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RESEARCH ARTICLE

CARDIOPROTECTIVE EFFECT OF SITAGLIPTIN IN TYPE 2 DIABETES MELLITUS

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ABSTRACT

Background: Recently, The dipeptidyl peptidase-4 (DPP-4) inhibitor, sitagliptin contributes to improvement of postprandial hyperglycemia and prevents risk of hypoglycemia through increasing the level of glucagon-like polypeptide (GLP-1) as new therapeutic target and novel pathway for correcting impaired glucose homeostasis in type 2 diabetes mellitus (T2DM).

Aim: This study was conducted to assess the cardioprotective effect of sitagliptin on cardiovascular complications in Egyptian male patients with T2DM.

Methods: The study enrolled 12 apparently healthy control subjects, 20 diabetic patients having no cardiovascular complications on 1 gm metformin orally daily for 3 months and 25 diabetic patients having cardiovascular complications on 1 gm metformin orally daily for 3 months then adding 100 mg Sitagliptin orally daily for 3 months. All subjects involved in this study are males having index of central obesity(ICO) < 0.55

The following parameters involved in this study are fasting plasma glucose (FPG), Glycated hemoglobin (HbA_{1C}), insulin, proinsulin, proinsulin/insulin (PI/IN) ratio, hemostasis model assessment of insulin resistance (HOMA-IR), total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL), high density lipoprotein (HDL), very low density lipoprotein (VLDL), oxidized low density lipoprotein (Ox-LDL), risk ratio 1&2 (RR1)(RR2), creatine kinase MB (CK-MB), lactate dehydrogenase (LDH), plasminogen activator inhibitor-1 (PAI-1), cardiac troponin-I (cTnI), and homocysteine

Results: Sitagliptin significantly reduced FPG, HbA_{1C}, insulin, proinsulin, proinsulin/insulin ratio, HOMA-IR index, TC, TG, LDL, VLDL, OX-LDL, RR 1, RR 2, CK-MB, LDH, PAI-1, cTnI AND homocysteine compared to non Sitagliptin group, whereas HDL was significantly increased in sitagliptin group compared to non Sitagliptin group.

Conclusion: Sitagliptin is effective not only on glycaemic control and insulin sensitivity but, also it ameliorates dyslipidemia, endothelial dysfunction and cardiovascular complications and in T2DM.

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INTRODUCTION

Diabetes mellitus (DM) is an increasingly prevalent condition worldwide The international diabetes federation predicts that the number of people living with diabetes will rise from 366 million in 2011 to 552 million by 2031 (Suseelal *et al.,* 2016). Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease attributed to genetic and environmental susceptibility, Characterized by progressive deterioration of β-cell function, side by side with increasing insulin resistance in peripheral tissues (in both the liver and the skeletal muscle) (Hu *et al.,* 2011). Endothelial dysfunction is a key event in the pathogenesis of diabetic micro and macrovasculopathy and has gained great focusing in the study of diabetes associated cardiovascular complications (Tabit *et al.,* 2010). The hallmark of endothelial dysfunction is the impaired nitric oxide (NO) bioavailability due to reduced production by NO synthase, increased breakdown by reactive oxygen species (ROS), or both (Addabbo *et al.,* 2009). The contributing factors causing endothelial dysfunction in diabetes include metabolic abnormalities such as hyperglycemia, excess liberation of free fatty acids (FFAs) and insulin resistance (IR) (Zhang *et al.,* 2012). Several pharmacological agents that target either the relative insulin deficiency or insulin resistance in patients with T2DM are available. However, these agents have several limitations, such as less optimal control of postprandial hyperglycemia, increased risk of hypoglycemia, weight gain, gastrointestinal side effects and oedema (Rosenstock and Zinman, 2007).Researches have focused on identifying new

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therapeutic targets and novel pathways for correcting impaired glucose homeostasis (Campbell, 2007). Looking to the future, incretin mimetic may come to the fore as prime agents because they can reduce weight and glycaemia with little significant hypoglycemia, thereby making tight glucose control easier to achieve. GLP-1, a prominent active compound of the incretin family, improves many processes in pancreatic islet. It potentiates insulin synthesis and secretion, inhibits glucagon secretion, increases islet cell proliferation, decreases β-cell apoptosis, and also slows down gastric emptying (Maiztegui *et al.,* 2011). Recently, DPP-4 inhibitors; prevent the inactivation of incretins and increasing the endogenous active incretin levels. Sitagliptin was the first DPP-4 inhibitor approved by the food and drug administration (FDA). It is a potent, highly selective DPP-4 inhibitor, had a neutral effect on body weight, and contributes to suppression of postprandial hyperglycemia and to diminish risk of hypoglycemia (Suzuki *et al.,* 2013). It leads to increases in insulin and C-peptide, reduction in glucagon, improvement in oral glucose tolerance and improvement in β-cell function and/or neogenesis (Raz *et al.,* 2006). The aim of this study was to examine if sitagliptin has positive effect in protection of diabetic patients against the cardiovascular complication of diabetes in Egyptian patients having cardiovascular complications.

Subjects and Methods

This study was performed on 57 adult males. They were attended for sampling between October 2012 and January 2013 and classified into 3 groups:

Normal group

Twelve adult normal males were recruited from the community through announcement, having ICO< 0.55 and served as normal healthy control. Their mean of age was (46.8 ± 1.29) years. They were apparently healthy, did not take any current medication or dietary supplements and had stable weight in the last 3 months before the study.

Non Cardiovascular complicated T2DM group

Twenty adult diabetic males have no cardiovascular complications and having ICO < 0.55. Their mean age was (44.8 ± 1.14) years and mean duration of diabetes of (6.98 ± 0.66) years, were receiving oral metformin 1 gm daily for 3 months.

Cardiovascular complicated T2DM group

Twenty five adult males and having ICO < 0.55 Their mean age was (43.8 ± 1.22) years and mean duration of diabetes of (6.98 ± 0.66) years were receiving oral metformin 1 gm daily for 3 months then received sitagliptin 100mg daily in addition to metformin 1gm daily for 3 months. Blood samples were taken from this group before and after treatment with sitagliptin. All diabetic patients had stable metabolic control in the previous 6 months. They were classified as diabetics if they stated that they had diabetes and were on treatment. The diagnosis was confirmed by FPG and HbA_{1c} determination. A detailed medical history and drug treatment(s) were collected from all subjects. They were excluded if they had clinically significant hepatic, renal, neurological, endocrinal or other systemic diseases including malignancies. Also, patients suffer from major cardiovascular events and smokers were excluded.

All the subjects were submitted to kidney and liver function tests and informed about the purpose, nature and potential risks of the study.

Blood sampling and anthropometric parameters for normal healthy control group and diabetic patients were done at the sampling room, AL Hussein hospital, faculty of medicine, AL-Azhar University, Cairo, Egypt.

Venous blood samples were withdrawn by BD vacutainer system from the antecubital vein after an overnight fasting in the sitting position after 10 minutes rest for determination of the following parameters;

- FPG, serum TC, HDL-C, TG and LDH by spectrophotometry.
- Serum CK-MB that was determined by spectrophotometry kinetic technique.
- Serum LDL-C, Ox-LDL, VLDL-C, cTn-1, insulin, proinsulin and Plasma PAI-1that was determined by Enzyme Linked Immunosorbent Assay ELISA technique**.**
- Serum homocysteine andHbA_{1C}that was determined by high performance liquid chromatography (HPLC) technique.
- Using pre-made kit and obeying the manufacturer procedure for each parameter.
- HOMA-IR was calculated with the formula: HOMA-IR = (Fasting insulin in mU/l× fasting plasma glucose in mg/dl)/ (405) (Matthews *et al.,* 1985).
- Lipoprotein ratios were calculated as follows:
  - Risk ratio 1 (RR 1) = LDL/HDL ratio(Millán *et al.,* 2009)
  - Risk ratio 2 (RR 2) = TG/HDL ratio(da Luz *et al.,* 2008)

Statistical analysis

All data were expressed as mean ± standard error of mean ($\bar{\chi}$ ± SEM). Descriptive statistics were performed using Microsoft Excel 2010. All analysis and graphics were performed using Graph pad prism (windows version 7; Graph pad software 2007). Difference between means were assessed by one way analysis of variance (ANOVA) followed by tukey's procedure. Differences were considered statistically significant at $P < 0.05$

RESULTS

Table 1. Mean ± standard error of mean ($\bar{\chi}$ ± SEM) of FPG,HbA_{1C}, TC, TG, LDL, HDL, VLDL, RR1 and RR2

	Control n=12	Diabetic control n=20	Sitagliptin before n=25	Sitagliptin after n=25
FPG	90.58±1.928	245.8±6.074[a]	243.9±7.454[a]	184.8±3.733[a,b,c]
HbA_{1C}	4.542±0.068	8.405±0.082[a]	8.316±0.087[a]	6.532±0.093[a,b,c]
TC	142.9±2.241	174.7± 4.584[a]	207.7±3.469[a,b]	169.7±3.088[a,c]
TG	119.8±2.614	153.6±3.153[a]	161.4±3.174[a]	122.9±2.764[b,c]
LDL	57.25±2.965	103.9±4.432[a]	136.4±4.021[a,b]	89.16±3.393[a,b,c]
HDL	61.50±1.607	45.60±1.424[a]	39.12±1.399[a,b]	56.28±1.187[b,c]
VLDL	23.98±0.522	31.80±0.794[a]	32.26±0.643[a]	24.64±0.541[b,c]
RR 1	2.343±0.078	3.874±0.127[a]	5.464±0.206[a,b]	3.049±0.083[a,b,c]
RR 2	0.951±0.068	2.186±0.105[a]	3.616±0.184[a,b]	1.608±0.077[a,b,c]

a: significant from control group.
b: significant from diabetic control group.
c: significant from sitagliptin before group.

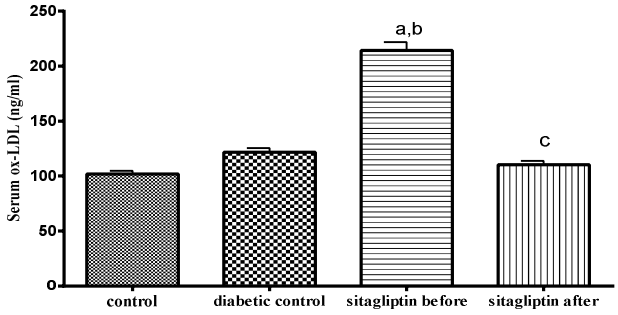

Figure 1. Serum ox-LDL ng/ml in studied groups

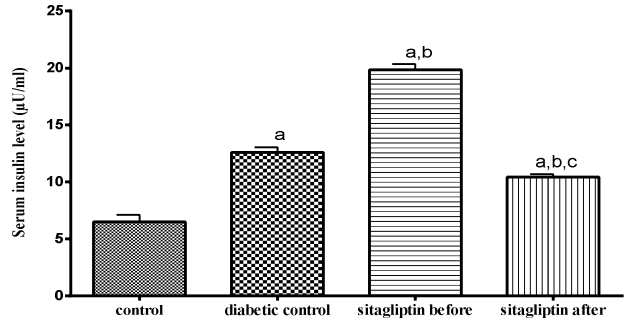

Figure 2. Serum insulin (µU/ml) level in studied groups

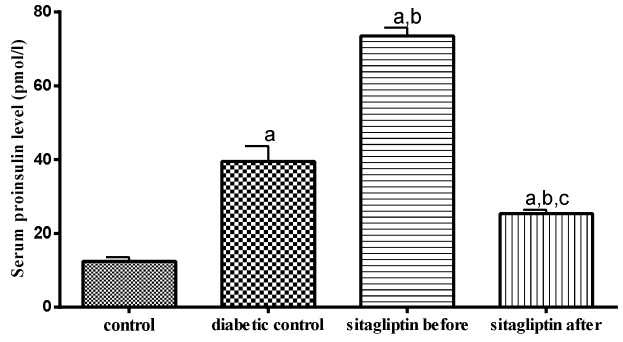

Figure 3. Serumproinsulin level pmol/l in studied groups

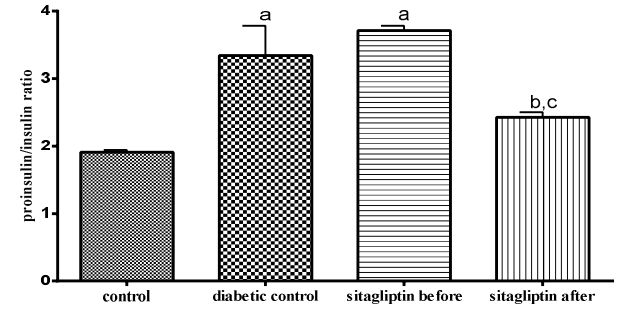

Figure 4. Proinsulin/insulin ratio in studied groups

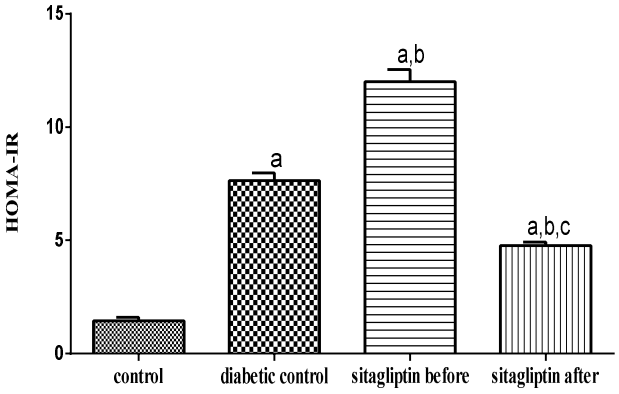

Figure 5. HOMA-IR index in studied groups

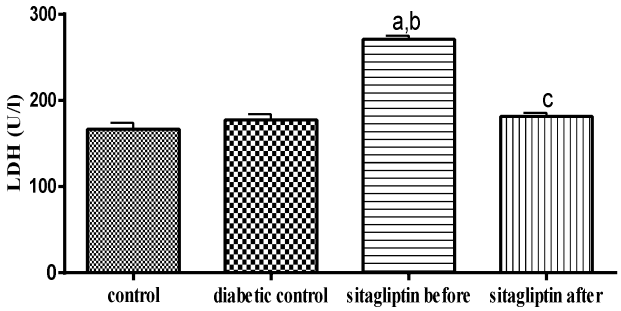

Figure 6. Serum LDH (U/l) in studied groups

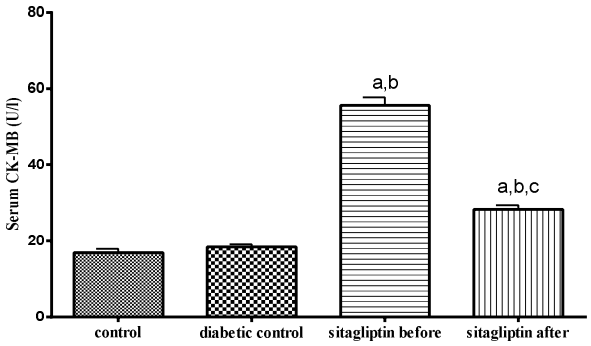

Figure 7. Serum CK-MB (U/l) in studied groups

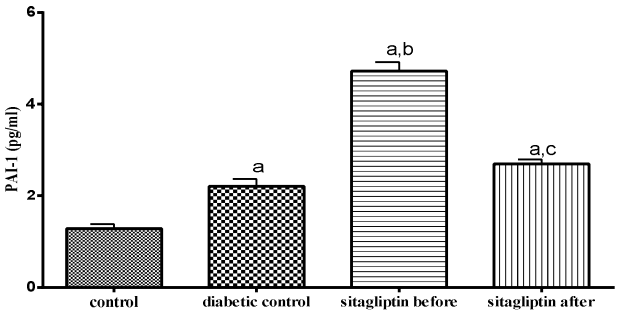

Figure 8. PAI-1 (pg/ml) in studied groups

DISCUSSION

In our study both FPG level and HbA_{1c} % level was lower in sitagliptin treated group compared to other diabetic groups. these results were in agreement with (Sakura *et al.,* 2016). Regarding effect of sitagliptin on lipid profile our data revealed that; there is a significant decrease in VLDL,LDL,TC and TG level in sitagliptin treated group compared to diabetic control and sitagliptin before groups while there is an increase in HDL in agreement of the study of (Fan *et al.,* 2016).

Together, these findings revealed that sitagliptin had additional specific benefits provided potential for cardiovascular prevention. Considering PAI-1 there was a significant decrease in sitagliptin treated group as compared to non-Sitagliptin group which is in agreement with (Tremblay *et al.,* 2014). This result could be explained by inhibition of DPP-4 with sitagliptin is effective in reducing low-grade inflammation and endothelial dysfunction in patients with type 2 diabetes, mainly through increased GLP-1 levels and global improvement of the glucose-insulin homeostasis (Tremblay *et al.,* 2014).

Table 2. $\bar{\chi}$ ± SEM ofox-LDL, insulin, proinsulin, proinsulin/insulin ratio and HOMA-IR

	Control n=12	Diabetic control n=20	Sitagliptin before n=25	Sitagliptin after n=25
ox-LDL	101.9±2.917	121.8 ± 3.823	214.4±7.546[a,b]	110.4±3.380[c]
Insulin	6.508±0.603	12.58±0.464[a]	19.84±0.512[a,b]	10.45±0.223[a,b,c]
Proinsulin	12.42±1.168	39.54±4.125[a]	73.50±2.227[a,b]	25.38±1.010[a,b,c]
PI/IN ratio	1.909±0.032	3.341±0.440[a]	3.710±0.070[a]	2.427±0.074[b,c]
HOMA-IR	1.454±0.140	7.642±0.335[a]	12.00±0.539[a,b]	4.777±0.150[a,b,c]

Table 3. $\bar{\chi}$ ± SEM of LDH, CK-MB, PAI-1 cTnI and homocysteine

	Control n=12	Diabetic control n=20	Sitagliptin before n=25	Sitagliptin after n=25
LDH	166.8±7.293	177.4±6.993	271.2±3.888[a,b]	181.7±3.784[c]
CK-MB	16.92±0.957	18.38±0.728	55.60±2.093[a,b]	28.28±1.087[a,b,c]
PAI-1	1.288±0.095	2.205±0.158[a]	4.716±0.198[a,b]	2.696±0.094[a,c]
cTnI	0.250±0.090	0.744±0.095[a]	2.273±0.090[a,b]	0.858±0.104[a,c]
Homocysteine	5.692±0.460	6.450±0.372	20.72±0.798[a,b]	10.94±0.434[a,b,c]

Regarding LDH and CK-MB in agreement with (Chang *et al.,* 2013, Al-Rasheed *et al.,* 2016b) there was a significant decrease in LDH and CK-MB in sitagliptin treated group as compared to non-sitagliptin one, this result could be explained by its potential to resist against oxidative stress through increasing the levels of super oxide dismutase and glutathione peroxidase (GSH-Px) and decreased the level of malondialdehyde (MDA) in myocardial tissues.

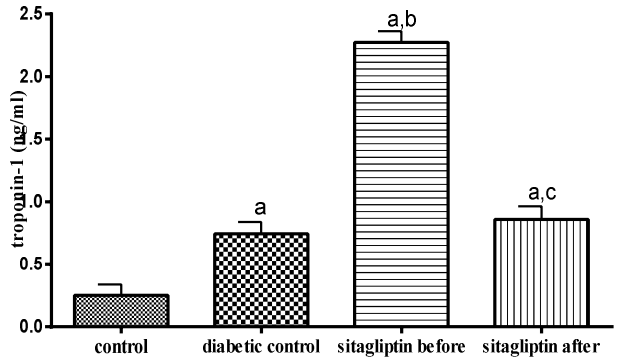

Figure 9. Serum cTn-I (ng/ml) in studied groups

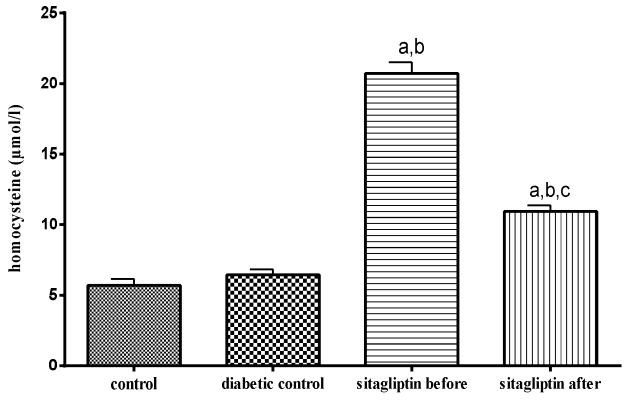

Figure 10. Serum homocysteine (µmol/l) in studied groups

As we all know, SOD and GSH-Px are key antioxidant enzymes, which constitute first line cellular defense against oxidative injury. MDA is one of the products of oxidative stress, which reflects the damage of cell caused by oxidative stress (Chang *et al.,* 2013). Considering HOMA-IR in agreement with (Barnard *et al.,* 2010, Derosa *et al.,* 2014b) there was a significant improvement in HOMA-IR in Sitagliptin treated group as compared to non-Sitagliptin treated groups, this result could be suggest the benefit use of Sitagliptin in improvement of insulin resistance. Regarding ox-LDL in agreement with (Makdissi *et al.,* 2012, Satoh-Asahara *et al.,* 2013) and disagreement with (Tremblay *et al.,* 2014) there was a significant decrease in ox-LDL level in sitagliptin treated group as compared to non sitagliptin treated groups. This beneficial effect of sitagliptin on both inflammation and endothelial function are most likely mediated by an elevation in plasma GLP-1 levels and global improvement of the glucose-insulin hemostasis (Satoh-Asahara *et al.,* 2013).

The discrepancy of these studies may be due to the different study design and the shorter period of treatment with sitagliptin (Tremblay *et al.,* 2014). Regarding cardiovascular risk indices (RR1) and (RR2) and cTn-1 in agreement with (Al-Rasheed *et al.,* 2016a) there was a significant decrease in these cardiovascular risk indices. Regarding fasting serum insulin level, fasting serum proinsulin level and fasting proinsulin-to-insulin ratio in agreement with (Kim, 2015) (Derosa *et al.,* 2014a)there is a great significance of all diabetic groups from control group and there is a significance of sitagliptin before group from diabetic control group while there was a significant decrease in serum insulin level after treatment with sitagliptin comparing to other diabetic groups.

Regarding serum homocysteine level, there is a significance decrease in plasma homocysteine level in Sitagliptin treated group compared to the groups not treated with Sitagliptin which may explained by the improvement in IR , many studies have been suggested the direct association between IR and hyperhomcystienemia in humans (Fonseca *et al.,* 1998, Giltay *et al.,* 1998, Abbasi *et al.,* 1999, Gallistl *et al.,* 2000, Emoto *et al.,* 2001), improvement of IR by Sitagliptin lead to improvement in hyperhomcystienemia.

Conclusion

From the previous results the following aspect could be concluded: Sitagliptin which is selective DPP-4 inhibitor has antidiabetic effect and cardioprotective effect, also improve IR.

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