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ORIGINAL RESEARCH

Abdominal Fat Is Directly Associated With Inflammation In Persons With Type-2 Diabetes Regardless Of Glycemic Control – A Jordanian Study

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Background and aim: Systemic inflammation is related to the progression of complications associated with diabetes. This study aimed to investigate the association between general and abdominal obesity and inflammation in patients with type-2 diabetes with or without glycemic control.

Methods: A total of 198 men (n=73) and women (n=125) diagnosed with type 2 diabetes participated in this study. General obesity markers, body mass index (BMI), and abdominal fat were assessed. Circulating concentrations of glycated hemoglobin (HbA1C), C-reactive protein (CRP), and serum interleukin-6 (IL-6) were determined. Poor glycemic control and good glycemic control were defined as having fasting HbA1C concentrations ≥7% and <7%, respectively. Multivariate adjusted analysis of covariance was used to determine the relation between BMI and abdominal fat and markers of inflammation in patients with good and poor glycemic control.

Results: Patients in <7% HbA1C category, those with high abdominal fat had ≈262% higher CRP and ≈30.6% higher IL-6 compared to those with low abdominal fat ($p<0.05$). Patients in ≥7% HbA1C category, those with high abdominal fat had ≈41.4% higher CRP and ≈33.9% higher IL-6 compared to those with low abdominal fat ($p<0.05$). Abdominal fat was directly related to CRP ($p<0.023$) and IL-6 ($p<0.002$) concentrations in both groups of type-2 diabetic patients with <7% and ≥7% HbA1C. In patients with ≥7% HbA1C, BMI was directly related to CRP ($p<0.02$) and IL-6 ($p<0.047$). Whereas in patients with <7% HbA1C, BMI was not associated with CRP or IL-6 concentrations.

Conclusion: High level of abdominal fat is associated with systemic inflammation in type-2 diabetes regardless of glycemic control. Abdominal fat is a better predictor (determinant) of inflammation than BMI in patients with type-2 diabetes with or without glycemic control.

Keywords: BMI, C-reactive protein, diabetes, IL-6, inflammation, obesity

Introduction

Type 2 diabetes mellitus (T2D) is a progressive, common disease characterized by hyperglycemia resulting from defects in insulin action. T2D is considered one of the costliest chronic diseases with strong association with many chronic diseases, such as renal failure, atherosclerotic vascular disease, hypertension, and dyslipidemia.[1–3]

Systemic inflammation is the continuous phenomenon of the immune response which can promote tissue damage.[4] Chronic systemic inflammation arises due to the persistence of a pro-inflammatory substance. This environment could be the result of a pro-inflammatory stimulus or inadequate determination of the inflammatory response.[5,6] The relationship between inflammation and diabetes is complicated.

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Intermediary role of inflammation has been established in many studies in the occurrence of T2D and its long-term complications.[7] Several connections have been proposed. One suggests that inflammation plays a vital role in diabetes pathogenesis through the induction of β cell apoptosis in T2D by the activity of reactive oxygen species and inflammatory cytokines.[8–11] A large body of research supports the finding that systemic inflammation is associated with insulin resistance.[12–14] Experiments conducted on animals and studies in humans displayed a strong association between low-grade inflammation and increased insulin resistance,[15,16] leading to elevated glucose concentrations.

Diabetes complications such as cardiovascular diseases, are often characterized by diabetes-induced systemic inflammation.[17,18] Elevated inflammation characterized by increased concentration of IL-6 was significantly related to progression of microvascular complications of diabetes.[19] Elevated inflammatory markers such as CRP and IL-6 are inversely related to nerve conduction velocities and directly related to peripheral neuropathy, even in non-diabetic persons.[20] Despite the continuous work dedicated to gaining an in-depth understanding of the relation between inflammation and diabetes pathogenesis and progression, the role of glycemic control in inflammation is not clear in Jordanian population. Therefore, this study aimed to investigate the association between general and abdominal obesity and inflammatory biomarkers in patients with or without glycemic control.

Methods

This study was conducted in accordance with the Declaration of Helsinki. The protocol of this study was approved by the Institutional Review Board at Jordan University of Science and Technology (JUST). Patients were recruited from the outpatient endocrinology unit at King Abdullah University Hospital, JUST Health Center, and private endocrinology clinics in the north of Jordan.

Initial screening included 1500 patients diagnosed with T2D. Due to the multiple co-variation nature of the relationship of interest, about 87% of the initially screened patients were excluded from the study. The final study sample comprised 198 patients (73 male and 125 female) diagnosed with type 2 diabetes. Patients were excluded if they met one of the following criteria: 1) diagnosed with T2D for less than one year; 2) also diagnosed with either rheumatoid arthritis, cancer, diabetic foot, kidney diseases, or any chronic or acute inflammatory disease; 3) had a recent major or minor surgery; 4) on non-steroidal anti-inflammatory drugs for less than two weeks prior to the blood sample collection; 5) women on oral contraceptives; and 6) women who were pregnant. All 198 patients completed the study. All subjects signed informed consent after all study procedures were explained.

Blood Specimen Collection And Analysis

A 10-mL blood sample was collected by venipuncture by a registered nurse. For measurement of HbA1c, blood samples were collected in ethylenediaminetetraacetic acid tubes. Then HbA1C was measured in whole blood using the immune-inhibition test for the quantitative determination of glycosylated hemoglobin (Beckman Coulter AU analyzers). For the measurement of CRP and IL-6, blood was collected in Z-Clot activator tubes. Blood was allowed to clot before centrifugation for 15 mins at 1000×*g*. Aliquots of serum were stored at ≤ −22°C in sterile small tubes prior to biochemical assay. CRP and IL-6 concentrations were analyzed within a month after collection of blood. The immuno-turbidimetric test was used to determine CRP levels (Beckman Coulter AU analyzers). IL-6 was measured using a human immunoassay kit from R&D SYSTEMS through sandwich-type enzyme-linked immunosorbent assay. An Absorbance Microplate Reader was used to measure the optical density of IL-6 (BioTek ELx800).

Anthropometrics And Body Composition

Weight and height were measured following World Health Organization (WHO) procedures.[21] Body weight was measured with the individuals wearing no shoes and light clothing. Height was measured using a measuring rod (Seca, Germany). Body mass index (BMI) was calculated using the ratio of weight (kilograms) to the square of height (meters) (kg/m^2). The WHO BMI cutoff points were used to classify patients into different body weight categories.[21]

Patients' abdominal fat percentage was determined using the bioelectrical impedance technique (TANITA, BC-418). The Segmental Body Composition Analyzer (TANITA, BC-418) used in this study was previously validated against hydro-densitometry in the assessment of body composition in healthy young adults.[22] The cutoff points for abdominal fat percentage were gender-specific, based on which patients were classified into low, average, and high abdominal fat.[23]

Statistical Analysis

Statistical Package for Social Sciences (SPSS, version 19, Chicago: SPSS Inc.) software was used in data analysis. Characteristics of subjects' variables were described using

frequency distribution for categorical variables and mean and standard deviation for continuous variables. Patients were classified as having good glycemic control if they had <7% HbA1C. If a patient had ≥7% HbA1C, that patient was categorized as having poor glycemic control. Multivariate-adjusted analysis of variance (MANOVA) was used to examine the differences in mean serum levels of CRP and IL-6 in patients with good and poor glycemic control. Analysis was adjusted for age, gender, use of lipid-lowering drugs, and diabetes duration. Least significant difference post-hoc MANOVA was conducted to determine which two means differ within the BMI and abdominal fat categories. A p-value of <0.05 was considered the cutoff level for statistical significance.

Results

Table 1 shows characteristics of the study participants. The majority of the participants were >50 years old. More than 2/3 of the sample (75.8%) were nonsmokers. The glycemic control was poor for 66.2% of the patients. Lipid lowering drugs were used by 19.7% of the participants. 7.1% of the participants had a normal BMI. 27.8% were overweight, and 65.1% were obese. Only 7.5% of the participants had abdominal fat at low level, while 68.7% presented with normal level, and 20.2% had high fat level. We performed an additional analysis on gender and age differences regarding inflation. We found no significant difference between men and women (except CRP in poor glycemic group) and between older and younger persons regarding CRP and IL-6 concentrations in both glycemic groups (data not shown). However, the analysis was adjusted for these variables.

Table 1 Participants' Characteristics – Glycemic Control (N=198)

Variable	Glycemic Control[a]	
	Good (n=67)	Poor (n=131)
Gender	n (%)	n (%)
Men (n=73)	25 (34.2)	48 (65.8)
Women (n=125)	42 (33.6)	83 (66.4)
Age (years)		
30–49 (n=48)	21 (43.8)	27 (56.2)
50–80 (n=150)	46 (30.7)	104 (69.3)
Diabetes duration (years)		
≤5 (n=94)	47 (50)	47 (50)
6–12 (n=61)	12 (19.7)	49 (80.3)
13–19 (n=24)	6 (25)	18 (75)
>20 (n=17)	2 (11.8)	15 (88.2)
Not reported (n=2)	0 (0)	2 (100)
Body mass index[b]		
Normal weight (n=14)	6 (42.9)	8 (57.1)
Overweight (n=55)	25 (45.5)	30 (54.5)
Obese (n=129)	36 (27.9)	93 (72.1)
Lipid-lowering drugs		
Yes (n=39)	15 (37.5)	25 (62.5)
No (n=159)	52 (32.9)	106 (67.1)
Smoking status		
Yes (n=48)	15 (31.3)	33 (68.8)
No (n=150)	52 (34.7)	98 (65.3)

Notes: [a]Good glycemic control is defined as having HbA1C <7%, while poor glycemic control is having HbA1C ≥7%. [b]Normal weight, BMI: 18.6 to <24.9 kg/m^2; overweight: BMI: 25 to 29.9 kg/m^2; obese grade I: BMI: 30 to 34.9 kg/m^2; obese grade II: BMI: 35 to 39.9 kg/m^2; and obese grade III: BMI: ≥40 kg/m^2.

Table 2 shows the association between BMI and abdominal fat and inflammatory biomarkers in patients with controlled glycemia. Patients with good glycemic control (<7% HbA1C) with high abdominal fat had ~262% higher CRP and ~30.6% higher IL-6 compared to those with low abdominal fat (p<0.05). Among patients with good glycemic control, no significant association was found between BMI and inflammatory markers (CRP or IL-6).

Table 3 shows the relation between BMI and abdominal fat and inflammatory biomarkers in patients with uncontrolled glycemia. Patients with poor glycemic control (≥7% HbA1C), with high abdominal fat had ≈41.4% higher CRP and ≈33.9% higher IL-6 compared to those with low abdominal fat (p<0.05). Patients with poor glycemic control with obesity grade III had ≈206% higher CRP and ≈50.2% higher IL-6 compared to those with normal BMI.

Discussion

An interesting finding of the current study is that the inflammatory markers studied (CRP, IL-6) were higher among patients with higher BMI; however, this finding was observed only among patients with poor glycemic control. In other words, obese patients with controlled diabetes (HbA1c <7%) had less systemic inflammation despite having diabetes and obesity. This might be explained by the impact of a consistent state of hyperglycemia (HbA1c >7%), which may lead to up-regulation of acute phase inflammatory markers such as amyloid A3 (SAA3) and pro-inflammatory cytokines such as IL-6, by adipose tissue under the stimulation of high blood glucose.[24] Elevation of IL-6 may in turn stimulate the production of CRP by the hepatocytes.[25,26] Ray et al stated that elevated levels of glucose resulting from obesity can create stress in pancreatic islets, adipose tissue, liver, and muscle.[27]

Table 2 Relation Between BMI And Abdominal Fat And Inflammatory Biomarkers In Patients With Type-2 Diabetes With Good Glycemic Control (<7% HbA1C)[a]

	CRP (mg/L)	P-value	IL-6 (pg/L)	P-value[b]
	Mean ± SE		Mean ± SE	
Body mass index[c]		0.269		0.666
Normal	3.73±1.22[e]		5.94±2.55[e]	
Overweight	4.54±0.66[e]		2.12±0.25[e]	
Obesity I	10.19±3.68[e]		3.96±1.02[e]	
Obesity II	10.09±1.85[e]		4.32±1.43[e]	
Obesity III	6.56±2.77[e]		6.35±2.55[e]	
Abdominal fat %[d]		0.023		0.002
Low	3.92 ± 0.86[e]		4.90± 2.26[ef]	
Average	5.53 ± 0.54[e]		2.68± 0.28[e]	
High	14.20 ± 1.24[f]		6.40± 2.08[f]	

Notes: [a]n=67. Means sharing different. [b]P-values for F-statistic in multivariate-adjusted analysis of variance. Analysis was adjusted for age, gender, use of lipid-lowering drugs, and diabetes duration. [c]Normal weight, BMI: 18.6 to 24.9 kg/m^2; overweight: BMI: 25 to 29.9 kg/m^2; obese grade I: BMI: 30 to 34.9 kg/m^2; obese grade II: BMI: 35 to 39.9 kg/m^2; and obese grade III: BMI: ≥40 kg/m^2. [d]Abdominal fat % cut-off points: low (<13.5% for men, <29.4% for women); average (13.5% - <29% for men, 29.4% - <54.6% for women) and high: (≥29% for men, ≥54.6% for women).[23] [e,f,g]Means in the same column sharing different letters superscripts are significantly different (P< 0.05).

Table 3 Relation Between BMI And Abdominal Fat And Biomarkers Of Inflammation In Patients With Type-2 Diabetes With Poor Glycemic Control (≥7% HbA1C)[a]

	CRP (mg/L)		IL-6 (pg/L)	P-value[b]
			Mean ± SEM	
Body mass index[c]		0.02		0.047
Normal	5.42±2.08[e]		4.06±1.82[e]	
Overweight	6.79±1.18[e]		3.38±0.62[e]	
Obesity I	7.80±0.97[e]		3.89±0.34[e]	
Obesity II	11.17±1.16[f]		4.41±0.44[ef]	
Obesity III	16.66±3.78[g]		6.10±0.93[f]	
Abdominal fat %[d]		0.014		0.049
Low	8.82±4.25[e]		3.30±2.14[e]	
Average	8.72±0.71[e]		4.24±0.31[f]	
High	12.47±2.67[f]		4.42±0.60[f]	

Notes: [a]n=137. [b]P-values for F-statistic in multivariate-adjusted analysis of variance. Analysis was adjusted for age, gender, use of lipid-lowering drugs, and diabetes duration. [c]Normal weight, BMI: 18.6 to 24.9 kg/m^2; overweight: BMI: 25 to 29.9 kg/m^2; obese grade I: BMI: 30 to 34.9 kg/m^2; obese grade II: BMI: 35 to 39.9 kg/m^2; and obese grade III: BMI: ≥40 kg/m^2. [d]Abdominal fat % cut-off points: low (<13.5% for men, <29.4% for women), average (13.5% - <29% for men, 29.4% - <54.6% for women), and high: (≥29% for men, ≥54.6% for women).[23] [e,f,g]Means in the same column sharing different letters superscripts are significantly different (P< 0.05).

Consequently, there is a surge in local production and release of cytokines and chemokines, such as IL-6 and TNF-α. These changes enhance further production and release of cytokines and chemokines.[27] Another mechanism through which high glucose increases the complications associated with diabetes is production of reactive oxygen species (ROS). These ROS suppress insulin production by inhibiting the transcription factors of insulin in β-cells of the pancreas. ROS cause endothelial dysfunction and induce synthesis of chemokines such as MCP-1, ICAM 1, and IL-1. This further upregulates the ROS production, leading to diabetes induced atherosclerosis.[28,29] Therefore, when serum glucose is controlled, even in the context of obesity, there could be a downplay of stress which in turn decreases the previously mentioned heightened release of cytokines and chemokines.

A few studies investigated the relation between obesity and inflammation among patients with diabetes according to their glycemic control. Mohan et al conducted a study on Asian Indian patients with diabetes, and demonstrated higher CRP levels among participants with increased HbA1c and

tertiles of body fat.[30] Zaciragic et al reported a direct relation between serum CRP concentrations and BMI in T2D.[31] The same relationship was documented by Rawson et al. Other obesity markers such as total fat percentage were also investigated in the literature in relation to inflammation among patients with diabetes.[32] The findings of our study are in line with previously published work that showed an association between circulatory markers of chronic inflammation (CRP, IL-6) and body fat percentage.[33–36] Other studies failed to find an association between inflammatory response and obesity among patients with diabetes, however.[37] Investigators interpret this controversy by the nonlinearity that may exist between the cytokine levels and BMI of diabetic patients.

The scenario was different when examining abdominal fat percentage. Regardless of the glycemic control of the patients, abdominal fat percentage was associated with an increased level of serum inflammatory biomarkers (CRP, IL-6). These results were supported by findings from numerous studies that depicted a positive correlation between CRP and abdominal body fat.[31,33,36] Rexrode et al and Park et al also reported a very clear positive trend concerning CRP levels.[38,39] A study was conducted on elderly type 2 diabetic patients by Pedersen et al in 2003.[40] They found that high circulatory inflammatory cytokines (IL-6 and TNF-α) were associated with increased abdominal fat mass in patients with good and poor glycemic control. The exact explanation of the relation between abdominal fat and inflammatory response is not yet fully understood. In vivo and in vitro studies detected amplified IL-6 production by subcutaneous adipose cells with defects in insulin action.[41] The distinctive role of intraperitoneal adipocytes as an active gland results in the secretion of several hormones and several adipocytokines.[42] Once these cytokines are secreted by adipocytes, this results in a boost in the CRP production via hepatocytes.[25,26]

It is worth mentioning that although absolute HbA1c levels were used as indicators of glycemic control, glucose variability was not measured in this study. Hoffman et al reported on 17 adolescents with type 1 diabetes, stating that increased glucose variability is associated with increased inflammation in this group,[43] suggesting that pathogenesis in type-1 diabetes is different from T2D. It would be interesting to determine whether patients in the non-controlled glycemia group had increased instances of intermittent hyperglycemia or whether it was sustained hyperglycemia. Animal studies have suggested that intermittent hyperglycemia has a more marked effect than sustained hyperglycemia in inducing oxidative stress and increasing inflammation;[44] however, studies in human adults have been less conclusive. Many studies in human adults have found no association between glucose variability and consequences of inflammation, such as microvascular or macrovascular complications, arterial stiffness, and carotid intimal thickness.[43] On the other hand, other studies stated that fluctuations in glucose, especially during post prandial periods, heightened the triggering effect on oxidative stress compared to sustained hyperglycemia.[45]

The major strength of this study is the stringent procedure we used for the selection of the participants to rule out any acute response to inflammation. Due to the cross-sectional nature of the study, results should not be viewed in terms of cause and effect relationship. Due to the small sample size in this study, results may not be applicable to the population at large in Jordan. For the same reason, we were unable to determine the relationship between body composition and inflammation using various hyperglycemic levels. Future studies should use more accurate body composition measurement methods such as DEXA rather than bioelectrical impedance methods that were used in this study.

In conclusion, the findings of the current study indicate that abdominal fat is related to increased inflammation regardless of glycemic control in Jordanian sample. General obesity is associated with systemic inflammation only among patients with poor glycemic control. Patients should maintain HbA1C concentrations below 7% to reduce the glucose induced inflammatory markers, as this has been linked to complications associated with diabetes. Longitudinal studies are needed to decipher the complex relationship between body composition and inflammation and its overall impact on progression of diabetes.

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Author Contributions

All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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