Does weight loss affect the parameters that are metabolically related to cardiovascular diseases?

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ABSTRACT

الأهداف: لتقييم الاختلافات في المؤشرات التي ترتبط الأيض بأمراض القلب والأوعية الدموية بعد فقدان الوزن لدى الناس الذين يعانون من السمنة المفرطة مع أمراض الشريان التاجي (CADs) .

الطريقة: أجريت هذه الدراسة على 184 مريضاً تم تشخيص إصابتهم ب CADs في مستشفى معهد القلب بجامعة إسطنبول، إسطنبول، تركيا. تم تقييم كلاص من مستويات اللبتين، الفيبرينوجين، الهوموسيستين ، بروتين سي التفاعلي عالي الحساسية (hs-CRP)، الدهون الثلاثية ، الكوليسترول الكلي، البروتين الدهني عالي الكثافة ، الكولسترول ، البروتين الدهني منخفض الكثافة (LDL-C)، نسبة الجلوكوز في الدم والبروتين الدهني المنخفض الكثافة، الهيموغلوبين، وحمض اليوريك للمرضى الذين يعانون من السمنة المفرطة والذين تم وضعهم على نظام غذائي مقيد السعرات الحرارية بأثر رجعي ومقارنتهم قبل وبعد فقدان الوزن. للمقارنة، تمت دراسة مجموعة التحكم غير البدينين. وأجرينا اختبار تي ومربع كاي للتحليل الإحصائي.

النتائج: كانت مستويات الهوموسستئين، والهيموغلوبين السكري، واللبتين أعلى بكثير في المرضى الذين يعانون من السمنة المفرطة مقارنة بالمرضى غير البدينين. فقد مرضى السكري الذين يعانون من أمراض الشريان التاجي والسمنة المفرطة (11.1%) والمرضى الذين لا يعانون من السكري (10.5%) من وزن الجسم في 6 أشهر. تحسنت كلاً من مستويات الكوليسترول، LDL–C، والفيبرينوجين بشكل كبير في كلا المجموعتين.

الخاتمة: أظهرت الدراسة أن المرضى الذين يعانون من السمنة المفرطة فقدوا الوزن بعد تناولهم وجبات غذائية مقيدة السعرات الحرارية وأظهروا تحسنا ملحوظا في مستويات الكوليسترول، وLDL–C، والفيبرينوجين. لم يكن هناك اختلاف كبير في مستويات الحمض الاميني، hs–CRP، واللبتين قبل وبعد فقدان الوزن في كل من المرضى البدناء المصابين بالسكري وغير المصابين.

Objectives: To assess the differences in the parameters that are metabolically related to cardiovascular diseases after weight loss in obese people with coronary artery diseases (CADs).

Methods: This study was conducted on 184 patients who were diagnosed with CADs in Istanbul University Cardiology Institute Hospital, Istanbul, Turkey. The levels of leptin, fibrinogen, homocysteine, high-sensitivity C-reactive protein (hs-CRP), triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C), fasting blood glucose and insulin, glycated hemoglobin, and uric acid of the obese patients who were put on calorie restricted diet were evaluated retrospectively and compared before and after weight loss. For comparison, non-obese control patients were also studied. Student's t-test and Chi-square test were used for the statistical analysis.

Results: Levels of homocysteine, glycated hemoglobin, and leptin were significantly higher in the obese patients than in the non-obese patients. Diabetic obese patients with CADs lost (11.1%) and non-diabetic obese patients with CADs lost (10.5%) of their body weight in 6 months. The levels of cholesterol, LDL-C, and fibrinogen were significantly improved in both groups.

Conclusion: The obese patients lost weight after being on calorie-restricted diets and showed significant improvement in the levels of cholesterol, LDL-C, fibrinogen. There was no significant difference in the levels of homocysteine, hs-CRP, and leptin before and after weight loss in both diabetic and non-diabetic obese patients.

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Adherence to healty dietary behaviors may improve cardiovascular health.[1] The major contributors to cardiovascular disorders are obesity, hyperlipidemia, oxidative stress, inflammation, and insulin resistance.[2] High concentration of high sensitivity C-reactive protein (hs-CRP), tumor necrosis factor -alpha (TNF-α), interleukin-6 (IL-6) are the markers of cardiovascular risk factor as well as anti-inflammatory markers (namely, low adinopectin). High sensitivity-CRP is not only a marker of cardiovascular risk but also a contributor to its pathogenesis.[4] Obesity is characterized by an accumulation of visceral and subcutaneous fat, which leads to cardiometabolic diseases. As visceral adipose tissue may produce pro-inflammatory chemokines (namely, leptin, resistin, and adiponectin), obesity is known as a risk factor for cardiovascular disease (CVD) and a type of chronic or low-grade systemic inflammation.[5,6] Leptin has a role in the pro-inflammatory status of obesity and affects vascular homeostasis, which may consequently affect endothelial function.[7] Leptin is increased in obese people and may induce oxidative stress that contributes to systemic inflammation.[8] Fibrinogen is one of the biomarkers of hemostasis and trombosis.[9] It is an important component of coagulation and inflammation process and also an independent predictor of coronary artery diseases (CADs).[10] Homocysteine has toxic effects on the endothelium and contributes to endothelial dysfunction by increasing oxidative stress, which leads to endothelial dysfunction and inhibits nitric oxide production, causing stimulating vascular smooth cell proliferation, and changing the vascular wall elasticity, all of which contributes to atherosclerosis and hypertension.[11] Previous studies have shown that weight loss is associated with improved inflammatory status and endothelial function and calorie restriction has been shown to be a successful intervention for weight loss that may also ameliorate the markers of oxidative stress.[12,13]

This retrospective research was conducted to examine the efficacy of weight loss accomplished by calorie-restricted diets on the plasma levels of leptin, homocysteine, fibrinogen, high-sensitivity C-reactive protein (hs-CRP), triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting blood glucose, insulin and uric acid in people with obesity. The aim of the study was to assess the differences in the parameters that are metabolically related to cardiovascular diseases after weight loss in obese people with CAD.

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

Methods. This study was conducted on 184 patients (77 male and 107 female) with a mean age of 54.64±11.23 years who were diagnosed with CAD in Istanbul University Cardiology Institute Hospital in Istanbul, Turkey. Medical records of the obese patients who were diagnosed with CAD and put on calorie restricted diet between 01 March 2017 to 31 August 2018 were evaluated retrospectively.

For comparison, non-obese control patients were also studied. The exclusion criterias of the study was: age less than 40 years or more than 75 years; pregnancy; heart failure, cardiomyopathy, rheumatic heart disease, current history of inflammatory, infectious, or malignant diseases; taking antithrombotic drugs or warfarin; and any bleeding, thrombophilic, or eating disorders.

The patients were divided into non-obese (Body mass index [BMI] <30 kg/m²) and obese (BMI≥30 kg/m²) groups according to the World Health Organization (WHO) BMI classification.[14] The present study included 72 non-obese (44 male, 61.11% and 28 female, 38.89%) and 112 obese (39 male, 34.82% and 73 female, 65.17%) patients whose weights and BMI were evaluated at baseline (BMI: 35.08±4.29 kg/m²) and 6 months after (BMI: 31.58±4.17 kg/m²) being put on a calorie-restricted diet. The patients with type 2 diabetes mellitus both in the obese group and control group were analyzed separately.

The height, body weight, the levels of hs-CRP, leptin, homocysteine, fibrinogen, HDL-C, LDL-C, total cholesterol, triglycerides, fasting blood glucose, glycated hemoglobin, fasting insulin, and uric acid of each patient were obtained and recorded on the patient's file and the BMI was evaluated as body weight divided by height squared (in kilograms per square meter) (kg/m²). The levels of analyzed parameters and BMI were compared before and 6 months after being put on a calorie-restricted diet.

The levels of hs-CRP, leptin, homocysteine, fibrinogen, HDL-C, LDL-C, total cholesterol, triglycerides, fasting blood glucose, glycated hemoglobin, fasting insulin, uric acid were analyzed in the laboratuary of Istanbul University Cardiology Institute Hospital based in Istanbul, Turkey, at baseline and 6 months after. Venous blood samples were collected from each subject before breakfast and at 10 o'clock in the morning after overnight fast.

The patients underwent a calorie restricted diet along with behavioral support from a registered

dietitian who designed individualized dietary plans that required energy intake from 50-55% carbohydrates, 15-20% protein, and 25-35% fat (saturated fatty acids <7%), a cholesterol intake of <200 mg/day, and soluble fiber intake of 5-10 g/day. The goal of the dietary plans was to achieve a 5-10% weight loss by energy deficit (a reduction of 400-500 kcal/day). The patients were recommended to walk on a flat road for 30-60 minutes per day, 5 days per week. They were advised to walk 2 hours after meal time and to not walk when they were hungry.

This study was found appropriate by the Ethics Committee of Istanbul Arel University in Istanbul, Turkey (Date: 20.03.2018, Number: 2018/03) and investigated under the guidance of the Declaration of Helsinki.

Statistical Package for Social Sciences (SPSS) Version 21.0 software (IBM Corp., Armonk, NY, USA) was used for the data analysis. Arithmetic means and standard deviations of the data were calculated (mean±SD) for the demographic characteristics of the patients. Categorical basic clinical data was evaluated by Chi-square test. A $p<0.05$ was accepted as a significant difference between the groups. The normal distribution of parametric data was compared with paired t-test and unpaired t-test. A p-value<0.05 was considered significant.

Results. There was no difference in the measures of central tendency and dispersion of type 2 diabetes and hypertension between the 2 patient groups (obese group: hypertension 45.40%, type 2 diabetes 45.54%; non-obese group: hypertension 44.60%, type 2 diabetes 44.44%). In addition, the levels of triglycerides, HDL-C, LDL-C, total cholesterol, fasting blood glucose and insulin, uric acid, hs-CRP and fibrinogen were similar in both patient groups. The levels of leptin ($p=0.0024$), homocysteine ($p=0.042$), and glycated hemoglobin ($p=0.031$) were significantly higher in patients with obesity than in the non-obese patients.

The mean values and ranges of the age, body weight, BMI, and biochemical parameters of the patients in the non-obese and obese groups according to type 2 diabetes mellitus are presented in **Table 1**. The levels of homocysteine, glycated hemoglobin, insulin, leptin, LDL-C, triglycerides, glucose, and uric acid were significantly higher in diabetic obese patients than in non-diabetic obese patients. In addition, there was no significant difference in the levels of homocysteine, insulin, leptin, LDL-C, triglycerides between diabetic non-obese group and non-diabetic non-obese group.

Table 2 shows the differences in the body weight, metabolic and clinical characteristics of the obese patients before and 6 months after losing weight. Six months after being on the calorie-restricted diets,

Table 1 - Comparison of obese and non-obese subjects with coronary artery diseases according to type 2 diabetes mellitus.

Parameters	Obese patients with CAD			Non-obese patients with CAD		
	Diabetic 51 (45.54)	Non diabetic 61 (55.46)	*P*-value	Diabetic 32 (44.44)	Non diabetic 40 (55.56)	*P*-value
	Mean±SD			Mean±SD		
Age (year)	61.73±9.11	58.91±9.44	0.11	66.11±6.98	63.20±8.46	0.12
Body weight (kg)	90.10±15.86	91.43±13.95	0.83	79.35±6.84	76.07±7.62	0.09
BMI (kg/m^2)	33.85±4.33	35.32±4.62	0.09	27.32±2.19	27.06±1.70	0.60
Homocystein (µmol/L)	14.65±9.50	11.00±5.60	0.012*	12.84±3.75	15.14±11.72	0.28
Glycated hemoglobin (%)	5.56±1.06	5.89±0.96	<0.0001*	6.2±0.35	5.65±0.63	<0.0001*
hs-CRP (mg/dL)	4.92±8.11	6.72±10.02	0.31	4.32±5.16	3.64±3.64	0.55
Insulin (mIU/L)	19.41±8.00	13.63±9.50	0.0047*	19.41±6.78	11.75±8.53	0.11
Leptin (ng/mL)	61.88±32.34	47.51±21.82	0.033*	20.23±9.28	39.42±45.78	0.16
Body weight (kg)	90.10±15.86	91.43±13.95	0.83	79.35±6.84	76.07±7.62	0.09
BMI (kg/m^2)	33.85±4.33	35.32±4.62	0.09	27.32±2.19	27.06±1.70	0.60
Cholesterol (mg/dL)	193.81±61.07	201.90±35.59	0.41	188.13±31.28	210.76±54.09	0.18
HDL-C (mg/dL)	40.41±10.89	42.41±11.35	0.39	54.50±19.93	50.62±13.97	0.63
LDL-C (mg/dL)	104.03±30.77	127.24±33.05	0.00091*	115.95±34.87	122.44±66.75	0.73
Triglycerides (mg/dL)	233.67±219.73	170.52±67.56	0.042*	139.88±71.76	142.27±79.81	0.94
Glucose (mg/dL)	122.44±31.54	96.80±9.90	<0.0001*	100.70±6.82	94.70±5.25	0.028*
Uric acid (mg/dL)	5.30±1.25	4.71±1.17	0.045*	5.99±0.94	4.95±1.12	0.035*
Fibrinogen (mg/dL)	328.38±77.85	347.43±88.33	0.33	465.49±185.81	439.94±117.92	0.74

CAD - coronary arter diseases, SD - standard deviation, BMI - body mass index, hs-CRP - high-sensitivity C-reactive protein, HDL-C - high density lipoprotein cholesterol, LDL-C - low density lipoprotein cholesterol. Unpaired Student's t-test. *$p<0.05$.

Table 2 - Body weight and parameters that are metabolically related to cardiovascular diseases before and after weight loss in obese subjects.

Parameters	Diabetic obese patients with CAD n=51; 45.5%					Non-diabetic obese patients with CAD n=61; 55.5%				
	Baseline	After 6 months	Difference	Difference (%)	*P*-value	Baseline	After 6 months	Difference	Difference (%)	*P*-value
Body weight (kg)	91.79±13.07	82.08±19.61	-9.97±6.92	-11.07	0.038*	91.11±16.99	82.03±11.59	-9.74±5.47	-10.53	0.00015*
HCY (µmol/L)	14.65±9.50	14.98±12.76	-0.29±12.01	13.76	0.91	11.00±5.60	14.01±9.19	-4.23±10.20	-31.53	0.057
Glycated Hb (%)	5.56±1.06	5.88±0.71	1.5±3.17	18.30	0.42	5.89±0.96	5.80±0.35	-2.09±8.30	-19.90	0.28
hsCRP (mg/dL)	4.92±8.11	5.00±2.13	2.67±13.69	4.03	0.96	6.72±10.02	4.32±4.13	3.82±12.26	16.68	0.29
Insulin(mIU/L)	19.41±8.00	12.81±4.56	17.49±21.26	41.73	0.06	13.63±9.50	8.93±5.45	6.27±10.22	41.35	0.028*
Leptin (ng/mL)	61.88±32.34	43.46±15.98	31.67±23.60	58.29	0.13	47.51±21.82	52.03±23.56	5.00±14.61	78.68	0.53
Cholesterol(mg/dL)	193.81±61.07	156.24±34.58	36.73±59.19	17.96	0.0013*	201.90±35.59	166.68±29.86	43.46±24.93	27.42	<0.0001*
HDL-C (mg/dL)	40.41±10.89	42.47±7.40	7.29±33.31	-2.14	0.34	42.41±11.35	46.17±13.91	20.38±58.36	-1.18	0.14
LDL-C (mg/dL)	104.03±30.77	82.82±33.65	25.28±37.95	19.23	0.0064*	127.24±33.05	99.58±27.94	9.57±57.80	7.98	<0.0001*
Triglyceride (mg/dL)	233.67±219.73	177.68±121.90	62.68±139.38	-1.02	0.17	170.52±67.56	124.05±57.54	21.42 ±83.90	-56.79	0.0004*
Glucose (mg/dL)	122.44±31.54	103.53±24.00	13.92±20.77	12.50	0.0038*	96.80±9.90	95.44±19.45	19.90±45.16	14.43	0.65
Uric acid (mg/dL)	5.30±1.25	4.65±1.60	1.19±2.03	22.27	0.076	4.71±1.17	4.45±1.23	0.77±1.84	9.20	0.31
Fibrinogen (mg/dL)	328.38±77.85	296.27±48.51	12.57±126.74	-94.75	0.045*	347.43±88.33	268.75±84.95	59.79±87.66	-3.49	0.0001*

Values are presented as Mean±SD. CAD - coronary artery diseases, Hb - hemoglobin, HCY - homocysteine, hs-CRP - high-sensitivity C-reactive protein, HDL-C - high density lipoprotein cholesterol, LDL-C - low density lipoprotein cholesterol. Paired student's t-test. *p<0.05

Table 3 - Parameters that are metabolically related to cardiovascular diseases at baseline and after 6 months in non-obese subjects.

Parameters	Non Obese Diabetic Patients with CAD n=32, 44.4%					Non Obese Non Diabetic Patients with CAD n=40, 55.7%				
	Baseline	After 6 months	Difference	Difference (%)	*P*-value	Baseline	After 6 months	Difference	Difference (%)	*P*-value
HCY (µmol/L)	12.84±3.75	14.12±6.19	-2.96±6.80	-48.46	0.44	15.14±11.72	14.43±5.53	1.28±13.95	-29.88	0.78
Glycated Hb (%)	6.20±0.35	6.10±0.19	-0.60±0.82	-12.50	0.54	5.65±0.63	5.56±0.84	-0.012±0.64	-0.51	0.65
hsCRP (mg/dL)	4.32±5.16	3.25±0.15	1.71±2.61	6.28	0.65	3.64±3.64	3.36±1.09	0.45±1.84	-4.08	0.75
Insulin (mIU/L)	19.41±6.78	16.73±7.16	14.21±5.53	44.12	0.90	11.75±8.53	13.28±9.61	7.30±8.01	14.76	0.99
Leptin (ng/mL)	20.23±9.28	30.75±12.22	-5.87±10.35	31.66	0.08	39.42±45.78	34.27±12.22	-8.85±10.35	-32.87	0.053
Cholesterol(mg/dL)	188.13±31.28	182.13±23.93	2.67±23.50	0.59	0.67	210.76±54.09	175.33±35.94	44.47±42.22	18.52	0.0073*
HDL-C (mg/dL)	54.50±19.93	56.75±19.34	-3.33±9.48	-8.21	0.82	50.62±13.97	51.56±12.86	0.71±9.66	-0.22	0.995
LDL-C (mg/dL)	115.95±34.87	115.68±27.76	0.70±22.66	-5.09	0.99	122.44±66.75	109.44±28.83	7.29±38.14	22.19	0.0038*
Triglycerides (mg/dL)	139.88±71.76	94.86±19.95	10.00±25.42	6.81	0.11	142.27±79.81	126.83±65.17	-1.35±60.46	-8.78	0.80
Glucose (mg/dL)	100.70±6.82	95.88±9.85	7.67±7.94	7.47	0.0041*	94.70±5.25	101.17±14.19	-5.59±14.46	-6.02	0.065
Uric acid (mg/dL)	5.99±0.94	5.87±1.34	-0.50±0.52	-8.92	0.85	4.95±1.12	4.51±0.28	0.46±0.79	9.20	0.28
Fibrinogen (mg/dL)	465.49±185.81	281.71±60.72	108.13±50.34	23.08	0.0073*	439.94±117.92	379.37±95.52	44.72±52.60	9.72	0.095

Values are presented as Mean±SD. CAD - coronary artery diseases, Hb - hemoglobin, HCY - homocysteine, hs-CRP - high-sensitivity C-reactive protein, HDL-C - high density lipoprotein cholesterol, LDL-C - low density lipoprotein cholesterol. Paired student's t-test. *p<0.05

diabetic obese patients with CADs lost 11.07% and non-diabetic obese patients with CADs lost 10.53% of their body weight. After the calorie-restricted weight loss, the levels of cholesterol, LDL-C, fibrinogen had decreased significantly in both diabetic obese and non-diabetic obese groups. Triglycerides level in non-diabetic obese group and glucose level of diabetic obese group improved after weight loss.

Table 3 shows the changes in the metabolic and clinical characteristics of non-obese patients before and after 6 months.

Discussion. The main findings of this study are that weight loss in CAD patients with obesity improved their lipid profile, fibrinogen levels and glycemic control, suggesting that weight loss by dietary interventions may facilitate the reduction of cardiovascular heart disease risk in obese people. Obesity is considered an independent risk factor for CVD, and low-grade inflammation is a common finding in CVD, obesity, and type 2 diabetes.[15]

Approximately 10% of weight loss is associated with reduced total cholesterol and triglycerides, elevated HDL-C and insulin sensitivity, and a pro-atherothrombotic state via decreased inflammation, thrombosis potential, and blood pressure.[16] A different study showed that 9.4% of the weight loss due to dietary and healthy lifestyle modifications was associated

with reduced plasma levels of leptin and hs-CRP and improved insulin resistance and lipid profiles.[17] All of these changes in the parameters and inflammatory profile indicate that weight loss facilitates amelioration of the inflammatory status.[18] A study that followed severely obese patients during a 15-week hypocaloric diet and daily moderate activity found that hs-CRP decreased and adiponectin increased significantly, indicating that a minimum of 10% of weight loss is necessary to improve the pro-inflammatory parameters in people with obesity.[3] Another study that was conducted with obese patients showed that dramatic weight loss decreased inflammatory markers, such as hs-CRP, and suggested that weight loss may independently reduce oxidative stress and inflammation.[19]

Obesity is known as a chronic or low grade systemic inflammation. In a study that recruited obese and overweight participants, the association between circulating levels of leptin and the biomarkers of oxidative stress were evaluated. Although serum hs-CRP level was found to be independently correlated with BMI and positively correlated with leptin, the results of the study did not demonstrate any significant association between leptin and BMI ranges.[20] Korybalska et al,[21] observed improved lipid profiles, increased insulin sensitivity, and decreased leptin concentration. Netto et al,[22] showed that the levels of pro-inflammatory biomarkers (hs-CRP, and leptin) decreased after excess weight loss. In the current study, the presence of low grade inflammation was assessed by measuring the levels of serum leptin and hs-CRP. There was no significant difference in the levels of hs-CRP and leptin after 6 months due to losing weight on calorie-restricted diets.

In a previous study, it was reported that impaired fibrinolysis in obesity was associated with high levels of plasminogen activator inhibitor-1 (PAI-1) and the development of CVD; however, the results also showed that there was no significant decrease in fibrinogen and PAI-1 levels following the weight loss.[23] In the current study, there was a significant reduce in the level of fibrinogen after weight loss on the calorie-restricted diets.

Hyperhomocysteinemia is known as an independent risk factor for CVD.[24,25] It has been reported that increased levels of homocysteine correlate with insulin resistance, hypertension, atherosclerosis, endothelial dysfunction, and increased oxidative stress. Epidemiological studies reported that the homocysteine levels of overweight and obese patients were higher than those of patients with normal weight.[11,26] Al-Bayyari et al,[25] reported that homocysteine was significantly and positively correlated with BMI and fat mass among overweight women. Yang et al,[24] reported a synergistic effect between homocysteine and age, obesity, dyslipidemia, and family history of hypertension.

Calorie restriction has been reported to promote longevity and reduce the morbidity of atherosclerosis, cancer, diabetes, renal, neurodegenerative, autoimmune, and respiratory diseases.[27]

It has been reported that weight loss ameliorates endothelium-dependent vasodilation in obese hypertensive patients in the context of a low-calorie diet.[28] Endothelial activation markers have been reported to improve in obese patients after weight loss by calorie restriction.[21]

Study limitations. Although obese patients had weight loss after calorie restricted diet, BMI averages at the end of 6 months were still within obese classification. If the calorie-restricted diet examined longer-term results, further improvement in parameters that are metabolically related to cardiovascular diseases could be observed.

In conclusion, the available literature suggests that weight loss has beneficial effects on cardiovascular health. Calorie-restricted diets have been reported to be a healthy weight loss intervention that may also improve oxidative stress. The data obtained in this study suggest that weight loss improves lipid profile, fibrinogen levels and glycemic control. Further studies investigating the effects of varying degrees of weight loss and use of cardiometabolic parameters are warranted for a more precise understanding of the interactions between obesity and CAD.

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