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Effects of *sitagliptin and sitagliptin* in combination with *omega-3* on newly diagnosed type 2 diabetic Iraqi patients

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ABSTRACT

Type 2 diabetes is a complex disease that is typically diagnosed in midlife and is characterized by progressive defects in insulin secretion and action. Objective: to compare the effects of dipeptidyl peptidase-4 (DDP-4) inhibitor sitagliptin and sitagliptin in combination with omega-3 on blood glucose level, serum insulin, high sensitivity C-reactive protein and oxidative stress state in newly diagnosed type 2 diabetic patients. Method: this is an open-label, randomized study carried out on 24 newly diagnosed type 2 diabetic patients. Patients were randomly divided into two groups and assigned for treatment with either sitagliptin (n=12) or sitagliptin in combination with omega-3 (n=12) for 2 months. The level of fasting blood glucose (FBG), post-prandial blood glucose (PPG), glycated hemoglobin (HbA1c), serum insulin, serum high sensitivity C-reactive protein (hs-CRP) and serum malondialdehyde (MDA) were calculated before and after one month and two months of treatment. Results: FBG, post prandial blood glucose and HbA1c significantly decreased in both treated groups after one month and two months of treatment. Serum insulin level increased non-significantly with sitagliptin and sitagliptin in combination with omega-3 after one and two months of treatment. Serum level of hs-CRP decreased significantly after two months of treatments with both sitagliptin and sitagliptin in combination with omega-3. The level of serum MDA decreased significantly in group treated with sitagliptin in combination with omega-3 after one month and two months of treatment, while insignificant decrease observed after one and two months in sitagliptin treated group. Conclusion: omega-3 has no significant effect on glycemic control and insulin secretion but has beneficial effect on oxidative stress state, sitagliptin executes anti-inflammatory effect in patients with type 2 diabetes.

Keywords: Type 2 DM, MDA, hs-CRP, sitagliptin, omega-3

INTRODUCTION

Diabetes is a problem with human body that causes blood glucose levels to rise higher than normal. Type 2 diabetes is the most common form of diabetes. Type 2 diabetes characterized by that the body does not use insulin properly. This is called insulin resistance. At first, the pancreas makes extra insulin to make up for it. But, over time it isn't able to keep up and can't make enough insulin to keep blood glucose at normal levels. type 2 diabetes seems to be associated with an increased risk of morbidity and mortality during the most productive years of life [1], such patients are at increased risk of developing macrovascular and microvascular complications. Whereas, patients with this form of diabetes may have insulin levels that appear normal or elevated, the higher blood glucose levels in these diabetic patients would be expected to result in even higher insulin values had their β-cell function been normal [2].

Chronic low-grade inflammation is one of the hallmarks of obesity and type 2 diabetes. C-reactive protein (CRP) is a sensitive physiological marker of subclinical systemic inflammation, produced by the liver during acute infection or inflammation and it is associated with hyperglycemia, insulin resistance, and overt type 2 diabetes [3].

Type 2 diabetes mellitus is associated with multiple metabolic derangements that result in the excessive production of reactive oxygen species and oxidative stress**.** Oxidative stress arises because of excessive production of reactive oxygen species (ROS) and impaired antioxidant defense mechanisms [4]. Multiple cellular studies have shown that under oxidative stress conditions, insulin signaling is impaired, resulting in insulin resistance of the cell [5].

Sitagliptin is a highly selective inhibitor of the enzyme dipeptidyl peptidase-4 (DPP-4), which metabolizes the naturally occurring incretin hormones glucagon-like peptide-1(GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) resulting in enhanced glucose-dependent insulin secretion from the pancreas and decreased hepatic glucose production. Since GLP-1 enhances insulin secretion in the presence of raised blood glucose levels, inhibiting DPP-4 activity will increase and prolong the action of GLP-1 by reducing its rate of inactivation in plasma [6].

Omega-3 polyunsaturated fatty acids (n-3 PUFA), include, alpha-linolenic acid (ALA, 18:3n-3) from plant sources, eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3) from seafood [7]. Omega-3 fatty acid from fish may play a role in glucose homeostasis, insulin action in peripheral tissues and pancreatic insulin secretion. Although the exact mechanisms are not well understood, the effects of omega-3

fatty acids on glucose metabolism could be partly mediated via alteration of both the phospholipid and protein components of cell membranes and regulation of peroxisome proliferator-activated receptor (PPAR) γ-dependent pathway [7].

In the present study, we sought to investigate the potential effects of omega-3 with sitagliptin on glycemic parameter, hs-CRP and lipid peroxidation in newly diagnosed type 2 diabetic Iraqi patients.

MATERIALS AND METHODS

Patient Selection

This study was carried out on twenty four patients (males and females) with type 2 diabetes mellitus; their ages range 40-55 years with newly diagnosed disease. They are randomly selected and assigned either to sitagliptin, or sitagliptin in combination with omega-3. They are maintained on dietary control program under the supervision of clinical nutrition specialist at National Diabetes Center for Treatment and Research/Al- Mustansiriyah University. All subjects were diagnosed with type 2 diabetes in accordance with the WHO diabetes diagnostic criteria of 1999 and had never been treated before.

METHOD

After 12 hours overnight fasting, blood samples were analyzed for FBG, HbA1c, fasting insulin, hs-CRP, MDA, and then a solid meal was given and the blood glucose level was measured after 2 hours to calculate post-prandial blood glucose. All subjects were orally administered with either sitagliptin 100 mg given as a single daily dose in a tablet dosage form or sitagliptin 100 mg given once daily and 1000 mg omega-3 given two times daily in a soft gel form. After one month and 2 months of the treatment, we measured the changes in these parameters. FBG measured by using ready-made kit based on enzymatic colorimetric method, post prandial blood glucose measured by using blood glucose monitoring system (Accu-chek active roche). HbA1c determined by high- performance liquid chromatography (HPLC)(Bio-Rad Variant, U.S.A). Serum insulin was measured by using ready-made kit. The insulin kit is a solid phase enzyme-linked immunosorbent assay (ELISA) based on the sandwich principle. Serum hs-CRP determined by readymade kit. The hs-CRP (ELISA) is based on the principle of a solid phase enzyme-linked immunosorbent assay. Serum MDA was measured by using ready-made kit (ELISA). This assay employs the competitive inhibition enzyme immunoassay technique.

Statistical Analysis

Data are expressed as means ± SD. Statistics were performed using SPSS (version 19). Differences from baseline were assessed by the paired Student's *t* test. A P-value of <0.05 was considered significant.

RESULTS

Patients

24 diabetic patients randomly allocated into two groups, first group includes: 12 patients treated with sitagliptin and second group includes: 12 patients treated with sitagliptin in combination with omega-3. All patients received the required doses of the study drug. There were no apparent differences between the two groups with respect to demographic and baseline characteristics (Table 1).

Efficacy

The changes from baseline to the end of the study are summarized in Table 2. FBG, PPG, HbA1c were significantly ($p<0.05$) decreased in both groups after one month and two months of treatment. Treatment with sitagliptin in combination with omega-3 showed no significant difference when compared with sitagliptin treated group ($p>0.05$) whether after one month or two months of treatment, with respect to the change in FBG, PPG, or HbA1c.Treatment with metformin alone or in
combination with omega-3 produced slightly but no significant decrease in serum insulin level ($p>0.05$), with no significant difference between these two groups after one month and two months of treatment ($p>0.05$). Treatment with metformin in combination with omega-3 produced significant decrease in serum MDA level compared to baseline values ($p<0.05$) after one month and two months of treatment, and significant reduction observed in metformin treated group after two months of treatment ($p<0.05$), meanwhile insignificant decrease observed after one month of treatment with metformin ($p>0.05$). Treatment with metformin in combination with omega-3 showed significant difference when compared with metformin treated groups after one month and two months of treatment ($p<0.05$).

Table 1: Patient characteristic at baseline

Variable/time point	Sitagliptin	Sitagliptin+omega-3
FPG (mg/dl)		
Baseline	221.75±10.47	219.25±14.89
After 1 month	192.08±8.79*[a]	189.25±10.07*[a]
Change from baseline	13.37%	13.68%
After 2 months	157.42±12.04*[a]	152.83±9.97*[a]
Change from baseline	29.01%	30.29%
PPG (mg/dl)		
Baseline	280.75±13.57	276.42±16.59
After 1 month	251.67±16.90*[a]	247.42±17.21*[a]
Change from baseline	10.35%	10.49%
After 2 months	217.83±17.38*[a]	209.67±12.93*[a]
Change from baseline	22.41%	24.14%
HbA1c (%)		
Baseline	9.75±1.69	9.82±1.18
After 1 month	8.68±1.14*[a]	8.55±1.12*[a]
Change from baseline	10.97%	12.93%
After 2 months	7.74±1.50*[a]	7.65±1.33*[a]
Change from baseline	20.61%	22.09%
Insulin (µIU/ml)		
Baseline	16.62±2.86	16.43±2.51
After 1 month	17.32±1.21[a]	17.03±1.88[a]
Change from baseline	4.21%	3.65%
After 2 months	17.77± 1.81[a]	17.45±1.37[a]
Change from baseline	6.91%	6.20%
Hs-CRP(mg/L)		
Baseline	5.66± 2.90	4.58± 2.42
After 1 month	4.91± 2.42[a]	3.75± 2.26[a]
Change from baseline	13.25%	18.12%
After 2 months	4.45± 2.68*[a]	3.00± 1.20*[a]
Change from baseline	21.37%	34.49%
MDA(*M*mol/L)		
Baseline	5.15±1.37	4.16±1.04
After 1 month	4.92±1.60[a]	3.45±0.96*[b]
Change from baseline	4.46%	17.06%
After 2 months	4.64±1.79[a]	2.70±1.62*[b]
Change from baseline	9.90%	35.09%

Table 2: Changes from baseline and after 1month and 2 months in glycemia, serum hs-CRP and MDA

Characteristic	Sitagliptin	Sitagliptin+omega-3
N=24	12	12
Age; years	40-55	40-55
FSG (mg/dl)	221.75±10.47	219.25±14.89
PPG (mg/dl)	280.75±13.57	276.42±16.59
HbA1c %	9.75±1.69	9.82±1.18
Insulin (µIU/ml)	16.62±2.86	16.43±2.51
Hs-CRP(mg/L)	5.66± 2.90	4.58± 2.42
MDA (µmol/l)	5.15±1.37	4.16±1.04

Data are given as mean ± SD for baseline and end of study values for change from baseline; *significantly different compared to baseline level (P<0.05); values with non-identical superscripts (a,b) among different groups are considered significantly different (P<0.05).

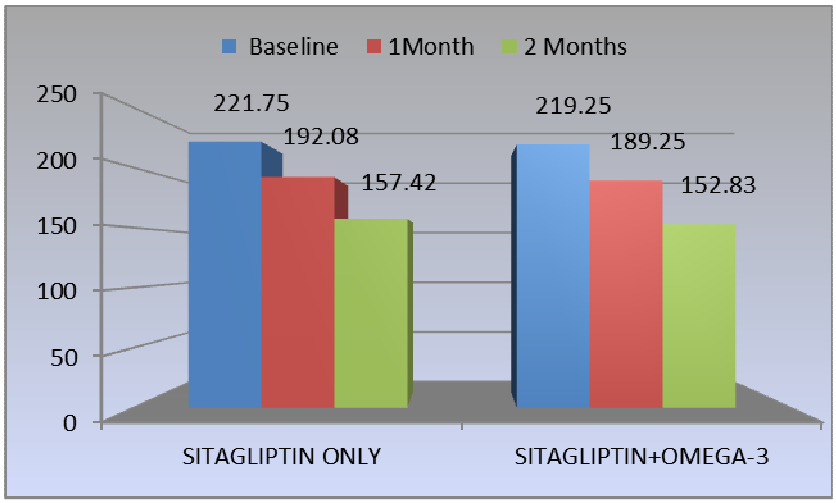

Figure1. Effects of sitagliptin and sitagliptin in combination with omega-3 on fasting blood glucose in type 2 diabetic patients.

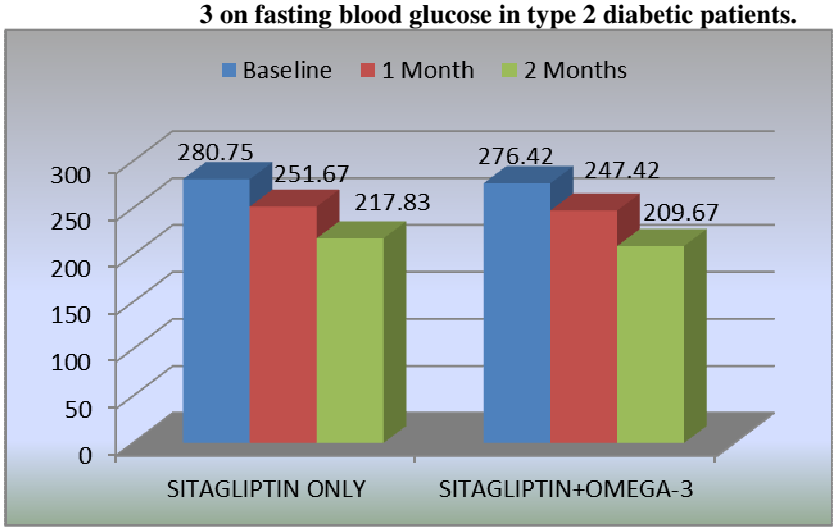

Figure 2. Effects of sitagliptin and sitagliptin in combination with omega-3 on postprandial blood glucose level in type 2 diabetic patients.

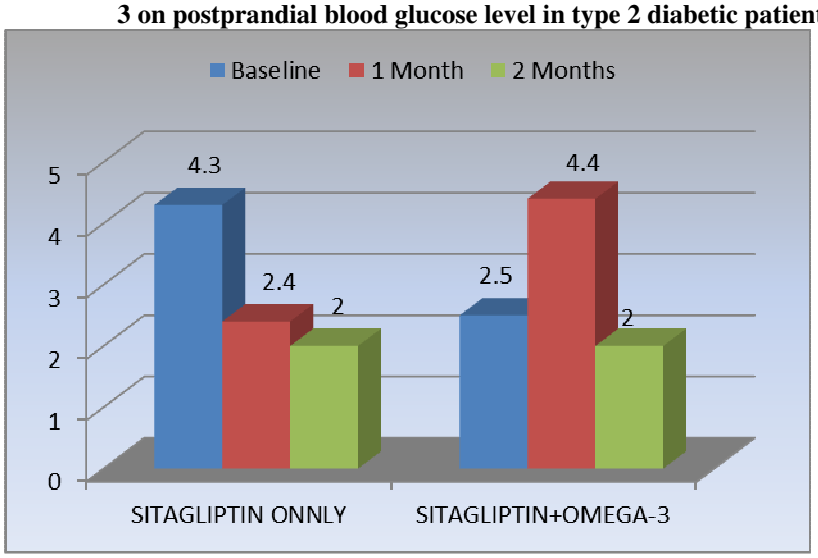

Figure 3. Effects of sitagliptin and sitagliptin in combination with omega-3 on glycated hemoglobin in type 2 diabetic patients.

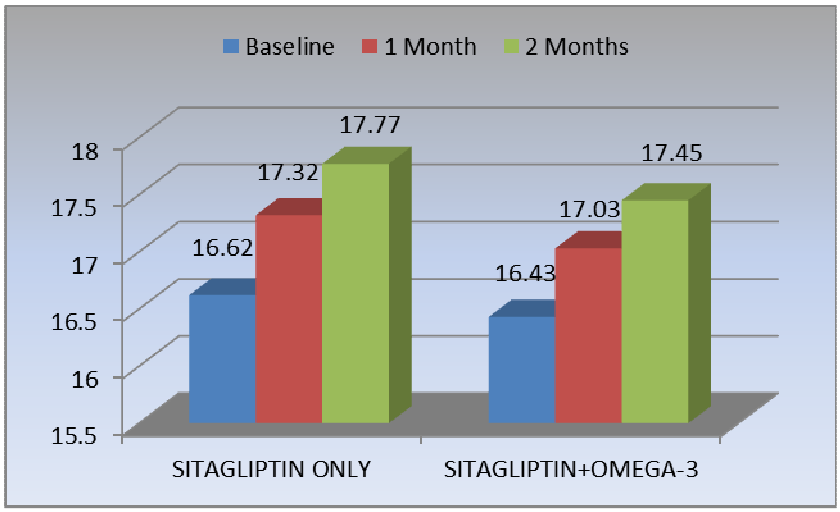

Figure 4. Effects of metformin and metformin in combination with omega-3 on serum insulin level in type 2 diabetic patients.

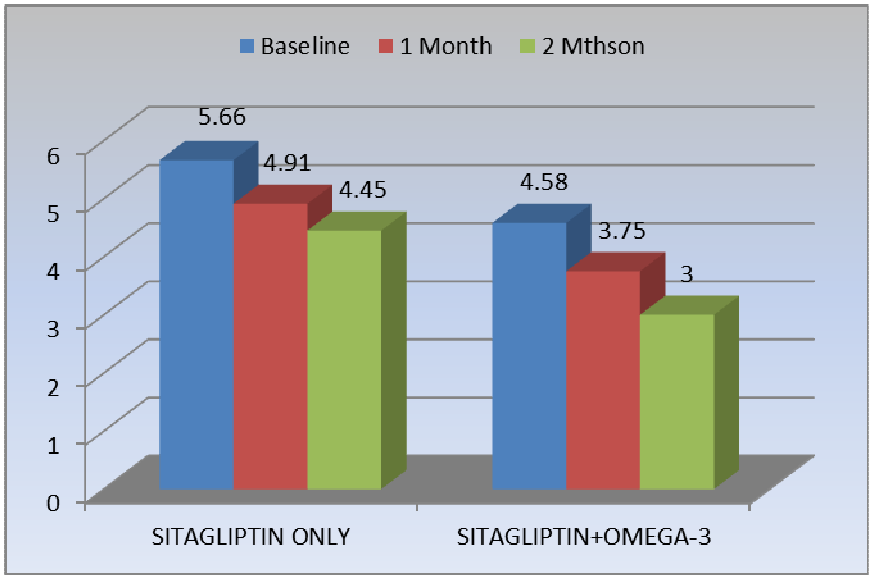

Figure 5. Effects of sitagliptin and sitagliptin in combination with omega-3 on serum insulin level in type 2 diabetic patients.

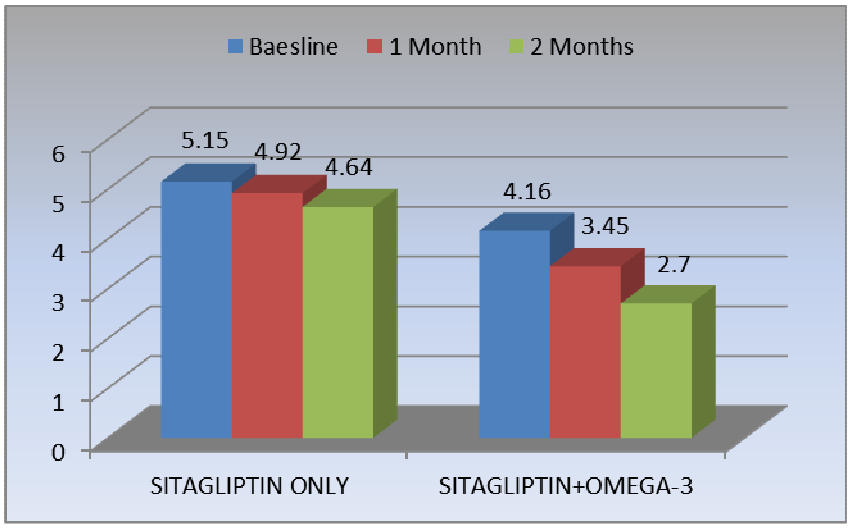

Figure 6. Effects of sitagliptin and sitagliptin in combination with omega-3 on serum MDA level in type 2 diabetic patients.

Discussion

Accelerated endogenous glucose production is thought to be a key factor in the development of fasting hyperglycemia in type 2 diabetes [8]. In the present study, the results regarding blood glucose and HbA1c indicated that there was a significant improvement in blood glucose levels and HbA1c after one month and two months of treatment with sitagliptin and sitagliptin plus omega-3, these results in agreement with previous studies [9,10]. Incretin hormones are rapidly degraded and removed from circulation by the enzyme DPP-4 [11,12]. Therefore, there is considerable interest in enhancing incretin action for treatment of type 2 diabetes. Sitagliptin, a selective DPP-4 inhibitor, reduces both fasting and post-prandial plasma glucose presumably by inhibiting the inactivation of GLP-1 and GIP, thereby prolonging their duration of action on pancreatic islets [13,14]. The results of the present study showed that the combination of omega-3 with sitagliptin has no statistically significant effect on glycemic control this is supported by reports of a non-significant change in fasting glucose after consumption of omega-3 fatty acids or fish oils [15]. Holman *et al*. found that administration of fish oil supplementation at relatively lower doses (1 to 2 g/day) for a period from 2-32 weeks may not have detrimental effect on glycemic status [16]. Shidfar *et al*. also reported that there was no effect on glycemic control or HbA1c with (2g/day) supplementation of omega-3 in patients with type 2 diabetes for 10 weeks and attribute disparate findings to differences in diabetes medications, the presence of insulin resistance, hypertension, and obesity [17]. In contrast, the other reports found a significant increase in HbA1c and fasting glucose in type 2 diabetes patients after a fish diet [16] or omega-3 fatty acids [18].

In type 2 diabetes, defects in insulin secretion, tissue insensitivity to insulin and abnormalities in adipose tissue metabolism have been well documented [19]. Moreover, the difference in severity or secondary consequences of type 2 diabetes might result in different degrees of insulin concentration and resistance.

In the present study, the results showed that treatment with sitagliptin led to a non- significant increase compared with baseline values in fasting serum insulin level in agreement with previous studies [20,21], this consistent with its mechanism of action that is highly selective DPP-4 inhibitors enhance levels of active incretin hormones, gut-derived peptides that are released into the circulation after ingestion of a meal [22]. GLP-1 and GIP account for the majority of incretin action [(23)]. In the presence of elevated glucose concentrations, GLP-1 and GIP increase insulin release and GLP-1 lowers glucagon secretion, thereby decreasing the post-meal rise in glucose concentration and reducing fasting glucose concentrations [23]. The results of the present study showed that there was no difference in fasting serum insulin level between metformin and metformin plus omega-3 and between sitagliptin and sitagliptin plus omega- 3 treated groups. This agrees with other studies that approved omega-3 supplementation has no effect on fasting serum insulin level in type 2 diabetes patients [24]. Kristian *et al*. found glucose utilization was not affected by omega-3 fatty acids; neither was insulin secretion in patients with type 2 diabetes [25].

Treatment with sitagliptin produced significant reduction in hs-CRP level after two months; the results of the sitagliptin treatment were in agreement with previous studies [26,27]. Derosa *et al.* found that both metformin and sitagliptin treatment produced significant decrease in serum level of hs-C reactive protein with no difference between both agents [28]. Activation of the sympathetic system has numerous implications, including

surges of heart rate, blood pressure but also pro-inflammatory and pro-coagulant effects, the anti-inflammatory effect of DPP-4 inhibitor may be partially explained by lack of repetitive sympathetic activations[29]. The results of the present study showed that sitagliptin plus omega-3 produced non-significant changes after one month of treatment, but decrease significantly after two months, with non-significant differences between sitagliptin and sitagliptin plus omega-3 treated groups, this mean that the addition of omega-3 supplementation produced non-significant reduction in hs-CRP level and the final effect may be due to combination effect of these two drugs. Our results in agreement with other several intervention studies that showed no significant effect of omega-3 supplementation on CRP for populations with type 2 diabetes [30,31]. C-reactive protein levels were not affected by omega-3 supplementation (3 g/day for eight weeks) in a randomized control trial for persons with type 2 diabetes [31]. Other study found no significant changes in CRP after two months supplementation with omega-3 for individuals with type 2 diabetes [30]. The mechanisms by which omega-3 fatty acids decreased CRP may be through the inactivation of TLR4, this receptor generates downstream signaling cascades that lead to NF-κB activation and expression of COX-2, inflammatory cytokines and adhesion molecules. Another possibility is through the farnesoid X receptor (FXR), omega-3 fatty acids are ligands for FXR. Farnesoid X receptor is a member of the nuclear hormone receptor super family that functions as a ligand-activated transcription factor. When activated, FXR can down-regulate the expression of IL-1 and IL-6 which are regulated the synthesis of CRP [32].

Oxidative stress is proposed to be an early event in the pathology of DM and may influence the onset and progression of late complications [33]. The present study showed non-significant reduction in serum MDA level after one month and two months of sitagliptin treatment consistent with previous studies [34]. Liliana Ferreira *et al*. observed that there was no significant difference in serum MDA level after sitagliptin treatment for 6weeks. On the contrary, they observed a significant reduction of pancreas and heart MDA in the sitagliptin-treated Zucker diabetic fatty rats [35].The possible explanation is through the activities of the superoxidase dismutase, glutathione peroxidase, glutathione S transferase were increased in sitagliptin treatment [36]. Our results showed that treatment with sitagliptin plus omega-3 resulted in significant reduction in serum level of MDA after one month and two months of treatment , with significant difference between sitagliptin and sitagliptin plus omega-3 treated groups. This confirms thatomega-3 fatty acid supplementation led to a significantly lower the level of MDA when compared with the baseline values, these results consistent with previous studies [17]. Other studies showed no effect of omega-3 on serum level of MDA after two months in type 2 diabetic patients [30], Brita *et al*. observed that there were no significant changes in serum MDA level after fishy diet rich in omega-3 fatty acids for 3.5 weeks in patient with type 2 diabetes [37].

Potential mechanisms for the decrease in MDA may be related to the assembly of omega-3 fatty acids in membrane lipids and lipoproteins making the double bonds less available for free radical attack, inhibition of the pro-oxidantenzyme phospholipase A2 and stimulation of anti-oxidant enzymes [38,39]. In this regard, omega-3 fatty acids upregulate gene expression of antioxidant enzymes and down regulate genes associated with production of reactive oxygen species [40].

CONCLUSION

- Omega-3 has no significant effect on glycemic control and insulin secretion but has beneficial effect on oxidative stress state.
- Sitagliptin executes anti-inflammatory effect in patients with type 2 diabetes.

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