Weight reduction ameliorates inflammatory cytokines, adipocytokines and endothelial dysfunction biomarkers among Saudi patients with type 2 diabetes

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Abstract

Background: Type 2 diabetes mellitus (T2DM) considered as one of the cardiovascular disorders (CVD) principle risk factor as diabetes is associated with abnormal levels of endothelial function, inflammatory and adipocytokines.

Objective: The aim of this study was to measure the impact of weight reducing on inflammatory cytokines, adipocytokines and endothelial function biomarkers among obese T2DM patients.

Methods: One–hundred T2DM patients enrolled in the present study; the age range was 35-55 year. Participants shared in this study were enrolled in group (A) received diet control and aerobic exercise on treadmill, while, group (B) had no intervention for 3 months.

Results: The mean values of body mass index (BMI), tumor necrosis factor –alpha (TNF-α), interleukin-6 (IL-6), leptin, inter-cellular adhesion molecule (ICAM-1) ,vascular cell adhesion molecule (VCAM-1), E-selectin and plasminogen activator inhibitor-1 activity (PAI-1 activity) were significantly decreased and adiponectin was increased significantly in the training group, however the results of the control group were not significant. Also, there were significant differences between both groups at the end of the study.

Conclusion: Weight reducing program modulates inflammatory cytokines, adipocytokines and endothelial function biomarkers among obese T2DM patients.

Keywords: Diabetes; endothelial dysfunction biomarkers; cytokines; adipocytokines; weight reduction.

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Introduction

Type 2 diabetes mellitus (T2DM) is one of the cardiovascular disorders (CVD) principle risk factor [1-3], the risk of coronary artery disease is 2-4 times among patients with diabetes than non-diabetic subjects and peripheral vascular diseases risk is 10 times higher in diabetics than non-diabetics [4-5]. Impaired endothelial function is an early predictor of CVD [6-10].

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Endothelial dysfunction means loss of endothelial ability in regulation of vascular homeostasis through control of vasoconstriction, inflammatory and thrombotic markers [11]. However, abnormal levels of endothelial function considered a predictor for CVD[12].

Non-insulin dependent diabetes usually associated with several CVD and other body systems which are related to impaired endothelial function [13-17]. Increased level of systemic inflammation markers and decreased plasma adiponectin promote endothelial dysfunction which could be considered as an important pathogenic factors and potential triggers for cardiovascular disorders, insulin resistance and atherosclerosis in T2DM patients[18-19]. However, weight reducing program composed of diet control and exercises associated with good prognosis as it modulated atherosclerosis and inflammatory biomarkers in T2DM patients [20-22].

As there is inconclusive data regarding the impact of weight reduction upon the inflammatory cytokines, adipokines and endothelial function in obese T2DM patients. Therefore, the study aimed to determine the impact of 12 weeks of weight reducing program on inflammatory cytokines, adipokines and endothelial function in obese T2DM patients.

Patients and methods

Subjects

One–hundred T2DM subjects who were out patients of the Internal Medicine Department at King Abdul Aziz University Hospital enrolled in the present study; the age range was 35-55 year. Hypertension, musculoskeletal disorders, smoking, congestive heart failure and intake of medicine that affect the endothelial function were the exclusion criteri. Participants shared in this study were enrolled in group (A) received diet control and aerobic exercise on treadmill, while, group (B) had no intervention (figure 1).

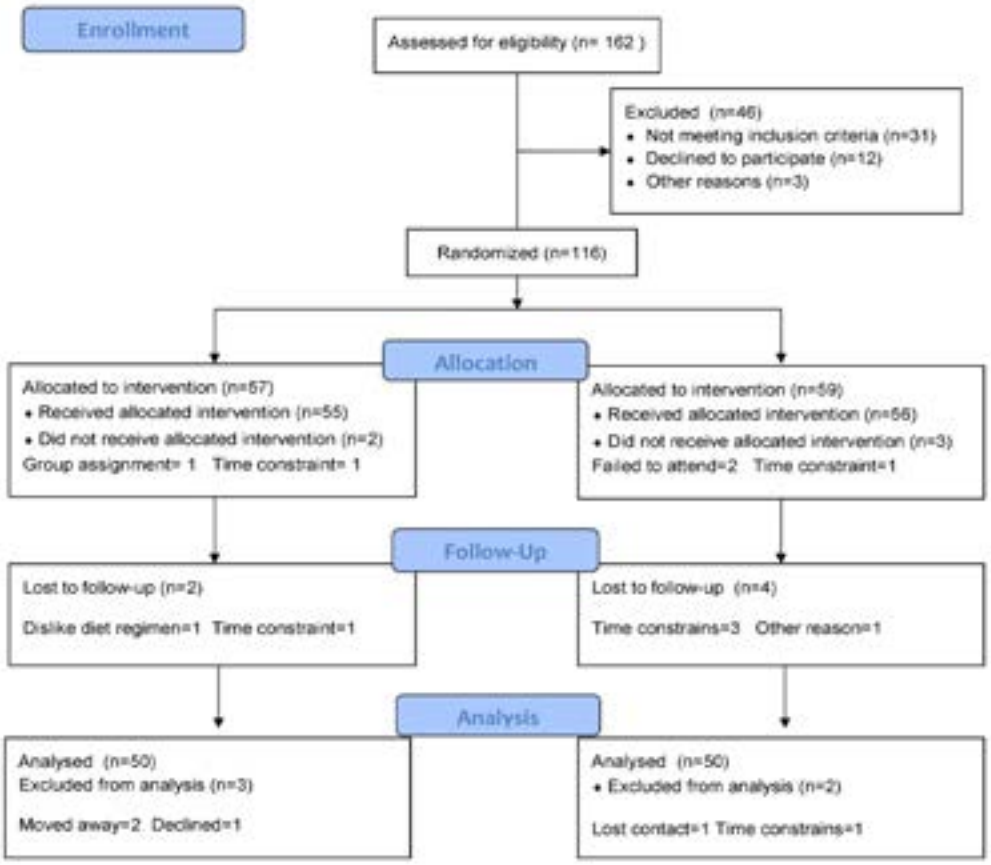

Figure 1 : Subjects screening and recruitment CONSORT diagram.

Measurements

A. Endothelial function biomarkers: Enzyme-linked immunosorbent assays (ELISAs) was used to measure inter-cellular adhesion molecule (ICAM-1) and vascular cell adhesion molecule (VCAM-1). While the level of PAI-1 activity was determined using a commercial kit (Hyphen BioMed for PAI-1, France).

B. Inflammatory cytokines and adipokines: Overnight fasting venous blood sample using ELISA was used to measure levels of Interleukin-6 (IL-6) and tumor necrosis factor- alpha (TNF-α) "Immulite 2000" immunassay analyzer (Siemens Healthcare Diagnostics, Deerfield, USA). Also, level of adiponectin and Leptin was measured with K2EDTA in plasma sample "Hitachi 7170 Autoanalyser, Tokyo, Japan".

Procedures

participants shared in the following groups:

1. Group (A) : Fifty type 2 diabetic patients received 3 months of aerobic treadmill exercise training conducted

according to of American College of Sports Medicine recommendations [23]. Exercise program included warming –up for five minutes as range motion and stretching exercises , thirty minutes of aerobic exercise training (60-70% of maximum heart rate) and cooling down for ten minutes (on treadmill with low speed and without inclination). Participants received three sessions /week for three months. Also, diet control supervised by a dietician and to prescribe the balanced low caloric diet that provide 1200 Kilocalories/day for 12 weeks.

2. Group (B): Fifty type 2 diabetic patients of both sexes conducted their usual life style without intervention.

Statistical analysis

Paired "t" test was used to detect significance level of the investigated parameters measured before and after the study in both groups. While, independent "t" test was used in comparing parameters between the two groups ($P<0.05$).

Results

One hundred patients with T2DM shared in the present study. However, basic criteria of all participants are shown in table (1). The majority of participants (66%) were men. However, there were no significant differences related to baseline criteria between the two groups.

Table (1): Mean value of baseline characteristics of subjects for participants in both groups

	Group (A)	Group (B)	Significance
Age (year)	41.53 ± 5.18	42.17 ± 4.85	P>0.05
Gender (male/female)	34/16	32/18	P>0.05
BMI (kg/m^2)	31.16 ± 2.89	30.58 ± 2.76	P>0.05
Duration of diabetes (years)	10.19 ± 4.15	9.76 ± 3.47	P>0.05
Waist circumference (cm)	101.32 ± 8.61	99.74 ± 9.39	P>0.05
Systolic blood pressure (mmHg)	141.75 ± 11.13	138.22 ± 10.68	P>0.05
Diastolic blood pressure (mmHg)	80.14 ± 6.51	78.96 ± 7.05	P>0.05
HBA1c (%)	8.26 ± 1.71	8.13 ± 1.58	P>0.05

BMI= Body Mass Index; HBA1c = glycosylated hemoglobin.

The mean values of BMI,TNF-α, IL-6, Leptin, ICAM-1, VCAM-1, E-selectin and PAI-1 activity were significantly decreased and adiponectin was increased significantly in the training group (table 2), however the results of the control group were not significant (table 3). Also, there were significant differences between both groups at the end of the study (table 4).

Table (2): Mean value and significance of BMI, TNF-α, IL-6, Leptin, Adiponectin, ICAM-1, VCAM-1, E-selectin and PAI-1 activity in group (A) before and after treatment.

	Mean +SD		T-value	Significance
	Pre	Post		
BMI (kg/m²)	31.16 ± 2.89*	26.81 ± 2.27	7.86	P<0.05
TNF-α (pg/mL)	4.62 ± 1.44*	3.21 ± 1.19	6.92	P<0.05
IL-6 (pg/mL)	2.48± 0.91*	1.76 ± 0.82	5.87	P<0.05
Leptin (Ng/ml)	32.11 ± 5.23*	25.74 ± 4.19	7.93	P<0.05
Adiponectin (µg/mL)	11.24 ± 2.26*	15.16 ± 2.73	6.76	P<0.05
ICAM-1 (ng/ml)	92.18 ± 6.22*	83.14 ± 5.71	8.23	P<0.05
VCAM-1 (ng /ml)	819.70 ± 32.21*	743.25 ± 27.95	9.18	P<0.05
E-selectin (ng/ml)	15.03 ± 2.91*	9.13 ± 2.34	7.65	P<0.05
PAI-1 activity (ng/ml)	0.57 ±0.21*	0.42 ±0.16	4.15	P<0.05

BMI= Body Mass Index; TNF-α = Tumor necrosis factor –alpha; IL-6= Interleukin-6; ICAM-1 = Inter-Cellular Adhesion Molecule; VCAM-1 = Vascular Cell Adhesion Molecule; PAI-1: Ac = Plasminogen Activator Inhibitor-1 Activity; (*) indicates a significant difference, P < 0.05.

Table (3): Mean value and significance of BMI, TNF-α, IL-6, Leptin, Adiponectin, ICAM-1, VCAM-1, E-selectin and PAI-1 activity in group (B) before and after treatment.

	Mean +SD		T-value	Significance
	Pre	Post		
BMI (kg/m²)	30.58 ± 2.76	32.23 ± 2.01	1.19	P>0.05
TNF-α (pg/mL)	4.13 ± 1.54	4.26 ± 1.43	0.75	P>0.05
IL-6 (pg/mL)	2.18 ± 0.92	2.31 ± 0.86	0.58	P>0.05
Leptin (Ng/ml)	30.74 ± 5.11	31.12 ± 5.15	1.04	P>0.05
Adiponectin (µg/mL)	11.15 ± 2.78	11.03 ± 2.75	0.87	P>0.05
ICAM-1 (ng/ml)	92.66 ± 6.43	94.05 ± 6.14	0.65	P>0.05
VCAM-1 (ng /ml)	822.12 ± 29.13	825.10± 29.21	0.98	P>0.05
E-selectin (ng/ml)	15.11 ± 3.91	15.86 ± 3.87	0.83	P>0.05
PAI-1 activity (ng/ml)	0.55 ±0.14	0.57 ±0.16	0.62	P>0.05

BMI= Body Mass Index; TNF-α = Tumor necrosis factor –alpha; IL-6= Interleukin-6; ICAM-1 = Inter-Cellular Adhesion Molecule; VCAM-1 = Vascular Cell Adhesion Molecule; PAI-1: Ac = Plasminogen Activator Inhibitor-1 Activity; (*) indicates a significant difference, P < 0.05.

Table (4): Mean value and significance of BMI, TNF-α, IL-6, Leptin, Adiponectin, ICAM-1, VCAM-1, E-selectin and PAI-1 activity in group (A) and group (B) at the end of the study.

	Mean +SD		T-value	Significance
	Group (A)	Group (B)		
BMI (kg/m²)	26.81 ± 2.27*	32.23 ± 2.01	6.32	P <0.05
TNF-α (pg/mL)	3.21 ± 1.19*	4.26 ± 1.43	5.48	P <0.05
IL-6 (pg/mL)	1.76 ± 0.82*	2.31 ± 0.86	4.76	P <0.05
Leptin (Ng/ml)	25.74 ± 4.19*	31.12 ± 5.15	6.54	P <0.05
Adiponectin (µg/mL)	15.16 ± 2.73*	11.03 ± 2.75	5.23	P <0.05
ICAM-1 (ng/ml)	83.14 ± 5.71*	94.05 ± 6.14	7.41	P <0.05
VCAM-1 (ng /ml)	743.25 ± 27.95*	825.10± 29.21	8.32	P <0.05
E-selectin (ng/ml)	9.13 ± 2.34*	15.86 ± 3.87	6.19	P <0.05
PAI-1 activity (ng/ml)	0.42 ±0.16*	0.57 ±0.17	3.75	P <0.05

BMI= Body Mass Index; TNF-α = Tumor necrosis factor –alpha; IL-6= Interleukin-6; ICAM-1 = Inter-Cellular Adhesion Molecule; VCAM-1 = Vascular Cell Adhesion Molecule; PAI-1: Ac = Plasminogen Activator Inhibitor-1 Activity; (*) indicates a significant difference, P < 0.05.

Discussion

Vascular disorders are common among T2DM patients [24, 25] which are related to impaired endothelial function and systemic inflammation [26]. Obesity is usually associated with abnormal levels of inflammatory cytokines that induce endothelial dysfunction [27-29]. Level of markers of endothelial function is predictor for CVD future events [30]. Weight reducing program is the key for management of obesity [31-33].

The principle results of the present study proved that weight loss ameliorated inflammatory cytokines (TNF-α, IL-6 and leptin) and endothelial function markers (ICAM-1 VCAM-1, E-selectin and PAI-1 activity) as well as improvement in adiponectin in T2DM patients, these findings agreed with Cotie et al . found that four months of weight reduction program modulated endothelial function and IL-6 [34]. Lang et al. proved that weight reducing program for 2 months ameliorated inflammatory cytokines and abnormal blood lipid profile.[35]. Choo et al stated that long term weight reduction program reduced atherosclerosis and CVD risk factors [36]. Several studies proved that weight loss associated with improvement of inflammatory cytokines and increase level of adiponectin levels [37-50].

Concerning endothelial function, results of the present study proved that weight reducing program resulted reduced levels of VCAM-1, ICAM-1 and PAI-1. These findings agreed with several studies [51-56]. While, Sharman and Volek found that 6-weeks of weight reducing program resulted in reduction in TNF-α, IL-6 and ICAM-1[57]. Forsythe et al. stated that three months of diet control resulted in weight loss and reduced TNF-α, IL-6, E-selectin, ICAM and plasminogen activator inhibitor-1 (PAI-1) [58]. Thomson et al mentioned that five months of diet control significantly reduced levels of VCAM-1, and ICAM-1 and PAI-1 among with polycystic ovary syndrome (PCOS) obese women [59].

The current study has important strengths and limitations. The major strength is the supervised nature of the study. Supervising food intake and physical activity removes the need to question compliance or to rely on food and activity questionnaires. Further, all exercise sessions were supervised and adherence to the diet and activities was essentially 100%. Moreover, the study was randomized; hence, we can extrapolate adherence to the general population. In the other hand, the major limitations is measuring selected cytokines (i.e. TNF-α and IL-6) even obesity does not only increase the cytokines selected by the authors, but also IL-5, IL-10, IL-12, IL-13 and IFN-γ [60], in addition small sample size in both groups may limit the possibility of generalization of the findings in the present study.

Conclusion

Weight reducing program modulates inflammatory cytokines, adipocytokines and endothelial function biomarkers among obese T2DM patients.

Acknowledgment

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Conflict of interest

None declared.

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