

Effect Of L-Carnitine Supplementation On Serum Adipokines (Leptin And Visfatin) Levels In Obese Type II Diabetes Mellitus Women With Hypocaloric Diet

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Abstract: Background: Obesity is reaching epidemic proportions worldwide and correlated with various comorbidities such as diabetes mellitus, fatty liver and cardiovascular diseases. Diabetes and obesity are combined with such frequency that it has been proposed for the term Diabesity. Carnitine in high doses has no side effects of other anti-obesity drugs. In this regard, we evaluated the effect of l-carnitine supplementation on serum leptin and visfatin levels (that almost are secreted from central and peripheral fat respectively) as markers of endothelial dysfunction. **Methods and Materials:** In this clinical trial, 60 obese Premenopausal females suffering type II diabetes with a BMI greater than 30 were randomly selected and divided into two groups. After measuring the weight, waist circumference and record the personal details of patients, their information about three-day food records were down in sheets. During the 8-week intervention group complement of L - carnitine (2 g daily) with low-calorie diet and the second group received placebo plus low-calorie diet. **Results:** Supplementation of carnitine with low calorie diet reduces anthropometric indices, serum level of leptin, visfatin and inflammatory markers ($p < 0.0001$), whereas the reduction in mentioned factors in controls was significant, but lower than case group. **Conclusion:** L-carnitine supplementation has pronounced and more significant impact on levels of leptin, visfatin, inflammatory markers and anthropometric indices, especially Adiposity (abdominal fat) in patients.

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1. Introduction

Obesity is reaching epidemic proportions worldwide; it is correlated with various comorbidities, among which the most relevant are dyslipidemia (Fried, 2008), diabetes mellitus (Pagotto, 2008), fatty liver (Marovic, 2008), and cardiovascular diseases (Artham, 2008).

Carnitine, synthesized primarily in the liver and kidneys (Woodworth, 2004), is involved in mitochondrial transport of fatty acids and is of critical importance for maintaining normal mitochondrial function. Mitochondrial dysfunction secondary to a disruption of Carnitine homeostasis may play a role in decreased NO signaling and the development of endothelial dysfunction (Sharma and Black, 2009).

L-Carnitine is a vitamin like compound (Woodworth, 2004) obtained from the diet that is also synthesized in the body from the essential amino acids lysine and methionine. It is essential for the transport of long chain fatty acids into the mitochondrial matrix through the action of specialized acyl transferases. L-

Carnitine is also reported to possess antioxidant properties (Izgut-Uysal, 2001). The antioxidant benefits have been implicated in several forms of toxicity (Demirdag, 2004; Chang, 2002). Furthermore, L-Carnitine is reported to have effects on insulin action. Clinically, L-Carnitine has been shown to improve insulin sensitivity in uremic (Gunal, 1999) and diabetic (Mingrone, 1999) patients.

Other established functions of L-Carnitine are the preservation of membrane integrity, the stabilization of a physiologic coenzyme A (CoA) acetyl-CoA (coASH) ratio in mitochondria, and the reduction of lactate production (Siliprandi, 1990; Brevetti, 1988). In vitro investigations have strongly supported the notion that L-Carnitine is able to inhibit apoptosis (programmed cell death) (Vescovo, 2002; Mutomba, 2000; Di, 1997).

Adipose tissue is a known endocrine organ secreting several soluble factors, known as adipocytokines or adipokines, some of these being adiponectin, leptin, resistin and more recently,

visfatin. They can partly explain the link between obesity, insulin resistance, beta-cell dysfunction, endothelial dysfunction, and atherosclerosis (Bulcau, 2006).

Visfatin was recently identified as a protein mainly expressed in visceral adipose tissue (Fukuhara, 2005). It can also be found in skeletal muscle, liver, bone marrow, and lymphocytes, where it was initially identified as a pre-B-cell colony-enhancing factor. Interestingly, pre-B-cell colony-enhancing factor expression is regulated by cytokines that promote insulin resistance, such as tumor necrosis factor- α and interleukin-6 (Ognjanovic, 2001).

Leptin is an obese gene product and is produced mainly in adipose tissue (Lonnqvist, 1995). Leptin was reported to control food intake and body-energy expenditure through hypothalamic receptors (Zhang, 1994; Stephens, 1995). However, studies about the relation between dietary Conjugated linoleic acid (CLA) and its effect on circulating leptin concentration in animals are scarce.

So the aim of this study was to evaluate the effect of L-Carnitine supplementation on leptin, and visfatin adipocytokines status in obese diabetic women with hypocaloric diet.

2. Material and Methods

In this clinical trial, 60 obese Premenopausal women with type 2 diabetes attending the diabetes clinic of Tabriz Crescent center in the age range of 20 to 50 years with a BMI greater than 30 that past at least one year of their diagnosis of diabetes and did not participate in any weight loss program in the last 6 months and had no swing weight more than 1 kg were selected and randomly were divided into two groups.

Inclusion criteria were lack of liver disease, or kidney cancer, lack of pregnancy and lactation and menopause, not following a particular diet except for diabetes.

Exclusion criteria were nutritional supplements and medications that affect balance of lipids as carnitine and vitamin C, and B6, insulin and non-adherence to the prescribed diet, lack of adherence to the study regimen during the project, other disease during the study.

Intervention period was 8 weeks. In the case group, L - carnitine supplement (2 grams daily twice a day, morning and evening) with a low calorie diet and a second group received the placebo with a low-calorie diet.

Low calorie diet has 500 kcal of energy lower than individual needs (that was calculated by Institute of Medicine, Food and Nutrition Board recommended formula). Dietary as daily intake units were instructed to the cases and also 7 days food samples were provided for them.

From each of the subjects, 5 ml of venous blood samples was taken after 12-10 hours fasting before and after intervention.

The protocol of this study was registered in Clinical Trial Registration System at www.irct.ir by the number of IRCT138903164105N1.

Quantitative variables were compared by using Student T-test and qualitative variables have been compared by using Chi-Square Test by SPSS™ 17 software. In all investigated cases, the results have been known statistically significant in case of $P \leq 0.05$.

3. Results

Of the 60 cases, 30 cases in case group and 30 were in the control group. The mean age of patients in case and controls was 37.03 ± 6.1 and 36.7 ± 5.6 years respectively. Mean weight of patients in case and control groups was 83.8 ± 8.21 and 84.23 ± 7.8 kg respectively. In addition, mean height of the patients was 157.6 ± 7.3 and 158.2 ± 7.5 cm in case and controls respectively. The mean BMI of the patient in the case and controls was 33.4 ± 2.78 and 33.7 ± 2.81 kg/m^2 respectively. The anthropometric indices evaluations in the two groups before and after treatment regimen were presented in table 1.

The results of the experiments carried out in two groups before and after dietary intake include:

• Leptin

In the case group, leptin level prior to treatment regimen was 36.5 ± 3.18 (Min = 31.2, Max = 39.75).

Leptin level after the treatment regimen was 24.91 ± 3.7 (Min = 19.6, Max = 27.1).

In the control group, leptin level prior to treatment regimens was 38.2 ± 2.5 (Min = 35.71, Max = 40.4).

Leptin level after the treatment regimen was 29.6 ± 3.2 (Min = 24.3, Max = 34.1).

• Visfatin

In the case group, visfatin level before treatment regimen was 33.87 ± 4.3 (Min = 27.46, Max = 35.2).

Visfatin level after treatment regimen was 20.83 ± 1.19 (Min = 18.3, Max = 23.59).

In the control group, visfatin level before treatment regimen was 33.6 ± 2.19 (Min = 29.6, Max = 35.68).

Visfatin level after treatment regimen was 25.1 ± 1.58 (Min = 24.9, Max = 28.4).

• IL-6

In the case group, IL-6 measured level before treatment regimen was 3.73 ± 1.74 (Min = 1.1, Max = 5.03).

IL-6 measured level after treatment regimen was 2.19 ± 1.81 (Min = 1.7, Max = 4.3).

In the control group, IL-6 measured level before treatment regimen was 3.68 ± 1.45 (Min = 1.6, Max = 4.93).

IL-6 measured level after treatment regimen was 3.49 ± 1.52 (Min = 1.75, Max = 4.68).

- **hs-CRP**

In the case group, hs-CRP measured level before treatment regimen was 3.06 ± 0.47 (Min = 1.35, Max = 4.45).

Hs-CRP measured level after treatment regimen was 2.44 ± 0.46 (Min = 1.3, Max = 4.4).

In the control group, hs-CRP measured level before treatment regimen was 2.84 ± 0.54 (Min = 1.36, Max = 4.46).

Hs-CRP measured level after treatment regimen was 2.53 ± 0.53 (Min = 1.35, Max = 4.45).

Leptin, visfatin and inflammatory markers (IL-6 and hs-CRP) levels measured in two groups before and after treatment regimen and the statistical analysis of related obtained data were presented in table 2.

Table 1. Anthropometric indices evaluation in two groups before and after treatment regimen

Variable		Case (N = 30)	Control (N = 30)	P value ^a
Weight (kg)	Before	83.8 ± 8.21	84.23 ± 7.8	0.62
	After	79.14 ± 7.65	81.56 ± 7.2	0.5
Changes		- 4.66 ± 0.56	- 2.67 ± 0.6	
P value ^b		0.047 *	0.07	
BMI (kg/m²)	Before	33.4 ± 2.78	33.7 ± 2.81	0.91
	After	31.62 ± 3.66	32.88 ± 2.7	0.87
Changes		- 1.78 ± 0.88	- 0.82 ± 0.11	
P value ^b		0.43	0.5	
WC (cm)	Before	97.68 ± 9.25	98.22 ± 9.14	0.72
	After	90.56 ± 8.91	93.78 ± 8.9	0.17
Changes		- 7.12 ± 0.34	- 4.44 ± 0.24	
P value ^b		0.03 *	0.06	
HC (cm)	Before	118.06 ± 8.2	117.31 ± 7.7	0.93
	After	111.86 ± 8.32	112.01 ± 7.5	0.69
Changes		- 6.2 ± 0.12	- 5.3 ± 0.2	
P value ^b		< 0.001 *	0.02 *	
WHR (%)	Before	0.827 ± 0.07	0.837 ± 0.08	1
	After	0.809 ± 0.08	0.838 ± 0.07	0.06
Changes		- 0.018 ± 0.01	0.001 ± 0.01	
P value ^b		0.064	1	
BF (%)	Before	41.12 ± 1.86	40.65 ± 1.81	0.86
	After	36.51 ± 1.65	37.96 ± 1.76	0.91
Changes		- 4.61 ± 0.21	- 2.69 ± 0.05	
P value ^b		0.046 *	0.053	

Note: Data are presented as Mean ± SD. P value ^a, Between groups analysis; P value ^b, Within groups analysis.

Abbreviation: BMI, WC, Waist circumference; HC, Hip circumference; WHR, Waist-To-Hip Ratio; BF, Body Fat.

4. Discussion

Obesity and insulin resistance are associated with an increase of cardiovascular risk factors, including inflammatory markers and adipocytokines (Fantuzzi, 2005). The incidence of obesity and associated comorbidities is clearly increasing worldwide. This epidemiologic evidence has led, in the past few years, to an increase in interest in adipose tissue as an active participant of the physiologic and pathological processes (Meier and Gressner, 2004).

Carnitine and L-Carnitine are both involved in the transport of fatty acids and acetyl groups into the mitochondria. L-Carnitine is also an intracellular energy reservoir of acetyl groups (McGarry and Brown, 1997).

Carnitine covers an important role in lipid metabolism, acting as an obligatory cofactor for oxidation of fatty acids by facilitating the transport of long-chain fatty acids across the mitochondrial inner membrane as acyl

Carnitine esters. There is also experimental evidence that L-Carnitine stimulates the activity of the pyruvate dehydrogenase complex by decreasing the intramitochondrial acetyl-CoA/CoA ratio through the trapping of acetyl groups (Uziel, 1988). The simultaneous reduction of acetyl-CoA levels in the cytosol further contributes to activate the glycolytic pathway (Amat di San Filippo, 2008), so L-Carnitine also covers a key role in glucose metabolism and assists in fuel-sensing.

The relationship of obesity to other types of diseases, such as type 2 diabetes mellitus (T2DM), is not easily understood.

The link is a group of proteins, collectively called adipokines, which are secreted by adipose tissue and adipose-resident macrophages and fibrocytes. Adipokines exert their effects in the central nervous system and peripherally, in tissues such as skeletal muscle and the liver. Leptin, adiponectin, resistin, visfatin, retinolbinding protein and tumor necrosis factor- α (TNF) are some of the main adipokines of interest (Obesity's missing links).

Adipocytes produce a variety of bioactive peptides, termed adipokines, which play a central role in whole body glucose and lipid metabolism but also in the pathogenesis of atherosclerosis (Sjoholm and Nystrom, 2006; Wellen and Hotamisligil, 2005). In 1994 visfatin was cloned by Samal et al. as a 52 kDa secreted molecule termed pre-B cell colony-enhancing factor (Samal, 1994) and 11 years later it was characterized as a novel adipokine (Fukuhara, 2005). In 2007, visfatin was suggested to function as a direct proinflammatory mediator of obesity-related vascular disorders with a potential role in plaque destabilization (Dahl, 2007).

Table 2. Leptin, Visfatin and inflammatory markers (IL-6 and hs-CRP) levels measured in two groups before and after treatment regimen

Variable		Case (N = 30)	Control (N = 30)	P value ^a
Leptin	Before	36.5 \pm 3.18	38.2 \pm 2.5	0.1
	After	24.91 \pm 3.7	29.6 \pm 3.2	0.026 *
Changes		- 11.59 \pm 0.52	- 8.6 \pm 0.7	
P value ^b		< 0.001 *	0.01 *	
Visfatin	Before	33.87 \pm 4.3	33.6 \pm 2.19	0.43
	After	20.83 \pm 1.19	25.1 \pm 1.58	0.052
Changes		- 13.04 \pm 3.11	- 8.5 \pm 0.61	
P value ^b		< 0.001 *	0.014 *	
IL-6	Before	3.73 \pm 1.74	3.68 \pm 1.45	0.99
	After	2.19 \pm 1.81	3.49 \pm 1.52	0.037 *
P value ^b		< 0.0001 *	0.9	
Hs-CRP	Before	3.06 \pm 0.47	2.84 \pm 0.54	0.44
	After	2.44 \pm 0.46	2.53 \pm 0.53	0.61
P value ^b		< 0.0001 *	0.14	

Note: Data are presented as Mean \pm SD. P value ^a, Between groups analysis; P value ^b, Within groups analysis.

Abbreviation: IL-6, Interleukin 6; hs-CRP, high-sensitivity C-Reactive Protein.

The major finding of this study was the significant decrease in circulating concentrations of the novel adipokine visfatin, after weight reduction, in mildly obese subjects on a hypocaloric diet. Previous research on molecular mechanisms has shown that visfatin activates the intracellular signaling cascade for insulin. Interestingly, visfatin activates the insulin receptor in a distinct manner from insulin.

Our results shown L- Carnitine administration in patients with hypocaloric diet

significantly decreased visfatin level in treatment group compared to control group.

L-Carnitine administration in obese diabetic patients with hypocaloric diet by correcting the dialysis-related Carnitine disorders influences the energy metabolism and could interfere with adipokines, since adipose tissue is deeply implicated in the energy metabolism (Csiky, 2010). This rationale could explain the significant decrease in the visfatin level after Carnitine supplementation. Visfatin was suggested to induce insulin resistance by

binding to the insulin receptor(Fukuhara, 2005; Moschen, 2007).

Of the adipokines, leptin has received the most attention. In 1995, leptin was identified as the fat cell-specific secretory factor that mediates the hormonal axis between fat and the brain. Leptin concentrations increase with increased body fat in all species studied including dogs and cats. Adequate energy stores are signaled by leptin and permit reproduction and normal immune function. Leptin also functions to reduce appetite (Obesity's missing links).

Studies have shown that leptin circulates in proportion to body fat mass in humans(Considine, 1996) serum leptin concentration falls after fasting (Boden, 1996). In addition, serum leptin concentrations fell following ultramarathon running in men and 12 wk of aerobic exercise in women without changes in adiposity(Landt, 1997; Hickey, 1997).

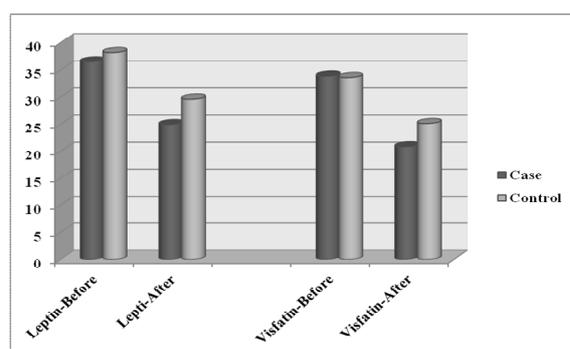


Figure 1. Visfatin and leptin serum levels before and after investigation in case and control groups

Follow by L- carnitin supplementation, we measured serum levels of leptin, which are involved in the regulation of nutrient metabolism(Danforth and Burger, 1989; Freake and Oppenheimer, 1995; Friedman and Halaas, 1998). Our serum leptin results (Fig.1) confirm previous observations that serum leptin levels decreased by L-carnitin administration (Schwartz, 1996).

Inflammation was shown to be diminished by L-Carnitine administration in obese diabetic patients with maintenance hemodialysis, especially CRP levels(Grazi, 2004; Bellinghieri, 2005) which appear to reflect the generation of proinflammatory cytokines leading to muscle wasting through the stimulation of protein catabolism(Kimmel, 1998; Bistrain, 1992). In the present study, we find a significant variation in CRP levels in L-Carnitine treatment group compared to control group.

Obesity (specifically as visceral abdominal fat), is the cause of various diseases including

hyperlipidemia, hypertension, type II diabetes and coronary artery disease. Leptin and visfatin almost are secreted from central and peripheral fat respectively. According to our results, the effect of L-carnitine on the reducing the visfatin level was greater than leptin serum level, thus we was observed more reducing in waist circumference in comparison with hip circumference in cases of L-carnitine supplementation combined with low calorie diet. It should be noted that this reduction would be very effective in preventing mentioned diseases.

Therefore it can be seen that L-carnitine supplementation has pronounced and more significant impact on levels of inflammatory markers and anthropometric indices, especially Adiposity (abdominal fat) in patients. These reductions in obese diabetics patients (like the ones in this study) are extremely valuable and that can prevent irreparable consequences of a disease that causes deterioration of the patient's clinical status and quality of life.

Conclusion

L-Carnitine supplementation seems to reduce endothelial dysfunction, as measured by flow mediated dilation, in obese diabetic patients with hypocaloric diet. The level of visfatin, which is accepted as a marker of endothelial dysfunction in patients is reduced after L Carnitine supplementation. L-Carnitine has significant effect on inflammation in obese diabetic patients.

Disclosure of potential conflict of interest

The authors have declared no potential conflicts of interest.

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