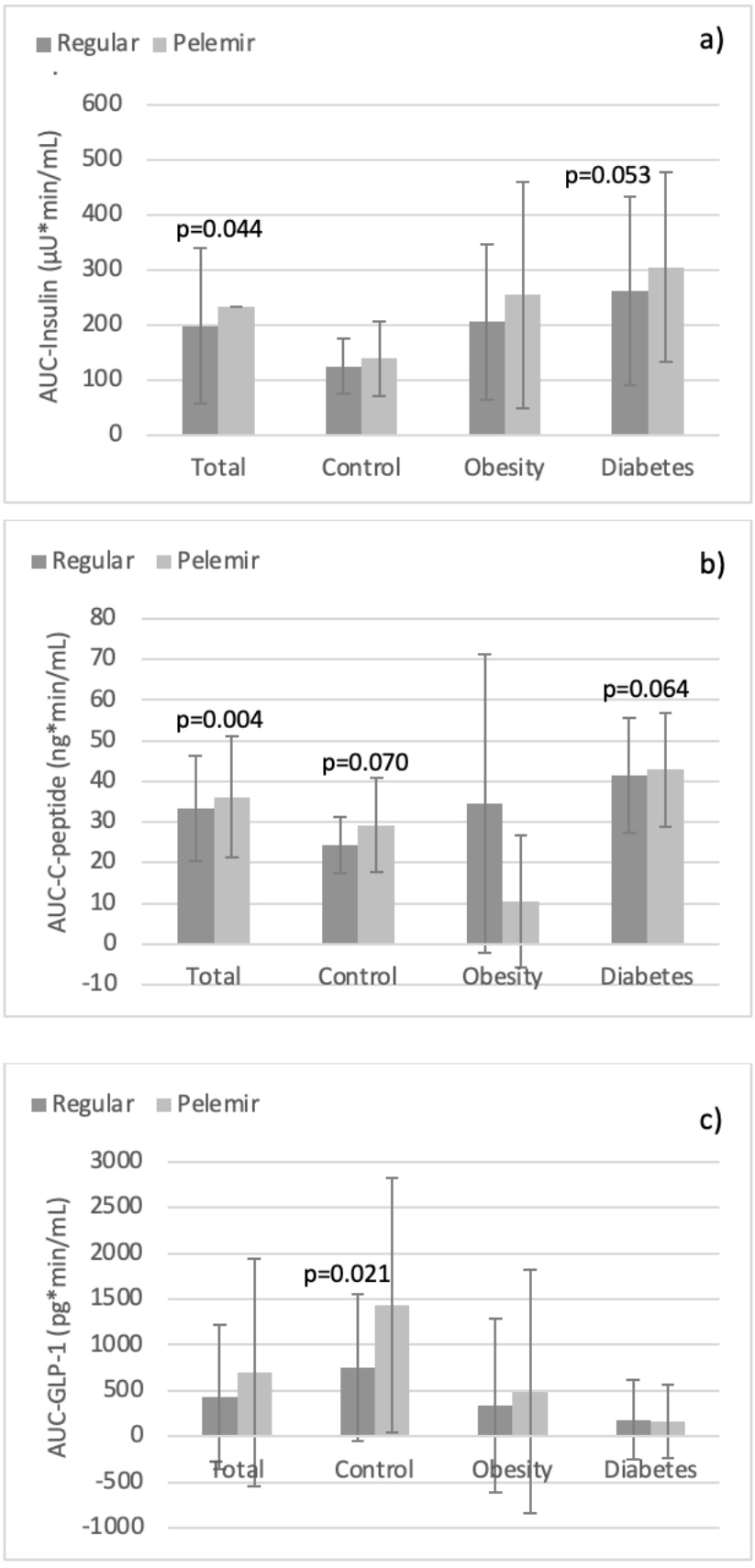

Figure 1. The AUC for postprandial hormonal responses to regular and pelemir bread meals in the study groups. a. AUC-Insulin, b. AUC-C-peptide, c. AUC-GLP-1 (based on 'mean±SD').

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In healthy group, AUC-GLP-1 was significantly higher with pelemir bread (p=0.021; Table 3, Figure 1c). Furthermore, AUC-C-peptide, AUC-PYY, and AUC-IL-6 exhibited upward trends with pelemir bread (p=0.07, p=0.073, p=0.097). The other AUCs did not differ between the two breads (Table 3).

In obesity group, AUC-Leptin and AUC-PYY revealed downward trends with pelemir bread (p=0.073, p=0.067). The other AUCs showed no significant difference between the two breads (Table 3).

In diabetes group, AUC-Insulin, AUC-C-peptide, and AUC-Ghrelin with pelemir bread displayed increased trends (p=0.053, p=0.064, p=0.091). The other AUCs did not differ between the two tests (Table 3).

Correlation analysis: The detected correlations were generally weak or moderate, except for those between AUC-Insulin and AUC-C-peptide. Overall, the correlations found with pelemir bread were more remarkable than with regular bread (Table 4).

Table 4a. Correlation analysis of biochemical parameters in total study population with regular bread.

a. Regular bread test	AUC-Insulin	AUC-C-peptide	AUC-Leptin	AUC-PYY	AUC-GLP-1	AUC-Ghrelin	HOMA-IR	QUICKI
AUC-Insulin	1	p<0.001 r=0.786	p<0.001 r=0.477				p<0.001 r=0.552	p<0.001 r=-0.470
AUC-C-peptide		1			p=0.013 r= -0.322	p=0.045 r= -0.262	p=0.001 r=0.421	p=0.001 r= -0.420
AUC-Leptin			1		p=0.022 r= -0.299	p=0.003 r= -0.374	p=0.001 r=0.435	p=0.001 r= -0.428
AUC-PYY				1				
AUC-GLP-1					1	p<0.001 r=0.470		
AUC-Ghrelin						1	p<0.001 r= -0.473	p<0.001 r=0.476
HOMA-IR							1	
QUICKI								1

Table 4b. Correlation analysis of biochemical parameters in total study population with pelemir bread.

b. Pelemir bread test	AUC-Insulin	AUC-C-peptide	AUC-Leptin	AUC-PYY	AUC-GLP-1	AUC-Ghrelin	HOMA-IR	QUICKI
AUC-Insulin	1	p<0.001 r=0.830	p<0.001 r=0.548		p=0.003 r= -0.387	p=0.041 r= -0.271		p<0.001 r= -0.512
AUC-C-peptide		1			p=0.017 r= -0.316		p=0.001 r=0.446	p=0.002 r= -0.401
AUC-Leptin			1		p=0.006 r= -0.355	p=0.002 r= -0.397	p<0.001 r=0.530	p<0.001 r= -0.493
AUC-PYY				1	p=0.002 r=0.399			
AUC-GLP-1					1	p<0.001 r=0.456	p=0.027 r= -0.293	
AUC-Ghrelin						1	p=0.016 r= -0.318	p=0.047 r=0.265
HOMA-IR							1	
QUICKI								1

AUC, area under the curve; PYY, peptide YY; GLP-1, glucagon like peptide 1; QUICKI, quantitative insulin sensitivity check index; HOMA-IR, homeostatic model assessment insulin resistance.

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Considering the total study population, with regular bread, AUC-Insulin was positively correlated with AUC-C-peptide, AUC-Leptin, HOMA-IR; but inversely correlated with QUICKI. Both AUC-C-peptide and AUC-Leptin–were positively correlated with HOMA-IR, but negatively correlated with AUC-GLP-1, AUC-Ghrelin and QUICKI. There was a positive correlation between AUC-GLP-1 and AUC-Ghrelin. In addition, AUC-Ghrelin was positively correlated with QUICKI but inversely correlated with HOMA-IR (Table 4a).

Contrariwise, with pelemir bread, AUC-Insulin positively correlated with AUC-C-peptide and AUC-Leptin, but inversely correlated with AUC-GLP-1, AUC-Ghrelin and QUICKI. AUC-C-peptide negatively correlated with AUC-GLP-1 and QUICKI, but positively correlated with HOMA-IR. AUC-Leptin was inversely correlated with AUC-GLP-1, AUC-Ghrelin and QUICKI, but positively correlated with HOMA-IR. There was a positive correlation between AUC-PYY and AUC-GLP-1. AUC-GLP-1 was positively correlated with AUC-Ghrelin but inversely correlated with HOMA-IR. Moreover, AUC-Ghrelin was negatively correlated with HOMA-IR and positively correlated with QUICKI (Table 4b).

Evaluation of the VAS scores: The AUC-VAS scores of the entire group and individual groups with regular and pelemir bread were evaluated in four categories:

Satiety: In the total and in the individual groups, AUC-satiety with pelemir bread was not different from regular bread (Figure 2a).

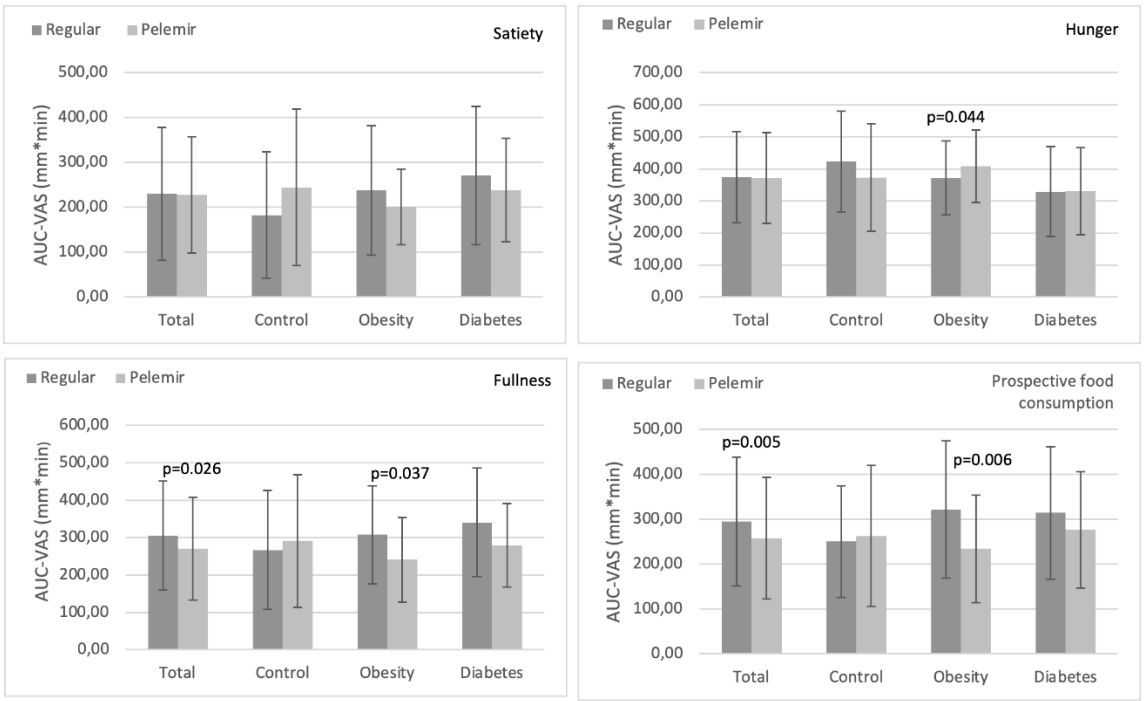

Figure 2. The AUC for VAS scores during regular and pelemir bread meals in the study groups. a. Satiety, b. Hunger, c. Fullness, d. Prospective food consumption (PFC).

Hunger: In the total, healthy and diabetes groups, AUC-hunger with pelemir bread was not different from regular bread. In obesity group, AUC-hunger with pelemir bread was significantly higher than regular bread (p=0.044) (Figure 2b).

Fullness: In the total and obesity groups, AUC-fullness with pelemir bread was meaningfully lower than regular bread (total: p=0.026, obesity: p=0.037). In diabetes group, there was also a tendency for a decrease in AUC-fullness with pelemir bread (p=0.094). In healthy group, there was no difference in AUC-fullness between the two bread tests (Figure 2c).

Prospective food consumption (PFC): In the total and obesity groups, AUC-PFC with pelemir bread was considerably lower than regular bread (total: p=0.005, obesity: p=0.006). In diabetes group,

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there was also a slight tendency for a decrease in AUC-PFC with pelemir bread (p=0.098). In healthy group, there was no significant difference in AUC-PFC between the two breads (Figure 2d).

4. Discussion

Nutrition plays a key role in the prevention and treatment of NCDs such as obesity and diabetes. Dietary modifications are more likely to be successful when they are compatible with the sociocultural and eating habits of societies. In Turkish society, carbohydrated foods with high-GI such as bread and baked goods play a crucial role in daily diet. Increasing the dietary fiber, protein, fat and polyphenol content of foods decreases their GI. Therefore, adding natural additives to foods consumed intensively has become a preferred method. *Cephalaria syriaca L.* (pelemir), which grows as a weed in wheat fields, is a plant rich in dietary fiber, protein, fat and polyphenols. It has been used as a natural additive to flour to improve the quality of dough in baking industry [11,15,34]. It is also used in traditional medicine due to anti-oxidant, prebiotic, anti-inflammatory, anti-diabetic, and immunomodulatory effects, and these effects have been evidenced in *in vitro* studies [11,13]. This study was planned to investigate the effects of pelemir-added bread on glucose and lipid metabolism, appetite-regulating hormones and inflammation in healthy subjects and patients with obesity or diabetes.

The addition of *Cephalaria syriaca* to wheat flour is expected to reduce the GI value of bread. A study conducted in 2020 showed that the GI of bread decreased by 17% with addition of 5% *Cephalaria syriaca* flour [26]. However in our study, the AUC-Glucose of pelemir bread was close to regular bread in healthy control, obesity, and diabetes groups. This might be due to the very low proportion of pelemir (0.3%) we used. In addition, the breads we used as reference and test contained comparable number of supplements such as protein (whey powder) and antioxidants (vinegar and ascorbic acid) which may have prevented the GI of pelemir bread from being sufficiently different from regular bread.

When the whole study population was evaluated, the ingestion of pelemir bread resulted in notably higher AUC-Insulin and AUC-C-peptide than regular bread. These results indicate that pelemir may stimulate the pancreas to secrete more insulin than the regular bread, which is an important effect for postprandial glucose control. The fact that AUC-Insulin with pelemir bread in diabetes group, and AUC-C-peptide in healthy and diabetes groups displayed higher trends than regular bread supports this idea. Meanwhile, the difference for AUC-Insulin and AUC-C-peptide that did not reach statistical significance may be due to the relatively small size of the groups.

In healthy control group, AUC-GLP-1 with pelemir bread was 2.1 times higher than regular bread (p=0.021), whereas in obesity and diabetes groups, AUC-GLP-1 with pelemir bread was not different from regular bread. This finding together with the increase in AUC-Insulin and AUC-C-peptide can be interpreted as the stimulatory effect of pelemir to release GLP-1 in healthy individuals. However, pelemir was not able to induce GLP-1 increase in diabetes and obesity groups as it is known that GLP-1 response to CHO ingestion is blunted in both conditions. Our findings are consistent with the results of our previous study where postprandial blood glucose and insulin responses were prominent, while GLP-1 response was blunted after ingestion of 50 g white bread in overweight and obese subjects with normal glucose tolerance [4]. GLP-1 is an incretin hormone, known to have ameliorating effects on glucose metabolism via stimulating insulin secretion by the pancreatic β-cells. [35] GLP-1 is also recognized to increase satiety by effects on central nervous system and slowing down the intestinal motility. Due to these effects, GLP-1 receptor analogues are widely used in the treatment of T2DM and obesity over the last two decades. These drugs have favorable effects on the secondary prevention of cardiovascular diseases and mortality. The AUC-GLP-1 response to pelemir bread findings in our healthy group is compatible to the *in vitro* studies which reported strong inhibitory effects of *Cephalaria syriaca* on α-amylase and α-glycosidase [11,13,14]. Inhibitors of these enzymes are known to increase GLP-1 and reduce postprandial glucose levels. Therefore, increase of GLP-1 secretion would be considered as favorable effects of Pelemir on CHO-rich nutrients like bread.

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GLP-1 and PYY are released from the L cells of the small intestine and colon. PYY is an anorexigenic hormone, acts to reduce appetite and food intake postprandially. Considering that GLP-1 is a glucose-dependent insulinotropic hormone and also reduces food intake, these two hormones are expected to act synergistically [36]. Our findings in obesity group, that pelemir bread tended to result in a lower AUC-PYY compared to regular bread (p=0.067), together with the positive correlation between AUC-GLP-1 and AUC-PYY during consumption of pelemir bread but not regular bread in the whole group verify the pathophysiology of these gut hormones. The findings with pelemir bread are notable because increase of these hormones is expected to decrease energy intake. Moreover, the inverse correlation between AUC-GLP-1 and AUC-HOMA-IR during ingestion of pelemir bread but not with regular bread, suggests that pelemir may be beneficial to decrease insulin resistance through secretion of GLP-1.

Leptin, mainly secreted by the adipose tissue is a hormone that normally increases the feeling of satiety. In our study AUC-Leptin was much higher in obesity and diabetes groups than in healthy control group, which may be related to leptin resistance. The fact that pelemir bread resulted in a lower AUC-Leptin compared to regular bread may also be considered a potential favorable effect of pelemir on leptin resistance [36–39].

Another gut hormone contributing to regulation of appetite is ghrelin, increases the feeling of hunger. Ghrelin is an orexigenic hormone primarily produced by enteroendocrine cells of the gastrointestinal tract, especially the stomach. In addition to being a "hunger hormone", ghrelin has much broader functions in regulating glucose and energy homeostasis through inhibition of insulin secretion, regulating hepatic glucose output, increasing adipogenesis, decreasing lipolysis and thermogenesis [40]. In diabetes group, pelemir bread resulted in approximately 40% higher AUC-Ghrelin than regular bread (p=0.091). The negative correlation between AUC-Leptin and AUC-Ghrelin during ingestion of both regular and pelemir breads in the entire population suggests that these two hormones are counteracting at least in case of high-CHO food exposure.

Due to the limited number of cases in individual groups, we did not find it appropriate to discuss the correlation results separately. However, it is noteworthy that in the entire population, AUC-GLP-1 was inversely correlated with AUC-insulin, AUC-C-peptide, and AUC-Leptin, but positively correlated with AUC-PYY with pelemir bread. Contrarily, negative correlations were observed between AUC-GLP-1 and AUC-C-peptide and AUC-Leptin, but not with AUC-insulin with regular bread test. Our findings support that pelemir bread may possess stronger metabolic effects compared to regular bread.

The postprandial state is assumed to be highly proinflammatory and prooxidative. In our study, AUC-IL-6 in healthy group increased with both breads, more robustly with pelemir bread. Our findings are consistent with the literature showing that IL-6 levels nearly doubled following both high-CHO and high-fat meals [41].

Although the self-rated VAS by the participants we used in our study is a subjective assessment and need to be carefully interpreted, the increase in satiety and decrease in hunger and fullness feelings during pelemir bread in healthy group are notable findings supporting the dynamics of gut hormones. Furthermore, the significant decrease in AUC-PFC with pelemir bread in obesity group and similarly, a lower trend for AUC-PFC in diabetes group can be considered another beneficial effect of pelemir addition to wheat flour. This suggests that consumption of pelemir bread may decrease subsequent eating or snacking desires.

The most important limitations of our study are that it was based on a single test and far from physiological conditions of real life since the breakfast used in the study included only regular or pelemir breads and water. Moreover, the test duration was limited to two hours, and the sample size in the groups was small. Another limitation is the low amount of pelemir (0.3%) in the flour that could not induce stronger hormonal responses. *Cephalaria syriaca* is very bitter as it contains non-toxic sugar esters (glycosides), therefore, it is not possible adding to wheat flour in higher proportions [15]. Lastly, protein and antioxidant contents of both breads might have contributed to a relatively weak response to pelemir bread in glucose metabolism. One of the strengths of our study is that we

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examined both glucose and lipid parameters and gut hormones related to appetite. Also, simultaneously evaluated hunger and satiety during consumption of two breads. Another strength of the study is that the experiments were conducted in three groups: healthy, obese and diabetic subjects. The present study is important as it is the first to examine the effects of pelemir *(Cephalaria syriaca L.)* on carbohydrate and lipid metabolism, gastrointestinal and appetite-regulating hormones.

In summary, single meal composed of wheat bread with 0.3% added pelemir, did not substantially shift circulating gut-derived hormones or indices of glucose metabolism, suggesting that longer-term exposures would be important in the evaluation of effects of *Cephalaria syriaca* on metabolic conditions. However, some of the potential preliminary effects we found in this study (e.g., the relationship between GLP-1 and PYY induced by pelemir bread, possible changes in insulin resistance and insulin sensitivity) suggest that this topic is worth further investigation.

5. Conclusions

The preliminary results of this single-center pilot study suggest possible positive effects of pelemir (*Cephalaria syriaca L.*) supplementation to high-CHO foods on glucose metabolism and dynamics of gut hormones, but long-term, large-scale, multicenter studies are needed. If these beneficial effects are confirmed, in addition to improving the quality of bread and other bakery products, the routine use of pelemir as food additive could be a useful nutritional approach for both healthy individuals and people with obesity and diabetes, which are increasing rapidly.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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