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Original Article

Comparative study to evaluate the effect of L-carnitine plus glimepiride versus glimepiride alone on insulin resistance in type 2 diabetic patients

Hadier M. El-sheikh [a,*], Sahar M. El-Haggar [a], Tamer A. Elbedewy [b]

[a] Clinical Pharmacy Department, College of Pharmacy, Faculty of Pharmacy, Tanta University, El- Guiesh Street, Tanta- El-Gharbia Government, 72513, Tanta, Egypt
[b] Internal Medicine Department, Faculty of Medicine, Tanta University, College of Medicine, El- Guiesh Street, Tanta- El-Gharbia Government, Tanta, Egypt

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ABSTRACT

Aim: Insulin resistance (IR) is predominant in type 2 diabetic patients. This study aimed to investigate benefits from adding L-carnitine to ongoing glimepiride compared to glimepiride monotherapy on IR in diabetic patients who failed to achieve their glycemic goals on glimepiride monotherapy.
Methods: 58 patients were recruited from Internal Medicine Department, Tanta University Hospital, Egypt then prospectively randomized to receive their glimepiride dose 2 mg twice daily (group 1) or glimepiride 2 mg twice daily + L-carnitine 1 g m twice daily (group 2) for 6 months. Fasting blood samples were collected at baseline, 3 and 6 months after treatment for analysis of fasting and post-prandial blood glucose [FBG &PPBG], glycated hemoglobin [HbA1c %], fasting insulin, extracellular part of insulin regulated aminopeptidase [IRAPe] as a novel marker, tumor necrosis factor-alpha [TNF-α], visfatin and lipid panel. Body mass index [BMI] and homeostasis model assessment of insulin resistance [HOMA-IR] were calculated. Data were statistically analyzed by SPSS using unpaired Student's t-test and one way analysis of variance; $p \leq 0.05$ was considered statistically significant.
Results: The obtained data suggested that adding L-carnitine to glimepiride has a significantly beneficial effect on FBG, PPBG, HbA1c, fasting insulin, HOMA-IR index, IRAPe, TNF-α, visfatin and lipid panel parameters but doesn't have effect on BMI and blood pressure.
Conclusion: The co-administration of L-carnitine with glimepiride represents a new therapeutic strategy for better controlling diabetic patients as it resulted in more beneficial effects on direct and indirect biomarkers of insulin resistance than glimepiride alone.

1. Introduction

Type 2 diabetes mellitus [T2DM] is growing in exponential proportions [1]. For T2DM to occur, both insulin resistance [IR] and inadequate insulin secretion must exist. IR, which has been attributed to elevated levels of free fatty acids and proinflammatory cytokines in plasma, leads to decreased glucose transport into muscle cells, elevated hepatic glucose production, and increased breakdown of fat [2].

One of the most important pathophysiological approaches of developing IR is change in glucose transporter [GLUT] [3]. Insulin acts to translocate GLUT-4 to the plasma membrane. An insulin-regulated aminopeptidase [IRAP] is a cellular protein required for insulin-stimulated translocation of GLUT-4 to the plasma membrane [4]. At the moment GLUT-4 is translocated to the plasma membrane, the extracellular domain of IRAP [IRAPe] is cleaved and secreted into the blood. The plasma concentration of IRAPe is inversely proportional to the degree of IR [5].

Concerning proinflammatory cytokines related to IR development, tumor necrosis factor-alpha [TNF-α] reduces the expression of GLUT-4 and increases serine phosphorylation of insulin receptor substrate-1 [IRS-1] [6]. Visfatin is an adipocytokine that exerts an insulin-like effect [7] but visfatin level was positively associated with IR, therefore it may be promising for predicting obesity, diabetes status and IR [8].

* Corresponding author.
E-mail addresses: Hadier_mohammed610@yahoo.com (H.M. El-sheikh), sahar2612@yahoo.com (S.M. El-Haggar), tamerelbedewy2006@yaho.com (T.A. Elbedewy).

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Enhanced lipolysis in adipose tissue, seen in IR state, results in elevation in circulating free fatty acids [FFAs] [9]. When the uptake of FFAs exceeds the rate of their β-oxidation, intramuscular lipids accumulate and different serine kinases that negatively modulate insulin action are activated [10]. This can decrease GLUT-4 effects, thereby suppressing glucose entry and inhibiting glucose oxidation and glycogen synthesis in the muscle [11]. Therefore, a prevailing view for improving insulin sensitivity is to enhance FFAs β-oxidation, thereby improving insulin sensitivity [12].

For better control on T2DM, attention must be paid for both inadequate insulin secretion and IR. Sulfonylureas as glimepiride lower glycemia by enhancing insulin secretion through the closure of ATP-sensitive potassium channels on beta cells. However, sulfonylureas have no effect on IR, the other arm of T2DM development. Therefore, many T2DM patients need to use sulfonylureas in combination with other drugs improving insulin sensitivity.

L-carnitine acts as an obligatory cofactor for β-oxidation of fatty acids [13]. In addition, it reduces acyl-CoA/CoA ratio in mitochondria, which in turn increases the activity of pyruvate dehydrogenase, thereby facilitating glucose oxidation [14]. The previous experimental and human studies of L-carnitine supplementation in T2DM focused on measurement of glucose oxidation markers but IR markers and related cytokines were never measured in T2DM patients. In addition, the available clinical studies include small sample size and the use of L-carnitine in combination with other strategies than ours.

Therefore, the aim of this study was to investigate the efficacy of adding L-carnitine to ongoing glimepiride therapy compared to glimepiride monotherapy on IR in T2DM patients who failed to achieve their glycemic goals on glimepiride monotherapy. We focused on direct biochemical markers of IR [fasting blood glucose [FBG], fasting blood insulin, homeostasis model assessment of insulin resistance [HOMA-IR] and IRAPe] and indirect markers linked to IR [visfatin, TNF-α and lipid panel].

2. Material and methods

2.1. Study patients

The study participants were recruited from Internal Medicine Department, Tanta University Hospital, Egypt. The study was designed and conducted in compliance with the ethical principles of Good Clinical Practice Guidelines and the Declaration of Helsinki [15]. The study protocol was approved by the National Research Ethics Committee [Tanta University Ethical Committee for Clinical Research]. An informed written consent was obtained from all patients before any study procedures were initiated according to the Tanta University Ethical Committee for Clinical Research.

Patients accepted in this study fulfilled the following criteria: T2DM patients on glimepiride alone, aged 30 years or more and both male and female subjects were included. Patients were excluded from the study if they were on insulin sensitizers as thiazolidinediones or biguanides, steroids, NSAIDs, warfarin or lipid lowering medications, having acute or chronic inflammatory diseases, end-stage renal disease undergoing dialysis, hypothyroidism or patients on thyroid hormones and epilepsy or patients on valproic acid. All pregnant women and breast-feeding women were excluded.

2.2. Study design

This study was a parallel randomized controlled prospective one. Out of 92 patients with T2DM screened for eligibility, 11 patients didn't meet inclusion criteria, 5 patients refused to be enrolled in the study, 4 patients were excluded, and 72 eligible patients were recruited and randomized to group 1 (n = 34), group 2 (n = 38). 27 patients in group 1 and 31 patients in group 2 completed the study as shown in Fig. 1.

Group 1; serves as a control group; received glimepiride alone 2 mg twice daily [Amaryl®, Sanofi-Aventis, Berlin, Germany]. Group 2 received glimepiride 2 mg twice daily plus L-carnitine 1 g m twice daily [Carnivita forte®, Eva Pharma, Egypt]. The treatment period was 6 months.

All patients were interviewed for complete history and clinical examination, which were carried out by a qualified physician from Internal Medicine Department, Tanta University Hospital. All patients were counseled to continue the same medications that they were receiving before the enrollment to this study. The addition of any antidiabetic drug other than the assigned glimepiride and L-carnitine was prohibited during the study period. All subjects were assessed monthly throughout the treatment period to assess adherence to the study protocol and to report any dropout or adverse events. BMI was calculated as $BMI = weight \div height^2$ [kg/m^2]. Systolic and diastolic blood pressures [SBP & DBP] were also evaluated at base line and after 3 and 6 months of treatment course.

2.3. Biochemical analysis

2.3.1. Samples collection

Venous blood samples (10 ml) were obtained from all the patients after a 10-h overnight fasting period before and after 3 and 6 months of treatment course. 2 ml of collected blood were added to tubes containing ethylenediaminetetraacetic acid (EDTA) for glycated hemoglobin [HbA1c %] assessment in the whole blood. The serum supernatant was separated immediately from the remaining 8 ml of blood by centrifugation for 15 min at 3000 rpm. Fresh serum was used in order to evaluate lipid profile. The remaining serum was divided, coded and stored at −80 °C for biochemical analysis.

2.3.2. Assay of blood glucose, HbA1c %, insulin and IRAPe

FBG and PPBG were measured using Accu-Chek Active meter. HbA1c % was assayed using Bio-Rad D-10™ Dual Program HbA2/F/HbA1c Calibrator based on chromatographic separation of the analytes by ion-exchange high-performance liquid chromatography (HPLC). Fasting plasma insulin [FPI] was assayed using Enzyme-Linked Immunosorbent Assay [ELISA] kits [Diagnostic Automation/Cortez Diagnostics, Inc., USA]. IRAPe was assayed using ELISA kits [Cloud-clone Crop, Uscn Life Science Inc., USA]. HOMA-IR index was also calculated [16].

2.3.3. Assay of visfatin and TNF-α

ELISA kits were used for assay of serum visfatin [RayBiotech, Inc., USA]. Quantitative detection of TNF-α was done using ELISA kits [TNF-α Platinum ELISA; eBioscience, USA].

2.3.4. Lipid panel

Fresh serum was used for assay of the lipid profile. Total cholesterol [TC] and triglycerides [TGs] were measured by enzymatic colorimetric methods using commercial kits [Spinreact, Spain]. High density lipoprotein [HDL-C] was determined by precipitation method using commercial kits [Spinreact, Spain]. Low-density lipoprotein cholesterol [LDL-C] was calculated using the Friedewald formula [17].

2.4. Statistical analysis

Data were tabulated and analyzed using SPSS statistical package version 23.0, IBM Corporation Software Group, USA. Data are expressed as the mean value (±standard deviation). One way analysis of variance test (one way ANOVA) followed by LSD post hoc

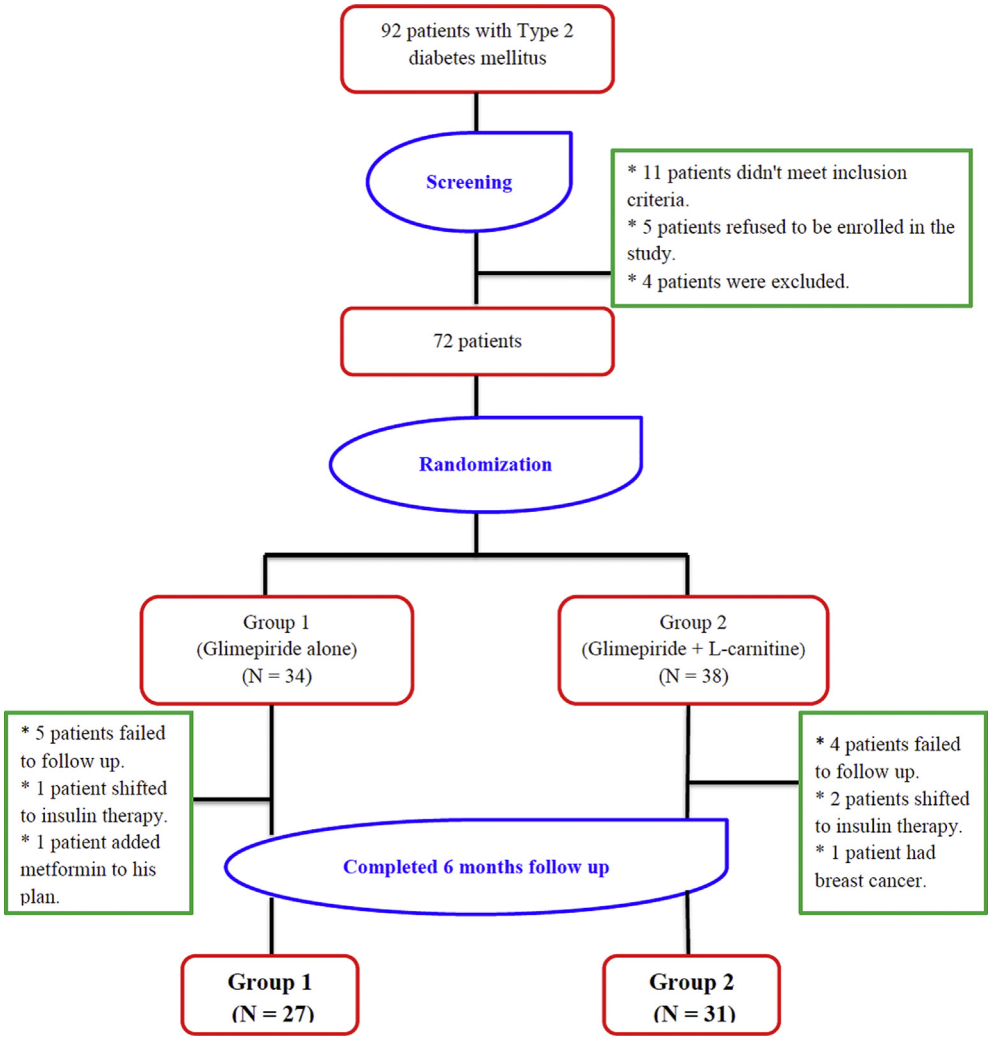

Figure 1. Study design.

test was used to assess any significant difference within each group between baseline values and after 3 and 6 months of treatment course. Unpaired *t*-test was used to assess any significant difference between the two groups. Pearson's correlation test was used to assess the correlation between measured parameters after the effective intervention. All probability values presented were two-tailed and $p \leq 0.05$ was considered statistically significant.

3. Results

3.1. Comparisons of baseline demographics and clinical data

Group 1 was aged 50.3 (±8.8) years (8 male: 19 female ratio) and group 2 was aged 50.9 (±8.6) years (11 male: 20 female ratio). There were no significant differences between the 2 groups in baseline demographics and clinical data (Tables 1 and 2**).**

3.2. Effect of treatments on anthropometric parameters and glycometabolic profile

A summary of the mean ± SD values of these variables for both groups at baseline, after 3 and 6 months of treatment period is presented in Table 1. Compared with baseline values, subjects of both groups showed no significant differences in BMI, SBP and DBP after 3 and 6 months of the evaluation period.

Comparing baseline values with those after 3 and 6 months of intervention period, group 2 revealed that there were significant decreases in FBG, PPBG, HbA1c, insulin and HOMA-IR while there was a significant increase in IRAPe. However, group 1 showed no significant changes in FBG, PPBG, HbA1c, insulin, HOMA-IR and IRAPe after 3 and 6 months of starting the study compared with their baseline values.

Comparing the two groups after 3 and 6 months of treatment, group 2 revealed significant decreases in FBG, PPBG, HbA1c, insulin and HOMA-IR with significant increase in IRAPe compared with group 1 as illustrated in Table 1.

3.3. Effect of treatments on inflammatory biomarkers and lipid profile

A summary of the mean ± SD values of these variables for both groups at baseline, after 3 and 6 months of treatment period is presented in Table 2.

Comparing baseline values with those after 3 and 6 months of intervention period, group 2 revealed that there were significant decreases in TNF-α, visfatin, TC, LDL-C and TGs with significant increase in HDL-C. However, group 1 showed no significant changes in TNF-α, visfatin, TC, LDL-C, HDL-C and TGs serum levels.

Table 1
Effect of glimepiride 2 mg daily versus glimepiride 2 mg daily + L-carnitine 2 g m daily on anthropometric data and glycometabolic profile of patients with T2DM on previous treatment with glimepiride 2 mg.

	Group 1	Group 2	P-value[$]
BMI (Kg/m^2)			
Before treatment	34.25 ± 5.6	34.46 ± 5.3	0.883
After 3 months	34.11 ± 6.1	33.98 ± 5.3	0.929
After 6 months	33.93 ± 5.5	33.7 ± 5.2	0.991
P-value[#]	a- 0.930	a- 0.719	
	b- 0.718	b- 0.571	
SBP (mmHg)			
Before treatment	127.04 ± 7.8	126.13 ± 11.7	0.734
After 3 months	127.78 ± 12.2	125.48 ± 12.3	0.481
After 6 months	128.89 ± 9.3	127.74 ± 13.8	0.717
P-value[#]	a- 0.785	a- 0.842	
	b- 0.495	b- 0.617	
DBP (mmHg)			
Before treatment	86.3 ± 7.4	85.48 ± 11.5	0.754
After 3 months	86.67 ± 9.2	84.19 ± 9.6	0.322
After 6 months	87.78 ± 6.9	85.16 ± 8.9	0.223
P-value[#]	a- 0.785	a- 0.842	
	b- 0.495	b- 0.617	
FBG (mg/dl)			
Before treatment	194.26 ± 28.3	195.42 ± 13.3	0.839
After 3 months	193.56 ± 28.4	186.16 ± 11.3	0.188
After 6 months	192.41 ± 27.4	179.61 ± 9.3	0.018
P-value[#]	a- 0.927	a- 0.002	
	b- 0.809	b- 0.000	
PPBG (mg/dl)			
Before treatment	263.63 ± 24.9	264.1 ± 7.7	0.921
After 3 months	258.11 ± 23.3	236.52 ± 11.4	0.000
After 6 months	256.07 ± 22.9	200.52 ± 10.2	0.000
P-value[#]	a- 0.396	a- 0.000	
	b- 0.246	b- 0.000	
HbA1c%			
Before treatment	9.84 ± 1.1	9.68 ± 0.9	0.538
After 3 months	9.63 ± 0.8	8.32 ± 0.9	0.000
After 6 months	9.5 ± 0.78	7.41 ± 0.5	0.000
P-value[#]	a- 0.396	a- 0.000	
	b- 0.179	b- 0.000	
Fasting blood insulin (μIU/ml)			
Before treatment	17.23 ± 4.7	17.83 ± 4.9	0.641
After 3 months	16.73 ± 4.6	14.06 ± 4.6	0.031
After 6 months	16.43 ± 4.6	9.98 ± 2.8	0.000
P-value[#]	a- 0.693	a- 0.001	
	b- 0.524	b- 0.000	
HOMA-IR			
Before treatment	8.28 ± 2.5	8.63 ± 2.6	0.607
After 3 months	8.02 ± 2.6	6.48 ± 2.2	0.017
After 6 months	7.8 ± 2.5	4.45 ± 1.3	0.000
P-value[#]	a- 0.699	a- 0.000	
	b- 0.505	b- 0.000	
IRAPe (ng/ml)			
Before treatment	90.62 ± 4.4	89.59 ± 3.7	0.333
After 3 months	91.41 ± 4.9	99.62 ± 9.4	0.000
After 6 months	91.88 ± 5.4	115.08 ± 15.3	0.000
P-value[#]	a- 0.561	a- 0.000	
	b- 0.352	b- 0.000	

Data are presented as mean ± standard deviation of mean.
BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose; PPBG: postprandial blood glucose; HbA1c: hemoglobin A1c; HOMA-IR: homeostasis model assessment of insulin resistance; IRAPe: extracellular part of insulin regulated amoinopeptidase.
P-value[$]: P-value between groups.
P-value[#]: P-value within groups.
a: P-value comparing after 3 months value with baseline value within the same group.
b: P-value comparing after 6 months value with baseline value within the same group.

Comparing the two groups after 3 and 6 months of treatment, group 2 revealed significant decreases in TNF-α, visfatin, TC, LDL-C and TGs with significant increase in HDL-C compared with group 1 as illustrated in Table 2.

Table 2
Effect of glimepiride 2 mg daily versus glimepiride 2 mg daily + L-carnitine 2 g m daily on inflammatory markers and lipid profile in patients with T2DM on previous treatment with glimepiride 2 mg.

	Group 1	Group 2	P-value[$]
TNF-α (pg/ml)			
Before treatment	4.74 ± 1.4	4.57 ± 1.3	0.645
After 3 months	4.81 ± 1.3	3.32 ± 1.1	0.000
After 6 months	5.44 ± 1.2	2.48 ± 0.79	0.000
P-value[#]	a- 0.84	a- 0.000	
	b- 0.052	b- 0.000	
Visfatin (ng/ml)			
Before treatment	95.9 ± 4.9	96.06 ± 3.4	0.881
After 3 months	96.07 ± 7.2	84.58 ± 3	0.000
After 6 months	95.67 ± 5.5	69.02 ± 2.9	0.000
P-value[#]	a- 0.918	a- 0.000	
	b- 0.886	b- 0.000	
TC (mg/dl)			
Before treatment	201.03 ± 29.7	200.56 ± 12.9	0.938
After 3 months	199.86 ± 24.07	177.67 ± 45.8	0.028
After 6 months	200.03 ± 17.9	171.16 ± 43.1	0.002
P-value[#]	a- 0.86	a- 0.017	
	b- 0.881	b- 0.002	
TGs (mg/dl)			
Before treatment	151.97 ± 23.4	150.81 ± 22.1	0.847
After 3 months	157.82 ± 25.8	128.13 ± 19.66	0.000
After 6 months	163.93 ± 34.25	123.32 ± 15.4	0.000
P-value[#]	a- 0.449	a- 0.000	
	b- 0.123	b- 0.000	
HDL-C (mg/dl)			
Before treatment	23.88 ± 4.3	22.51 ± 5.1	0.274
After 3 months	23.81 ± 3.94	32.52 ± 3.5	0.000
After 6 months	23.7 ± 3.9	42.61 ± 8.3	0.000
P-value[#]	a- 0.946	a- 0.000	
	b- 0.866	b- 0.000	
LDL-C (mg/dl)			
Before treatment	146.74 ± 31.6	147.88 ± 14.6	0.857
After 3 months	144.48 ± 24	119.53 ± 44.8	0.012
After 6 months	143.54 ± 19.9	103.88 ± 42.8	0.000
P-value[#]	a- 0.747	a- 0.003	
	b- 0.648	b- 0.000	

Data are presented as mean ± standard deviation of mean.
TNF-α: tumor necrosis factor-alpha, TC: total cholesterol, TGs: triglycerides, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol.
P-value[$]: P-value between groups.
P-value[#]: P-value within groups.
a: P-value comparing after 3 months value with baseline value within the same group.
b: P-value comparing after 6 months value with baseline value within the same group.

3.4. Correlation between measured parameters

A correlation study between measured parameters in group 2 after treatment period revealed significant negative correlations between IRAPe versus TC, LDL-C and fasting insulin as illustrated in Fig. 2.

3.5. Tolerability

L-carnitine was well tolerated in almost 100% of patients. Only one patient in group 2 reported mild insomnia that was tolerated to some extent and he completed taking L-carnitine for the whole study period. Patients were evaluated for tolerance at baseline and for the next 6 months every 4 weeks.

4. Discussion

Adipose tissue insulin resistance (Adipo-IR), that is, the impaired suppression of lipolysis in the presence of high insulin levels, has been associated with glucose intolerance, and elevated

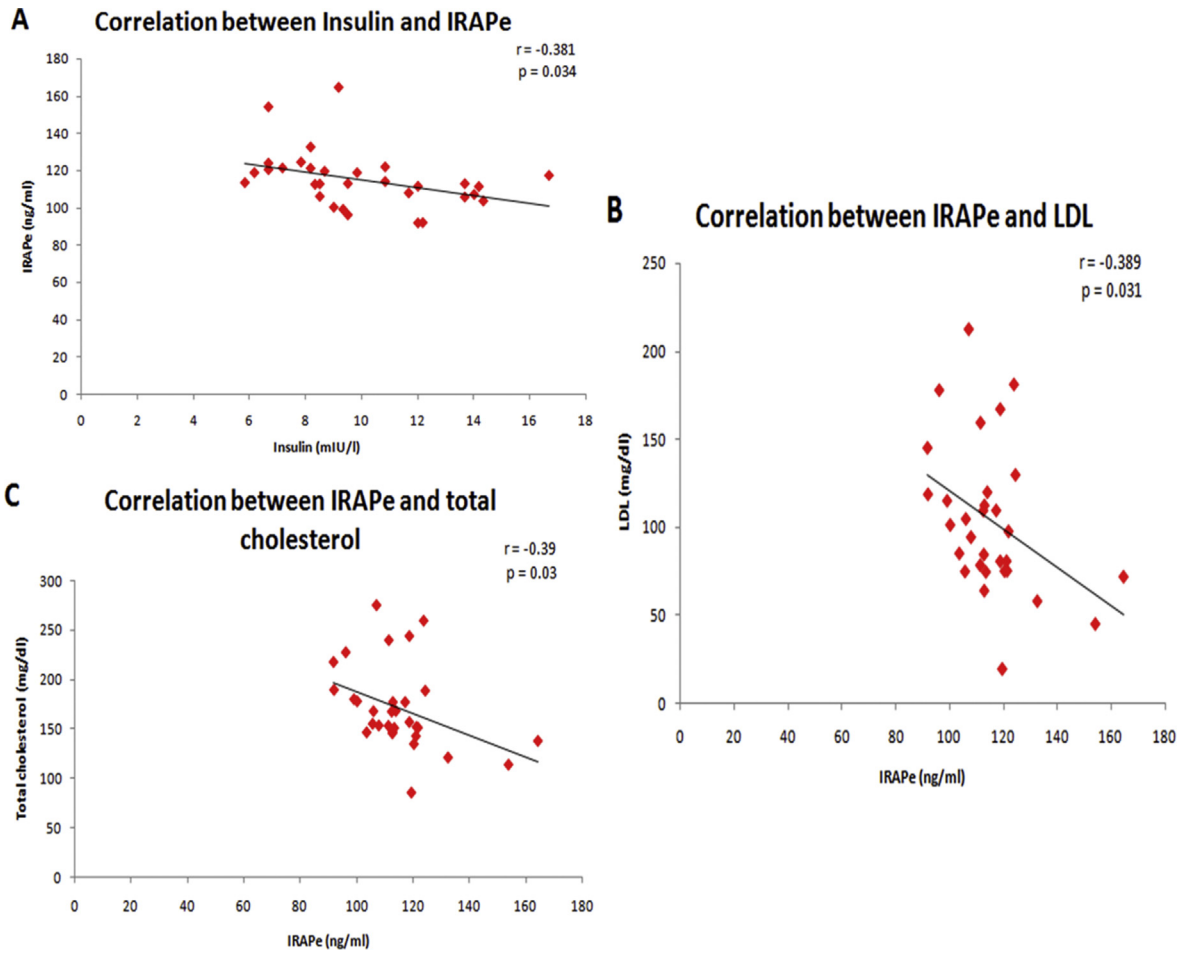

Figure 2. Correlation results (A) Negative correlation between fasting insulin and IRAPe (B) Negative correlation between IRAPe and LDL (C) Negative correlation between IRAPe and total cholesterol.

plasma FFA levels have been shown to impair muscle insulin signaling, promote hepatic gluconeogenesis, and impair glucose-stimulated insulin response [18]. Therefore, suppression of adipose tissue IR is considered an important line of T2DM treatment. The present study evaluates whether L-carnitine supplementation could have an impact on Adipo-IR in T2DM patients.

According to the best of our knowledge, this current study is considered the first study to evaluate the efficacy of L-carnitine on IR biomarkers, inflammatory adipokines, associated with IR, and lipid profile in T2DM patients on previous treatment with glimepiride monotherapy. According to literature review, the most widely used dose of L-carnitine in human studies was 2 g m/day, so this was the dose used in our study for group 2 [19–24].

Our study showed no significant reduction in BMI by twice daily administration of 1 g m L-carnitine in patients with T2DM receiving glimepiride after 6 months of treatment when compared with their baseline values and also when compared with group 1. In agreement with our results, the results of L-carnitine supplementation to T2DM patients on glyburide or metformin resulted in no significant changes in BMI [25]. However, results of oral carnitine supplementation in women with polycystic ovary syndrome (PCOS) revealed significant decrease in body weight and BMI. This contrariness may be attributed to the fact that women with PCOS who participated in this study were all overweight ($BMI = 29{\cdot}1 \pm 3{\cdot}4$) and no obesity was found in any of them [26].

Results of our study showed that 1 g m twice daily dose of L-carnitine in patients with T2DM receiving glimepiride resulted in no significant reduction in SBP and DBP. The results of a systemic review and meta-analysis of the clinical trials evaluating the metabolic effects of L-carnitine on T2DM support no changes in blood pressure following L-carnitine administration in analyzed clinical trials23. Results from spontaneously hypertensive rats treated with L-carnitine found significant decrease in SBP with less effect on DBP but no significant effects on blood pressure in normotensive rats [27].

Fasting blood glucose, post prandial blood glucose and HbA1c are the 1st and easy to measure parameters for glycemic control for T2DM patients [28]. Our study showed significant reduction in FBG, PPBG and HbA1c in group 2 compared with group 1. Derosa G. et al. agreed with our results regarding FBG, PPBG and HbA1c in two studies of L-carnitine effect on IR in obese diabetic patients when added to orlistat [20] and when added to sibutramin [21]. In addition, L-carnitine significantly reduced FBG when given to women with polycystic ovary syndrome [26]. Also, L-carnitine addition to glyburide or metformin in T2DM patients resulted in significant reduction in FBG without changes in HbA1c [25]. The better improvement of FBG, PPBG and HbA1c with L-carnitine is probably due to L-carnitine role in stimulating the activity of the pyruvate dehydrogenase complex by decreasing the intra-mitochondrial acetyl-CoA/CoA ratio through the trap-ping of acetyl groups leading to improvement of insulin effect on muscle and liver cells [21].

As a widely validated clinical and epidemiological tool for estimating IR and β-cell function, HOMA-IR index is derived from a mathematical assessment of the balance between hepatic glucose output and insulin secretion from fasting levels of glucose and insulin [29]. Our study showed a significant decrease of fasting insulin level and HOMA-IR index in group 2 compared with group 1 after treatment period. These results is consistent with the results obtained from women with polycystic ovary syndrome using oral carnitine [26], diabetic patients who received sibutramin and L-carnitine [21], obese diabetic patients who received orlistat and L-carnitine [20], non-alcoholic steatohepatitis patients on L-carnitine for 6 months [22] and also in diabetic subjects at increased cardiovascular risk receiving 1 g m L-carnitine twice daily [24].

For the first time in both animal and human studies, we evaluated the serum level of the extracellular part of insulin regulated aminopeptidase [IRAPe] in T2DM patients according to the treatment schedule. We wanted to focus on a new, direct and specific parameter for IR detection and monitoring. The diagnostic method based on the titration of circulating domain named IRAPe of the IRAP protein. Therefore, the results of our study which showed that the concentration of IRAPe is increased after 6 months treatment with L-carnitine confirms that L-carnitine improves insulin sensitivity in muscle and adipose tissue, allows GLUT4 translocation to plasma membrane, translocation of IRAP to plasma membrane and cleavage of its extracellular part in the systemic circulation. In addition, our results showed a negative correlation of IRAPe with insulin, LDL-cholesterol and total cholesterol. Therefore, IRAPe was confirmed to be a new, very important, easy to measure and specific marker for direct detection of IR.

TNF-α has been implicated as a causative factor in obesity-associated IR and the pathogenesis of T2DM [30]. Our results showed that treatment with glimepiride plus L-carnitine twice daily reverses the increase in TNF-α in those with T2DM. This effect is consistent with the results obtained from nonalcoholic steatohepatitis patients treated with L-carnitine [22], Coronary artery disease patients treated with L-carnitine [31], rats with doxorubicin induced cardiotoxicity reversed by L-carnitine administration [32].

Visfatin impacts insulin sensitivity as evidenced by observations that women with gestational diabetes mellitus having higher levels of visfatin show more severe IR than normal pregnant women [33]. Our study showed that L-carnitine addition to glimepiride in T2DM patients significantly reduced visfatin serum levels. This result is in agreement with decrease in visfatin serum level observed in obese diabetic patients treated with orlistat and L-carnitine [20] and diabetic patients treated with sibutramin and L-carnitine [21]. Study of the effect of L-carnitine supplementation on serum adipokines levels in obese T2DM women with hypocaloric diet revealed significant decrease in visfatin serum levels in L-carnitine group compared with control group [34].

Moreover, it is well known that amplification of fatty acid esterification pathway and triglycerides formation could be implicated in hepatic IR. Stored free fatty acid (FFA) can be mobilized from adipose tissue through lipolysis. This process is headed by glucagon, IR, sudden weight loss or starvation, glucocorticosteroids, leptin, and TNF-α [22]. In addition, elevated serum levels of LDL-C and TGs and low levels of HDL-C are strongly associated with increased risk for macrovascular events among patients with T2DM [35]. Our results showed that addition of L-carnitine to glimepiride significantly decreased TC, TGs and LDL-C serum levels and increased HDL-C. These observed results are consistent with patients with nonalcoholic steatohepatitis on L-carnitine [22] and patients with T2DM treated with L-carnitine plus simvastatin compared with simvastatin alone [36]. Also, the observed decrease in TC, LDL-C and TGs is consistent with the results achieved in both obese diabetic patients treated with orlistat and L-carnitine [20]and diabetic patients treated with sibutramin and L-carnitine [21].

Agreed with our results regarding TC and LDL are the results in coronary artery disease patients treated with L-carnitine [37]. L -carnitine binds to fatty acyl-CoA and regulates their transport into the mitochondrial matrix for β -oxidation. L -carnitine deficiency causes reduced oxidation of FFA and accumulation of long-chain fatty acyl-CoA and diabetic complications [22].

Regarding L-carnitine tolerance, our study showed that treatment with L-carnitine was remarkably well tolerated in all patients except one who suffered from mild insomnia which was tolerated. This is consistent with previous reports in other clinical settings [24,38,39].

5. Conclusion

L-carnitine addition to oral sulfonylureas resulted in better control on hyperglycemia, hyperinsulinemia, IR and hyperlipidemia in patients with T2DM who failed to achieve their therapeutic target by oral sulfonylureas therapy alone. Therefore, L-carnitine is a promising line as supplementation to anti-diabetic drugs to improve IR and diabetic control and delay or prevent diabetic complications.

6. Study limitations

The limitations of our study include the lack of using range of L-carnitine doses since Rhew and sachan reported a dose-dependent effect of L-carnitine in an experimental study [40]. Also lower carnitine dosages than 2 g were not tested in the previous studies therefore the possibility cannot be ruled out that lower dosages might have been sufficient to positively impact glucose tolerance. In addition, the number of patients investigated in our study is considered small.

Conflicts of interest

All authors declare that they have no conflicts of interest.

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