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Cholesterol to saturated fat index (CSI), metabolic parameters and inflammatory factors among obese individuals

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Abstract

Background The role of dietary fat quality in promotion of cardiovascular diseases is studies before. However, the results are inconsistent. Recently, cholesterol to saturated fatty acid index (CSI) is suggested as a novel indicator of the atherogenicity and thrombogenicity potential of a diet. However, due to limited number of studies, in the current cross-sectional study, we aimed to evaluate the role of CSI in metabolic and inflammatory response among obese individuals.

Methods In the current cross-sectional study 488 obese individuals aged 18–50 years old were involved in volunteer based invitation from outpatient obesity clinics. Subjects underwent anthropometric assays including weight, height, waist circumference (WC) and body composition and their fasting blood sample were obtained for biochemical assessments including blood sugar, serum lipids, hs-CRP and IL-6 concentrations by commercial kits. Physical activity was also assessed by short form of international physical activity questionnaire (IPAQ).

Results According to our results, being at the top tetile of CSI was associated with higher anthropometric indices including weight, height, WC, FFM, and basal metabolic rate (BMR) compared with those at the lowest tertile ($P < 0.05$). Similarly, those at the highest category of CSI had significantly higher levels of serum glucose and hs-CRP both in crude and adjusted models in ANCOVA and in multinomial logistic regression models ($P < 0.05$).

Conclusion In the current study, for the first time, we identified the possible triggering role of dietary cholesterol to saturated fat index in increasing serum glucose and hs-CRP levels. due to cross-sectional design of the current study, causal inference is impossible. Further studies will help for better scientific justification.

Keywords Cholesterol to saturated fat index, CSI, Glycemic status, Inflammation

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Introduction

Nowadays, non-communicable disease (NCDs), including cardiovascular disease (CVD), diabetes, cancers and stroke and lung disease, together account for more than 74% of all deaths worldwide; according to the world health organization report, NCDs kill 41 million people each year, while more than three quarters of this global NCD deaths (31.4 million) occur in middle and low income countries [1]. Obesity, unhealthy dietary behaviors, sedentary life style, smoking and stress are all well-known risk factors of NCDs. Among them, obesity, defined as excessive fat accumulation that presents a risk for health, is one of the key risk factors for many NCDs such as coronary heart disease, hypertension, certain types of cancer, type 2 diabetes and stroke [2]. Obesity, as a chronic low grade inflammatory disorder, increases the level of inflammatory parameters like c-reactive protein and interleukins in body and due to obesity induced intravascular inflammation and interstitial arterial thickness, vascular elasticity decreases and hypertension and CVDs occur [3]. Among the modifiable risk factors for obesity, CVDs and other NCDs, diet is the most important one that has a great link with health [4]. Among dietary ingredients, dietary fat amount and quality have been shown to have a major effect on vascular health and is a well-known risk factor for obesity and CVDs [5]. Higher dietary saturated fatty acids' intake has a well-established role in increased low-density lipoprotein cholesterol (LDL-c) and increase the risk of CVDs that is mostly attributed to the possible direct and indirect role of SFA in increasing inflammatory factors including CRP and IL-6 and reduced adiponectin levels [3, 6, 7]; evidence suggest that replacing dietary SFA with whole grains, polyunsaturated fatty acid (PUFA) and plant protein but not with refined grains and dairy fat reduces the risk of CVD [8]. Artaud-Wild SM et al. [9] in a globally representative assessment of the coronary mortality in 40 countries, reported that the differences in coronary mortality in 40 countries can be explained by differences in saturated fat and cholesterol intakes in almost all of the countries except in France and Finland probably due to more dietary intake of plant food and vegetable. Cholesterol-Saturated Fat Index (CSI), as a new dietary fat quality index, is proposed by Connor et al. [10]. The index is calculated based on a modification of a regression equation computed from previous metabolic studies designed to lower plasma lipids; a lower CSI denotes lower saturated fat and cholesterol content and is an indicator of low atherogenicity and thrombogenicity potential of a diet [10]. After its development, Mitchell DTC et al. [11], developed and validated a CSI Scorecard as a self-monitoring tool for patients consuming a cholesterol-lowering diet; the scorecard was developed by numerically illustrating the saturated fat and cholesterol content of foods and facilitates dietary self-monitoring and self-efficacy of patients to evaluate adherence to low-cholesterol diet. Very limited number of studies evaluated the possible role of CSI in metabolic health; one study among overweight/ obese subjects reported that higher CSI was associated with higher atherogenicity and higher association with atherogenic index of plasma [12], while other study among obese women, showed no difference in serum lipids, insulin and CRP level in different teriles of CSI [13]. Due to very limited and inconsistent findings of available studies that evaluated the possible role of CSI on health, in the current cross-sectional study, we evaluated the association between CSI and metabolic risk factors, glycemic markers and inflammation in obese individuals.

Materials and methods

Participants

The current cross-sectional study was performed among obese volunteers (18–50 years old) that were invited by pamphlets and posters and invitation letters to participate in the study. The subjects were referred to outpatient obesity clinics of Hospital at Tehran-Iran and underwent initial screening to assess their eligibility (Fig. 1). Volunteers who were willing to participate and had BMI 25–40 kg/m^2 and were not pregnant, lactating and taking anti-hyperlipidemia, anti-hypertensive, anti-diabetic and any weight loss medications or supplements at least three months prior participation in the study. Also, those with any history of CVD, diabetes, thyroid, renal or hepatic disease were excluded. Subjects were fully informed about the aims of the study and about the study protocol and signed a written consent before starting the clinical screening. The flowchart of the study is shown in Fig. 1.

Demographic and anthropometric assays

Under supervision of a trained team member, participants were asked to complete the demographic data including information about age, gender, education, occupation and marital status. Weight and height were measured to the nearest 100 g and 10 mm, respectively using Seca scale (Seca co., Hamburg, Germany). Body mass index (BMI) was estimated as weight (kg) divided by square of the height (m2). WC was measured at the midpoint between the lowest rib margin and the iliac crest. Hip circumference was also measured with a non-stretchable tape as the distance around the largest part of the hips. Body composition including fat mass (FM) and fat free mass (FFM) and also basal metabolic rate (BMR) were assessed using the bioelectrical impedance analysis (BIA) method (Tanita, BC-418 MA, Tanita Corporation, Tokyo, Japan). Measurement by BIA was done while

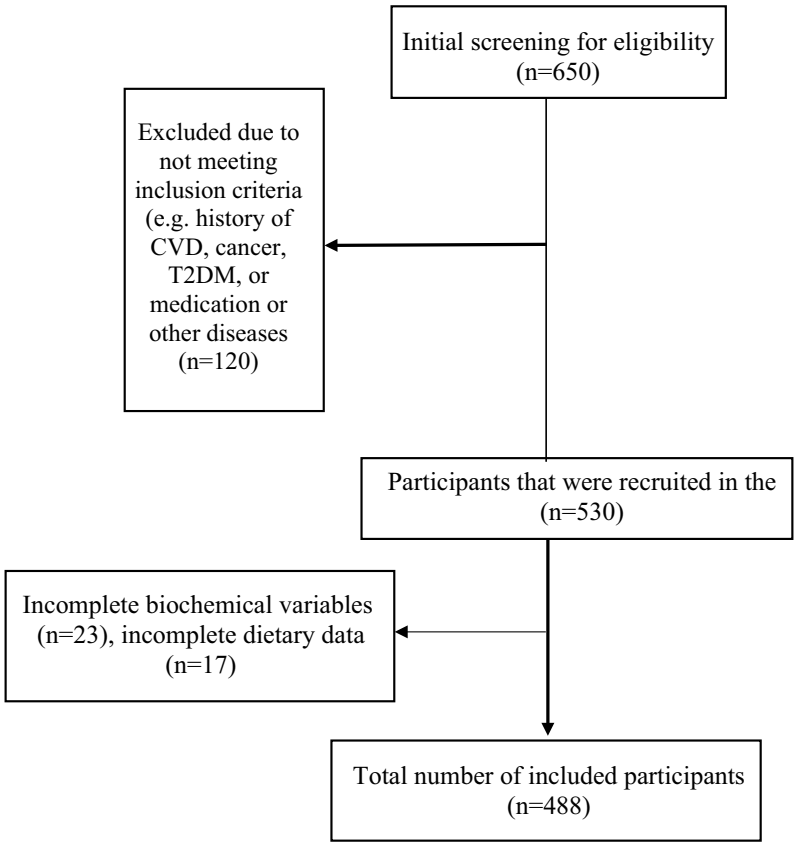

Fig. 1 Study Flowchart

subjects were in a fasting and urinated state. They also removed any metal material or jewelry and were avoided to use any caffeinated beverages and spices at least 12 h before measurements [14].

Diet and physical activity measurements

A food frequency questionnaire was used to assess dietary intake of participants; its validity and reliability was established before [15]. Subjects were asked to report their usual frequency of food consumption in the in the past year, throughout the day, week, and month under supervision of an expert dietitian. Data of nutritional intake was gathered using a food frequency questionnaire based on individuals past year dietary intake. Therefore, the data reflect individuals' dietary habits in the past year (yearly/ monthly/ weekly/ daily). The dietitian was one of the staff of the hospital and after all of the assessments, we referred the participants to her office to complete the dietary information. The sampling procedure was completed in near six months. Using NUTRITIONIST 4 (First Data Bank, San Bruno, CA) food analyzer, all of the dietary data were extracted individually. Therefore, the dietary cholesterol and SFA was obtained for all of the individuals based on their usual dietary intake in the past year. Then, the mean dietary cholesterol and SFA intake was used for CSI calculation for all of the individuals by dividing cholesterol into the saturated fat content of foods as below:

$$CSI = {}^{Cholesterol}/_{Saturated\ fat}$$

A lower CSI denotes a lower risk of hypercholesterolemia and atherosclerosis [10] and it is calculated according to a modification of a regression equation achieved from metabolic studies designed to lower plasma lipids. Physical activity was assessed by international physical activity questionnaire (IPAQ) with previously confirmed validity and reliability [16].

Blood pressure and biochemical assays

A standard mercury sphygmomanometer (OMRON M6) was used to assess blood pressure with a trained physician. The results of systolic blood pressure (SBP) and diastolic blood pressure (DBP) then were recorded as an average of two measurements after 15 min resting. For biochemical assays, 10 ml of overnight fasting

blood samples were obtained. Sera were extracted and stored frozen until assay. The Roche/Hitachi Cobas 6000 Auto- Analyzer (Roche Diagnostics, 9115 Hague Road, Indianapolis, IN, USA) was used to measure serum lipids including serum triglycerides (TG), cholesterol, high-density lipoprotein cholesterol (HDL-C) and fasting serum glucose (FSG) by enzymatic assays. Serum insulin levels were measured by commercial kits (Bioassay Technology Laboratory, Shanghai Korean Biotech, Shanghai City, China). The Friedewald equation was used to calculate the low-density lipoprotein cholesterol (LDL-C) [17]. The homeostatic model assessment of insulin resistance (HOMA-IR) value was calculated as below: HOMA-IR = glucose (mg/dl) × insulin (mU/L)/405 [18]. Pre-diabetes was defined as fasting serum glucose between 100–125 mg/dl according to the American Diabetes Association classification [19]

Statistical analysis

Statistical analyses were done using SPSS version 23.0 (SPSS, Chicago, IL, USA). The comparison of variables across CSI were performed by analysis of variance (ANOVA) and analysis of co-variance (ANCOVA) with adjustment for potential confounders, including age, sex, BMI, physical activity and energy intake. Nutrient intakes were expressed as energy adjusted using the residuals from the regression model, with absolute nutrient intake as the dependent variable and total energy intake as the independent variable. The ORs (odd ratios) and their 95% confidence intervals (CIs) for metabolic parameters were calculated after adjusting for age, sex, BMI, physical activity and energy intake using multinomial logistic regression model. In this analysis, the first tertile of CSI was considered as the reference category. P-Values less than 0.05 were accepted as statistically significant threshold.

Results

Table 1, represents the comparison of demographic information by CSI tertiles among study participants. Those at the highest tertile of CSI had significantly higher weight, height, WC, FFM, and basal metabolic rate (BMR) compared with those at the lowest tertile ($P < 0.05$). Also, higher energy intake, higher meat, fish, poultry, egg (MFPE) consumption and lower dietary carbohydrate was also observed among highest versus lowest category of CSI ($P < 0.05$; Table 2). The comparison of biochemical risk factors among study participants by tertiles of CSI is represented in Table 3. As shown in this Table, being at the highest category of CSI was accompanied by higher levels of serum glucose and hs-CRP both in crude and confounder (e.g. age, sex, BMI, physical activity and energy intake)-adjusted models. While, no significant difference among other biochemical variables was observed. Table 4, shows the odds of biochemical risk factors in the second and third tertile of CSI compared with first tertile. As shown, being at the second tertile of CSI, was associated with higher serum glucose concentrations in crude and adjusted models (OR $_{crude}$: 1.017; CI: 1.012–1.078; $P = 0.011$ and OR $_{adjusted}$: 1.032; CI:

Table 1 General characteristics of study participants by tertiles of CSI

Variable	CSI tertiles	N	Mean	SD	*P*-value
Age (y)	1st (≤ 7.90)	162	41.79	9.74	0.26
	2nd (7.90–11.29)	163	40.15	9.05	
	3rd (≥ 11.29)	163	40.00	8.73	
Gender (n[%] of males)	1st (≤ 7.90)	162	88	66.10	0.07
	2nd (7.90–11.29)	163	90	60.90	
	3rd (≥ 11.29)	163	64	53.50	
Weight (kg)	1st (≤ 7.90)	162	88.38	13.16	**0.002**
	2nd (7.90–11.29)	163	92.80	15.62	
	3rd (≥ 11.29)	163	94.97	13.73	
Height (cm)	1st (≤ 7.90)	162	165.73	9.65	**0.004**
	2nd (7.90–11.29)	163	167.88	9.85	
	3rd (≥ 11.29)	163	170.09	9.78	
BMI (kg/m^2)	1st (≤ 7.90)	162	32.20	4.86	0.46
	2nd (7.90–11.29)	163	32.87	5.03	
	3rd (≥ 11.29)	163	32.90	4.58	
WC (cm)	1st (≤ 7.90)	162	105.03	8.97	**0.03**
	2nd (7.90–11.29)	163	106.57	10.46	
	3rd (≥ 11.29)	163	108.40	9.06	
WHR	1st (≤ 7.90)	162	0.92	0.07	0.21
	2nd (7.90–11.29)	163	0.93	0.084	
	3rd (≥ 11.29)	163	0.95	0.063	
FM (%)	1st (≤ 7.90)	162	35.69	9.13	0.10
	2nd (7.90–11.29)	163	34.01	10.08	
	3rd (≥ 11.29)	163	32.09	7.82	
FFM (%)	1st (≤ 7.90)	162	57.78	11.87	**0.001**
	2nd (7.90–11.29)	163	62.05	12.33	
	3rd (≥ 11.29)	163	66.08	11.65	
BMR (kcal)	1st (≤ 7.90)	162	1773.48	327.42	**0.009**
	2nd (7.90–11.29)	163	1919.86	472.13	
	3rd (≥ 11.29)	163	1995.06	333.79	
HC (cm)	1st (≤ 7.90)	162	114.19	9.36	0.49
	2nd (7.90–11.29)	163	115.71	9.78	
	3rd (≥ 11.29)	163	114.62	8.53	
PA (Met. min/week)	1st (≤ 7.90)	162	1984.76	3477.57	0.75
	2nd (7.90–11.29)	163	2067.84	2980.88	
	3rd (≥ 11.29)	163	2402.30	3281.50	

CSI Cholesterol to saturated fat index, *BMI* Body mass index, *WC* Waist circumference, *WHR* Waist to hip ratio, *FM* Fat mass, *FFM* Fat free mass, *BMR* Basal metabolic rate, *HC* Hip circumference, *PA* Physical activity, *SD* Standard deviation

Table 2 Dietary intake of study population according to tertiles of CSI

Dietary item		N	Mean	SD	*P*-value
Energy (kcal/d)	1st (≤ 7.90)	162	3213.67	1237.57	**0.03**
	2nd (7.90–11.29)	163	3013.03	1049.69	
	3rd (≥ 11.29)	163	2825.12	953.89	
Carbohydrate (%)	1st (≤ 7.90)	162	1928.64	724.41	**0.003**
	2nd (7.90–11.29)	163	1687.82	662.29	
	3rd (≥ 11.29)	163	1695.81	566.59	
Fat (%)	1st (≤ 7.90)	162	1124.74	497.73	0.08
	2nd (7.90–11.29)	163	961.94	395.71	
	3rd (≥ 11.29)	163	860.43	342.18	
Protein (%)	1st (≤ 7.90)	162	399.88	151.07	0.29
	2nd (7.90–11.29)	163	370.71	129.40	
	3rd (≥ 11.29)	163	405.37	134.08	
Grain (g/d)	1st (≤ 7.90)	162	15.35	7.18	0.15
	2nd (7.90–11.29)	163	13.03	7.20	
	3rd (≥ 11.29)	163	14.69	6.38	
MFPE (g/d)	1st (≤ 7.90)	162	2.45	1.44	**< 0.001**
	2nd (7.90–11.29)	163	3.15	1.67	
	3rd (≥ 11.29)	163	4.01	1.78	
Fiber (g/d)	1st (≤ 7.90)	162	79.19	42.54	0.32
	2nd (7.90–11.29)	163	67.11	49.19	
	3rd (≥ 11.29)	163	71.79	39.01	
Vegetable (g/d)	1st (≤ 7.90)	162	4.45	2.88	0.06
	2nd (7.90–11.29)	163	3.78	2.03	
	3rd (≥ 11.29)	163	3.47	1.83	
Fruit (g/d)	1st (≤ 7.90)	162	4.63	3.30	0.29
	2nd (7.90–11.29)	163	4.22	3.38	
	3rd (≥ 11.29)	163	3.73	2.65	
Dairy (g/d)	1st (≤ 7.90)	162	2.11	1.51	0.57
	2nd (7.90–11.29)	163	2.18	1.13	
	3rd (≥ 11.29)	163	1.94	1.32	
Beans (g/d)	1st (≤ 7.90)	162	0.81	0.95	0.67
	2nd (7.90–11.29)	163	0.76	0.69	
	3rd (≥ 11.29)	163	0.68	0.47	

CSI Cholesterol to saturated fat index, *MFPE* Meat-fish-poultry-egg, *SD* Standard deviation

1.010–1.078; P = 0.02). Also, being at the third tertile of CSI, was associated with higher hs-CRP levels both in crude and adjusted models (OR $_{crude}$: 1.012; CI: 1.001–1.089; P = 0.025 and OR $_{adjusted:}$ 1.025; CI: 1.001–1.090; P = 0.01). The comparison of CSI and biochemical factors between those with normal serum glucose and pre-diabetes is shown in Table 5. Predaibetic subjects had higher serum glucose, cholesterol, triglyceride and HOMA-IR values in crude and confounder-adjusted models (P < 0.05). There was no significant difference between CSI and other biochemical variables between those with pre-diabetes and normal serum glucose concentrations.

Discussion

In the current study, we evaluated the association between CSI, metabolic and inflammatory parameters among obese individuals. According to our findings, being at the highest category of dietary CSI, was associated with higher serum glucose and hs-CRP concentrations. Also, higher FFM and WC and BMR were observed at highest categories of CSI. No significant difference for other parameters was observed. It is the first study that evaluated the possible association between CSI and metabolic and inflammatory parameters. As mentioned previously, a higher CSI denotes a higher risk of hypercholesterolemia

Table 3 Biochemical variables in study population according to tertiles of CSI

Variable		N	Mean	SD	*P*-value*	*P*-value**
SBP (mmHg)	1st (≤ 7.90)	162	123.32	18.11	0.69	0.86
	2nd (7.90–11.29)	163	121.66	15.30		
	3rd (≥ 11.29)	163	123.28	15.08		
DBP (mmHg)	1st (≤ 7.90)	162	82.50	13.01	0.83	0.47
	2nd (7.90–11.29)	163	80.55	11.33		
	3rd (≥ 11.29)	163	81.93	10.75		
Glucose (mg/dl)	1st (≤ 7.90)	162	90.86	13.48	**0.03**	**0.04**
	2nd (7.90–11.29)	163	93.89	24.63		
	3rd (≥ 11.29)	163	96.67	18.43		
Cholesterol (mg/dl)	1st (≤ 7.90)	162	193.14	40.25	0.47	0.20
	2nd (7.90–11.29)	163	193.59	33.37		
	3rd (≥ 11.29)	163	188.19	36.61		
Triglyceride (mg/dl)	1st (≤ 7.90)	162	157.79	116.52	0.39	0.85
	2nd (7.90–11.29)	163	141.08	70.26		
	3rd (≥ 11.29)	163	152.54	86.95		
HDL (mg/dl)	1st (≤ 7.90)	162	43.58	10.07	0.33	0.78
	2nd (7.90–11.29)	163	44.45	9.52		
	3rd (≥ 11.29)	163	42.57	8.88		
LDL (mg/dl)	1st (≤ 7.90)	162	125.53	34.23	0.56	0.16
	2nd (7.90–11.29)	163	123.93	27.93		
	3rd (≥ 11.29)	163	121.06	33.62		
Insulin (mIU/l)	1st (≤ 7.90)	162	15.99	10.40	0.24	0.09
	2nd (7.90–11.29)	163	14.47	9.58		
	3rd (≥ 11.29)	163	17.04	18.79		
HOMA-IR	1st (≤ 7.90)	162	3.67	2.61	0.33	0.64
	2nd (7.90–11.29)	163	3.44	2.77		
	3rd (≥ 11.29)	163	4.18	4.17		
Hs-CRP (mg/dl)	1st (≤ 7.90)	162	3.67	2.61	**0.04**	**0.04**
	2nd (7.90–11.29)	163	3.95	2.77		
	3rd (≥ 11.29)	163	4.95	4.17		
IL-6 (mg/dl)	1st (≤ 7.90)	162	0.33	0.04	0.55	0.85
	2nd (7.90–11.29)	163	0.34	0.04		
	3rd (≥ 11.29)	163	0.33	0.03		

CSI Cholesterol to saturated fat index, *SBP* Systolic Blood Pressure, *DBP* Diastolic Blood Pressure, *HDL-C* High Density Lipoprotein Cholesterol, *LDL-C* Low Density Lipoprotein Cholesterol, *HOMA-IR* Homeostatic model assessment of insulin resistance, *hs-CRP* high sensitive C reactive protein, *IL-6* interleukin 6, **P*-values one-way ANOVA; ** *P*-values of analysis of covariance adjusted for age, sex, BMI, physical activity and energy intake

and atherosclerosis; CSI, is an indicator of a food's hypercholesterolemia/ atherogenic potential of a diet because it is reflection of diets' cholesterol and saturated-fat content [10]; CSI, is calculated according to a modification of a regression equation achieved from metabolic studies designed to lower plasma lipids [10]. Given the lack of previous studies on the CSI with metabolic and inflammatory parameters, our results shed light on this scientific area. Dietary cholesterol and saturated fatty acid intakes, are two most important atherogenic ingredients of a diet; dietary cholesterol drives glucose synthesis in the body; some studies have documented that plasma lipids are involved in blood glucose homeostasis [20, 21]. In a mouse model of a diabetogenic diet, feeding a high fructose, high fat and cholesterol diet, led to insulin resistance, glucose intolerance, and increases in fasting blood glucose, and all of these changes were dose-dependently associated with dietary cholesterol amount, suggesting the diabetogenic role of dietary cholesterol [22].

In our study, there was no significant difference between dietary CSI among those with pre-diabetes versus those without it. No study has evaluated the role of dietary CSI in pre-diabetes before. In the study

Table 4 The odds of high metabolic and inflammatory parameters in second and third tertile of CSI versus first tertile in study population

CSI tertiles		OR-crude	95% Confidence Interval		*P*- value *	OR-adjusted	95% Confidence Interval		*P*- value **
			Lower Bound	Upper Bound			Lower Bound	Upper Bound	
1st (≤ 7.90) Ref									
2nd (7.90–11.29)	**SBP (mmHg)**	1.01	0.98	1.05	0.37	1.02	0.26	1.06	0.26
	DBP (mmHg)	0.98	0.94	1.02	0.31	0.97	0.24	1.02	0.24
	Glucose (mg/dl)	1.02	1.01	1.08	**0.01**	1.03	1.01	1.08	**0.02**
	Cholesterol (mg/dl)	1.01	0.98	1.04	0.37	0.99	0.22	1.01	0.22
	Triglyceride (mg/dl)	0.99	0.99	1.01	0.35	0.99	0.89	1.01	0.89
	HDL (mg/dl)	0.99	0.95	1.03	0.56	0.99	0.75	1.04	0.75
	LDL (mg/dl)	0.98	0.95	1.01	0.26	0.99	0.85	1.04	0.65
	Insulin (mIU/l)	0.98	0.96	1.01	0.30	0.95	0.87	1.06	0.58
	HOMA-IR	0.97	0.86	1.08	0.61	0.87	0.74	1.02	0.08
	Hs-CRP (mg/dl)	1.01	0.86	1.08	0.12	1.01	0.98	1.06	0.09
	IL-6 (mg/dl)	0.68	0.59	1.01	0.78	0.99	0.58	1.04	0.85
3rd (≥ 11.29)	**SBP (mmHg)**	1.01	0.98	1.04	0.44	1.01	0.58	1.05	0.59
	DBP (mmHg)	0.99	0.96	1.04	0.92	1.00	0.99	1.05	0.99
	Glucose (mg/dl)	1.01	0.99	1.04	0.22	1.01	0.47	1.04	0.47
	Cholesterol (mg/dl)	1.01	0.98	1.04	0.46	0.99	0.98	1.09	0.32
	Triglyceride (mg/dl)	0.99	0.99	1.01	0.54	1.01	0.52	1.01	0.52
	HDL (mg/dl)	0.97	0.93	1.01	0.19	1.01	0.88	1.05	0.88
	LDL (mg/dl)	0.98	0.95	1.01	0.17	0.98	0.89	1.03	0.72
	Insulin (mIU/l)	1.01	0.99	1.03	0.47	0.97	0.17	1.01	0.17
	HOMA-IR	1.04	0.95	1.14	0.37	0.93	0.80	1.08	0.36
	Hs-CRP (mg/dl)	1.01	1.01	1.09	**0.02**	1.02	1.01	1.09	**0.01**
	IL-6 (mg/dl)	0.98	0.85	1.02	0.12	0.98	0.85	1.02	0.12

CSI Cholesterol to saturated fat index, *SBP* Systolic Blood Pressure, *DBP* Diastolic Blood Pressure, *HDL-C* High Density Lipoprotein Cholesterol, *LDL-C* Low Density Lipoprotein Cholesterol, *HOMA-IR* Homeostatic model assessment of insulin resistance, *hs-CRP* high sensitive C reactive protein, *IL-6* Interleukin 6; ***P*-values of crude model of multinomial logistic regression; ** *P*-values of adjusted model of multinomial logistic regression for age, sex, BMI, physical activity and energy intake

by Al-Mssallem MQ et al., high dietary saturated fatty acid intake from milk and milk products was associated with lipid abnormalities and higher glucose among those with pre-diabetes [23]. Although, some other studies did not support this finding. For example, in a 12-year follow up study, there was no association between dietary SFA and incident pre-diabetes [24], also, some other epidemiological studies [25] experimental studies in human subjects [26] have questioned the impact of dietary SFA on T_2DM or glucose intolerance. Further studies will be helpful to address this inconsistency.

In other experimental study, feeding high dietary cholesterol led to the sequential progression of steatosis, enhanced glucose intolerance and insulin resistance in mice [27]. Dietary cholesterol also changes the activity of some of the enzymes that are involved in carbohydrate metabolism like depression in the activities of glucose-6-phosphate dehydrogenase, NADP-malic enzyme, liver glucokinase and pyruvate kinase' depression of the activity of these enzymes were inversely associated with an increase in cholesterol amount in the liver [28]. Also, high dietary cholesterol and saturated fat intake promotes fatty liver disease and Metabolic Syndrome Associated Steatotic Liver Disease (MASLD) via provokig insulin resistance and endotoxinemia and increased harmful plasma ceramides [29]. Also, it is suggested that saturated free fatty acids trigger several intracellular reactions, including cytokine release and macrophage activation, leading to lipotoxic stress and pro-inflammatory states [30, 31]. Therefore, future studies are suggested to identify the role of dietary cholesterol to saturated fatty acid in liver function and related disorders.

In our study, increased dietary CSI was not accompanied with significant changes in serum lipids. Similar

Table 5 The comparison of biochemical variables between prediabetic versus those with normal blood glucose

Variable		N	Mean	SD	*P*-value *	*P*-value **
CSI	Normal	368	10.58	6.67	0.78	0.92
	Pre-diabetics	120	10.83	6.33		
SBP (mmHg)	Normal	368	122.38	16.63	0.123	0.36
	Pre-diabetics	120	125.75	14.92		
DBP (mmHg)	Normal	368	81.72	11.27	0.77	0.66
	Pre-diabetics	120	82.17	13.27		
Glucose (mg/dl)	Normal	368	86.58	7.83	**< 0.001**	**< 0.001**
	Pre-diabetics	120	116.64	29.41		
Cholesterol (mg/dl)	Normal	368	187.60	35.86	**< 0.001**	**0.001**
	Pre-diabetics	120	206.61	35.99		
Triglyceride (mg/dl)	Normal	368	145.22	87.17	**0.004**	**< 0.001**
	Pre-diabetics	120	181.45	113.81		
HDL (mg/dl)	Normal	368	43.18	8.98	0.566	0.87
	Pre-diabetics	120	43.91	11.46		
LDL (mg/dl)	Normal	368	121.26	31.58	**0.005**	0.04
	Pre-diabetics	120	133.24	31.22		
Insulin (mIU/l)	Normal	368	15.69	14.00	0.281	0.62
	Pre-diabetics	120	18.01	12.16		
HOMA-IR	Normal	368	3.40	3.01	**< 0.001**	**0.002**
	Pre-diabetics	120	5.18	3.83		
Hs-CRP (mg/dl)	Normal	368	3.89	2.02	0.54	0.67
	Pre-diabetics	120	4.56	1.98		
IL-6 (mg/dl)	Normal	368	0.34	0.03	0.78	0.34
	Pre-diabetics	120	0.36	0.02		

CSI Cholesterol to saturated fat index, *SBP* Systolic Blood Pressure, *DBP* Diastolic Blood Pressure, *HDL-C* High Density Lipoprotein Cholesterol, *LDL-C* Low Density Lipoprotein Cholesterol, *HOMA-IR* Homeostatic model assessment of insulin resistance, *hs-CRP* high sensitive C reactive protein, *IL-6* Interleukin 6; **P*-values one-way ANOVA; ** *P*-values of analysis of covariance adjusted for age, sex, BMI, physical activity and energy intake

results were observed in the study by Rasaei N et al. [32], while no significant difference was observed between lipid profile including TC, TG, LDL and HDL between CSI quartiles among overweight and obese women. This might be attributed to the dietary sources of CSI which was mostly attributed to higher meat/ fish/ poultry and egg consumption in Raesi N et al. [32] and our study that obtained similar results. Whereas, high fat dairy products probably, have the greater effect on lipid abnormalities [23, 33].

Some other animal models have found that excessive cholesterol intake may increase serum amyloid A concentrations as an inflammatory marker; also it has been suggested that excessive dietary intake of cholesterol elevates cholesterol content, and this elevated plasma cholesterol activates the pro-inflammatory signal cascade and leads to insulin resistance [34, 35]. High intake of dietary cholesterol and saturated fatty acids increase serum hs-CRP level as a potent inflammatory parameter [34]. This is similar to our finding of higher hs-CRP level in the highest versus lowest tertile of dietary CSI. Similarly, higher dietary intake of saturated fatty acids was in direct association with serum hs-CRP levels among urban Asian Indian adolescents and young adults [36]. Several reports have demonstrated that high dietary saturated fatty acids and cholesterol intake, enhance serum IL-6 concentration [37], and as a result, increased IL-6 concentrations increase hepatic secretion of hs-CRP [38]. Hepatic fat accumulation as a result of dietary cholesterol- induced gut microbiota dysbiosis and insulin resistance is also reported [27]. We did not observe any difference in serum IL-6 concentrations between different tertiles of CDI. Moreover, cholesterol accumulation in islets promotes β-cells damage [39] and involves in progression of diabetes. These pathways are illustrated in Fig. 2.

This study, has some limitations; its cross-sectional design that prevents any casual inference and the self-reported data of dietary intake that stems for recall or response bias. Therefore, the results should

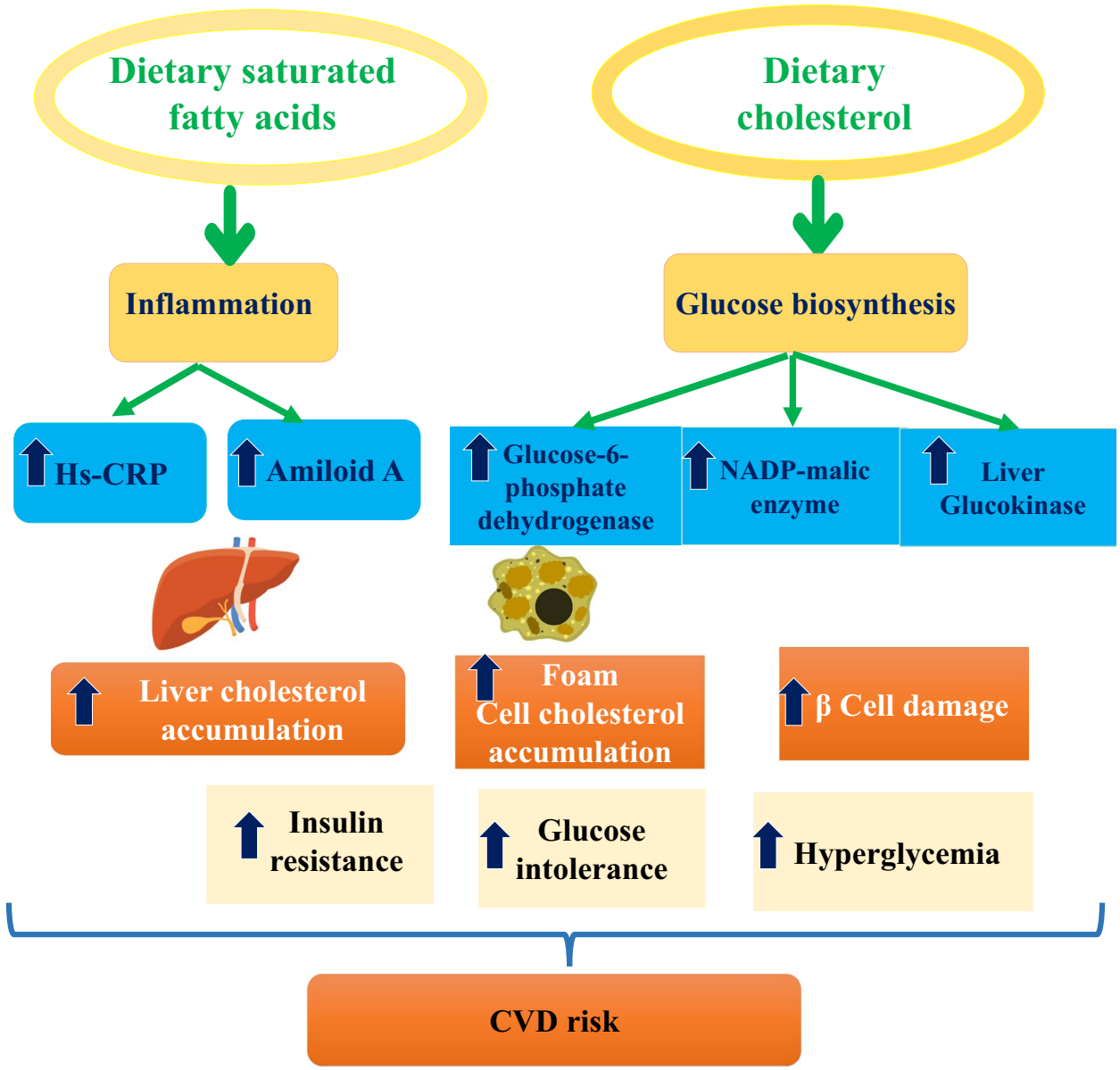

Fig. 2 The underlying mechanisms of the association between dietary saturated fatty acid and cholesterol intake and risk of CVD

be interpreted with caution. As a conclusion, in this cross-sectional study, for the first time, we found a significantly higher serum glucose and hs-CRP levels in highest versus lowest tertiles of CSI among obese individuals. For future studies, it is suggested that serum HbA1C and liver function tests be measured to better elucidate the underlying mechanisms. Further interventional studies will help to infer casualty and confirmation of our results.

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Authors' contributions
MS, AS and SS were involved in data collection and subjects' recruitment. NAS, YAZ and BAZ were involved in hypothesis generation and statistics. SS was involved in data collection, data analysis and supervision of the project. HMAQ and MA were involved in statistical approaches and drafting the paper. NN was also involved in data collection and revision of the paper. All of the authors contributed in writing the draft of manuscript and agreed to its submission.

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Availability of data and materials
The datasets of the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Written consent was obtained from all of the participants of the study. All methods in the current research were performed in accordance with the declaration of Helsinki's guidelines and regulations. The protocol of the current study is approved by ethics committee of Islamic Azad University.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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