GSC Biological and Pharmaceutical Sciences

eISSN: 2581-3250 CODEN (USA): GBPSC2

Cross Ref DOI: 10.30574/gscbps

Journal homepage: https://gsconlinepress.com/journals/gscbps/

(RESEARCH ARTICLE)

Check for updates

Clinical assessment of saxagliptin therapy in diabetic patients with corpulence

Feryal Hashim Rada *

Department of Pharmaceutics, College of Pharmacy, Al-Nahrain University, Iraq.

GSC Biological and Pharmaceutical Sciences, 2022, 21(01), 109–115

Publication history: Received on 07 September 2022; revised on 10 October 2022; accepted on 13 October 2022

Article DOI: https://doi.org/10.30574/gscbps.2022.21.1.0389

Abstract

Saxagliptin is an oral hypoglycemic agent act by inhibiting dipeptidyl peptidase 4 and prescribed for the management of diabetes alone or with other anti-diabetic drug. The idea of the research is to clarify the impact of saxagliptin treatment on adipokines of corpulence in diabetic patients. Of seventy-three diabetic patients with corpulence (43 males and 30 females), aging (45± 7) years of either sex were appointed to take Saxagliptin (5 mg/day) for 5 months periods. Data were pooled on fasting state prior treatment and after five months treatment. The variables involved body mass index, HOMA -IR, blood levels of lipid profile, glucose, insulin, visfatin, adiponectin, and leptin. The results of this treatment approach yielded high significant reduction in the sign of body mass ($P<0.0002$), and in the blood levels of hemoglobin A1c percentage ($P<0.0002$), lipid profiles ($P<0.005$), fasting glucose ($P<0.0002$), leptin ($P<0.01$), and visfatin ($P<0.005$). Contrarily, a high significant elevation ($P<0.005$) in adiponectin levels was reported. Eventually, Saxagliptin treatment modulate glycemic index and lessen patient's weight. As well, attenuation in insulin resistance index and in blood levels of leptin and visfatin were achieved. Likewise, the blood level of adiponectin was ameliorated.

Keywords: Adiponectin; Glycemic index; Leptin; Visfatin

1. Introduction

Corpulence is a state if continued without control or treatment may guide to many metabolic diseases such as cardiovascular disease and diabetes. The defect in releasing of insulin hormone from B-cell of pancreas with or without presence of external hindrances to the action of insulin, lead to hyperglycemia and cause chronic disease called type 2 diabetes mellitus [1].

Many classes of antidiabetic drugs with different mechanism used to resolve the hyperglycemic state and /or to enhance the release of insulin from pancreas thereafter to obtain a normal glycemic blood level and to lessen the intricateness of diabetes. Dipeptidyl peptidase 4 (DPP-4) inhibitor is a category of drugs that used for controlling diabetes by increasing the half-life of incretin hormones, glucagon-like peptide 1 (GLP-1) and glucose dependent insulin tropic peptide, by hindering their catabolic enzyme and thereby escalating glucose dependent insulin discharge and de-escalating glucagon discharge [2].

During the digestion of food that contain glucose, the endocrine cell of small intestine will liberate the GLP-1 hormone that arrive the pancreas by the circulation and binds to its specific receptor on the B-cell causing secretion of insulin in a level that is relevant to glucose concentration in the intestine. The half-life of this hormone is short about two minutes; thence it is dissociated by peptidase enzyme called dipeptidyl peptidase 4 [3].

Many studies found that GLP-1 has numerous properties like control of blood glycaemia, slowing the movement of the stomach to minimize the feeding and feeling of surfeit, and conserved effect on heart, blood vessels, and kidneys [4].

* Corresponding author Feryal Hashim Rada
Department of Pharmaceutics, College of Pharmacy, Al-Nahrain University, Iraq.

Adipocyte can release DPP-4 with a higher level in obese subjects than in lean subjects. Therefore, high level of circulating DPP-4 may participate to obesity and existence of insulin receptor resistance [5]. Presently, the DPP-4 inhibitors drugs that include alogliptin, sitagliptin, linagliptin, vildagliptin, Saxagliptin are clinically used for the treatment of diabetes and amending the glycemic blood level of those patients [3].

Interestingly, the adverse effects of antidiabetic drug like hypoglycemia, over weight and swelling have seen with sulfonylurea, thiazolidinediones [6] and insulin. Conversely, DPP-4 inhibitors drugs have no relevancy to these adverse effects [7]. Saxagliptin (onglyza, astrazeneca) is one of the DPP-4 inhibitors drugs that delay the catabolism of GLP-1hormone resulting in enhancing glucose mediated insulin discharge. It certified to treat diabetes in assistant to dietary and act as mono therapy [8] or as co therapy to metformine [9]. Saxagliptin exhibit weight unchanging and less incidence of hypoglycemia, unless added to insulin or Sulfonylurea [10].

Leptin is adipokine produced by adipocyte and it is directly relevance to insulin hindrances, fatness, and cardiovascular diseases [11]. Adiponectin is adipokine also produced by adipocyte and it has a role in enhancing the sensitivity of insulin, inflammation antagonist, inhibit the apoptosis of many cells, and activate energy disbursement so diminish the weight [12,13].

Nicotinamide phosphoribosyl transferase (Nampt) or visfatin is adipokine that secreted by adipocyte and expressed vastly in the internal fat. This expression with high plasma level of visfatin was comparable with fatness. Many properties of visfatin reported. Enzymatically, visfatin has an essential action in the forming of nicotinamide mononucleotide, insulin imitative activity of visfatin by connecting to its specific binding site on insulin receptor, encouraging growth of B-cell, and precluding fall off (apoptosis) of neutrophil [14].

The intend of this research is to scrutinize the clinical impacts of Saxagliptin (5 mg/day) for five months treatment in corpulent patients with type 2 diabetes on adipokines of corpulence by measuring various clinical bioassays that concerned with glycemic control and corpulence. These assays include glycemic index HbA1c % which is used to check the state of oxidative stress [15] ,insulin resistance (HOMA-IR), lipid profile, adipocyte cytokine (leptin, adiponectin, visfatin).

2. Material and methods

2.1. Study design and patients' selection

This research conducted at Al yarmouk hospital in Iraq and included seventy- three corpulent patients (43 males and 30 females), aging (45± 7) years of either sex, with type two of diabetes.

All diabetic patients participated in this study were haphazardly selected and were scrutinized through documented their medical histories and routine clinical laboratory tests. The diagnosis of diabetic patients constructed on norms of World Health Organization of blood glucose level during fasting and after meal.

Preclusion criteria eliminated the diabetic patients with other complication such as ketoacidosis, coma with non-ketotic hyperosmolar, abnormality of the liver function and /or kidney function and cardiovascular impairment. Written and oral permissions are given to each suitable participant to join in this study. The protocol of this study adapted with the proper strategies of the Helsinki pronouncement and accepted by the institution's ethics committee.

2.2. Data collection and laboratory measurements

At baseline (before treatment), and after five months of the treatment with Saxagliptin (AstraZeneca)^{R} in a dose of 5 mg daily, the blood samples were drawn after 12-hours overnight fasting then analyzed and evaluated . During the periods of the study, all adverse events stated to appraise adequacy and acceptability of this treatment.

We computed the Body mass index by portioning the patient's weight in kilograms to the patient's height in squared meters. Congruously to the manufacturer, enzyme-linked immuno-sorbent assays (ELISA) kit used to scrutinize the serum levels of leptin, adiponectin, and visfatin. While serum levels of total cholesterol, triglyceride, glucose and glycated hemoglobin percentage (HbA1c %) assayed by using Photometric Colorimetric methods. Friedewald's formula [16] used to obtain low-density lipoprotein cholesterol (LDL-C). Homeostasis model assessment (HOMA) rule used to obtain Insulin resistance (IR) [17]:

[Fasting glucose (mmol/L) x Fasting insulin (μU/mL)] / 22.5

2.3. Statistical analyses

Results documented as mean ± standard deviation with the interval of confidence equal to 95%. Continuous variables compared by using paired student's *t*-test. Most of statistical auditions are two-tailed and *P* values of < 0.05 account as cut-off point for significance. All statistical analyses executed by using series SPSS version 18 and Microsoft Excel.

3. Results

In (Table 1), the outline of demographic features, laboratory analyses, and statistical consequences illustrated for the studied patients. Most adverse events are simple or temperate in nature, therefore it does not discontinuing the study.

Obviously, a highly significant diminished (P<0.0002) in the sign of body mass (BMI) noted after five months treatment with Saxagliptin (5 mg daily) as matched to the baseline level (Table 1). Moreover, this treatment high significantly suppressed the levels of plasma glucose (P<0.0002), hemoglobin A1C percentage (HbA1c %) (P<0.0002) and HOMA-IR (P<0.005) as matched to their baseline mean level. In contrast to prior treatment (Table 1), inferences of lipid profiles that involved blood levels of cholesterol, low-density lipoprotein (LDL) and triglyceride revealed high significant decreased (P<0.005) after five months treatment with Saxagliptin (5 mg daily).

Concerning the alteration in the levels of adipocyte cytokines after five months treatment with Saxagliptin (5 mg daily), there were least noteworthy decline (P<0.01) in mean plasma levels of leptin and high noteworthy decline (P<0.005) in mean plasma levels of visfatin (Table 1). These changes equal to (0.82, and 0.73) folded respectively as compared to their baseline mean levels (Fig. 1).Contrariwise, as analogous to before treatment, the plasma level of adiponectin was more superior (P<0.005) with intake of Saxagliptin (5 mg daily) for five months treatment (Table 1) and it was seem (1.268) folded elevated as elucidated in (Fig.1).

Figure 2 plotted the imperative power analysis for the minimum detectable effect of Saxagliptin (5 mg daily) for five months treatment on plasma levels of leptin, adiponectin, visfatin . There were 80 % possibilities that the treatment with Saxagliptin (5 mg daily) for five months initiated the recognition of 3.3 ng/mL (16.3%) decreases in mean plasma level of leptin, 2.84 µg/mL (20.6%) increases in mean plasma level of adiponectin, and 5.6 ng /mL (21.27%) decreases in mean plasma level of visfatin.

Table 1 Demographic and clinical bioassays data for patients through the period of the study.

Variables	Baseline (prior treatment)	After 5 months with Saxagliptin (5 mg/day)
Number (n)	73	73
Gender (males/females)	43 / 30	43 / 30
Age (years)	45 ± 7	45 ± 7
BMI (kg/m^2)	29.4 ±2.4	27.6 ± 1.8 ***
HOMA-IR	4.2 ± 2.1	3.3± 1.7 **
HbA1c%	8.3 ±1.25	7.6 ± 0.87 ***
Glucose (mg/dL)	133.2 ±15.7	120.3 ± 13.6 ***
Total Cholesterol (mg/dL)	252.3± 13.4	246.6 ± 10.5 **
Triglyceride (mg/dL)	183.5± 15.6	175.8± 13.4 **
LDL-C (mg/dL)	165.34 ± 11.4	160.2± 10.2 **
Leptin (ng/mL)	20.2± 8.3	16.5 ± 7.6 *
Adiponectin (µg/mL)	13.8 ± 6.3	17.5 ± 7.4 **
Visfatin (ng/ml)	26.4 ± 14.3	19.3 ±12.8 **

List of data offered as mean ± SD for continuous variable, (*) least significant difference (LSD) P<0.01 vs. baseline, (**) high significant difference P<0.005 vs. baseline, (***) high significant difference P<0.0002 vs. baseline.

Abbreviations

- BMI: body mass index
- HbA1c%: hemoglobin A1c percentage
- HOMA-IR: homeostasis model assessment-insulin resistance
- LDL-C: low- density lipoprotein cholesterol

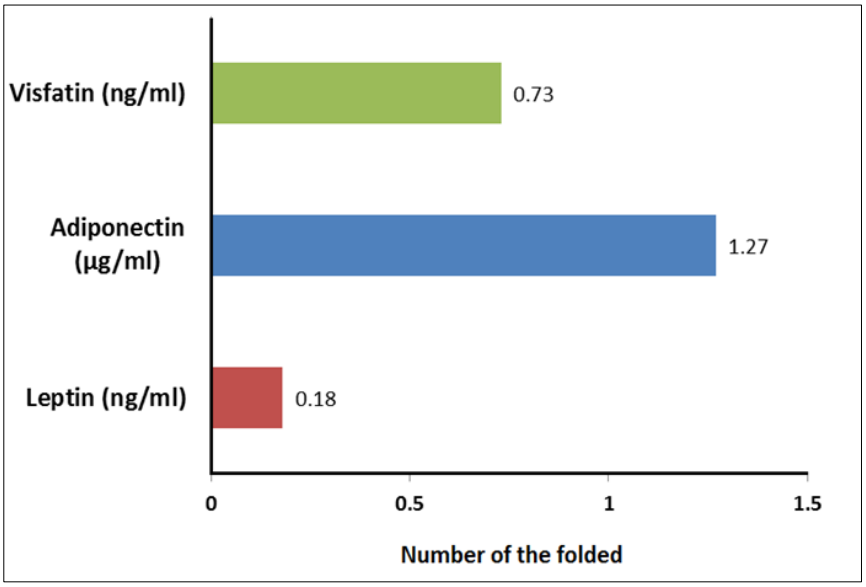

Figure 1 The number of the folded changes for adipokines after five months treatment with Saxagliptin (5 mg daily) in diabetic patients with corpulence

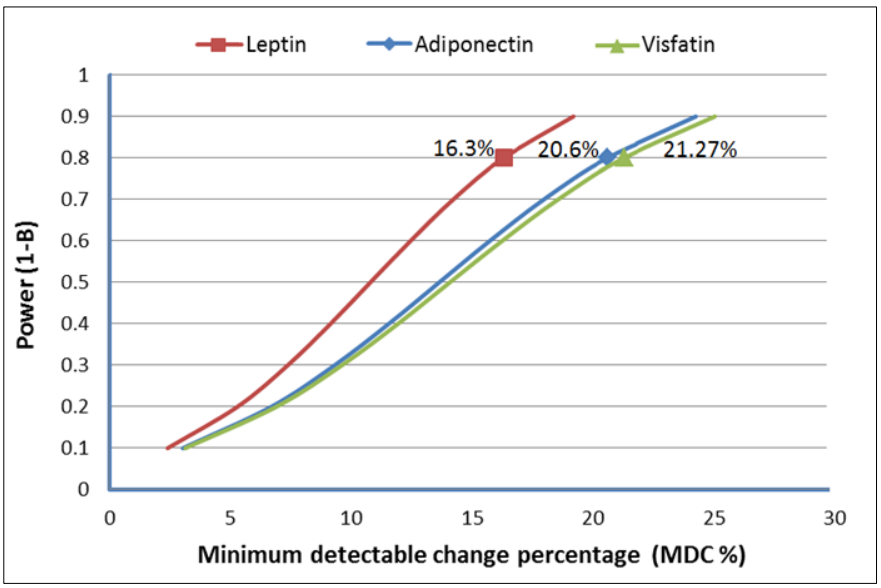

Figure 2 Power analysis for the minimum detectable effects of saxaglipitin (5mg daily) for five months treatment on blood levels of leptin, adiponectin, and visfatin

4. Discussion

The selection of suitable drug for the treatment of diabetes mellitus with less adverse effect is a difficile task. However, in this study with the use of Saxagliptin drug (5 mg/day) for five months treatment the level of glycemic index was more improved and the index of insulin resistance was more suppressed in those treated patients. These results were compatible with other study [18].

Generally, DPP4 inhibitors drugs based on glucose – dependent action of GLP-1 hormone which has the capability to reduce the blood level of glucose only in hyperglycemic state. Therefore, in this study and other study, the reported incidence of hypoglycemia is low with the use of DPP4 inhibitors drugs [19].Although, the patients were more acceptable to this treatment but some minor side effect implied as headache, nausea, nasopharyngitis and skin sensitivity. Likewise, these events were agreeable with other study [20] .

Many complications followed diabetes as gradual deterioration of B-cell function and elevated incidence of insulin resistance. However, with the use of Saxagliptin, these complications may be minimized [21]. Clinical practice guidelines advised the use of DPP4 inhibitors drugs as an initial step of therapy for diabetic patients who disallowed to take metformine [22].

Regarding the effect of sex on Saxagliptin response, no association has been found in this study between sex and Saxagliptin response on HbA1c %, this result was aligned with other study [23]. Contrarily, other study found that men exhibit higher response to DPP4 inhibitors than women do [24]. Although Incretin-analogue class of drugs are more effective in lessening BMI and glycemia than DPP4 inhibitors ,but the low adverse events that seen with DPP4 inhibitors and minor cost make DPP4 inhibitors drugs more usable by diabetic patients [25].

As noted in this study the BMI values were significantly decrease with Saxagliptin treatment for five months and this result adjoined with another research [26] and unlike another research that documented the use of DPP4, inhibitors not effect on the weight of the patients [19].

The impact of Saxagliptin treatment on lipid profile yield significant dropping in serum levels of triglyceride, cholesterol, and LDL and those current results consistent with other study that stated a prominent declined in the serum level of LDL with use of DPP4 inhibitors for 24 weeks treatment [26]. Oppositely, other study found that Saxagliptin treatment for 4 months causes lessening in serum level of triglyceride and non-significant lessening in serum levels of cholesterol and LDL [27].

Concerning the effect of Saxagliptin treatment on adipokine cytokines that involve leptin, adiponectin and visfatin, the statistical results of current study reveal lowering blood levels of leptin and visfatin and elevating blood level of adiponectin. Those results are consistent with another study [28]. Visfatin is another adipokine secreted by adipocyte and linked with fatness, therefore it is level increased in corpulent subject or patients as noted in this study and erstwhile [28] .Unlike other study that confirm decreased blood level of visfatin in corpulent subjects [29].

5. Conclusion

Saxagliptin is a well-tolerated drug used for controlling diabetes by reducing glycemia and insulin resistance. As well, the drug may amend adipokines levels of corpulence by decreasing blood levels of leptin (P<0.01) and visfatin (P<0.005) and increasing blood level of adiponectin (P<0.005).

Compliance with ethical standards

Acknowledgments

The author would like to impart their sincere thanks to the president of Al-Nahrain University/ Iraq, for the strengthening to execute this research.

Disclosure of conflict of interest

No conflicts of interests to assert.

Statement of ethical approval

The protocol of this study accepted by Al-Nahrain University /College of Pharmacy ethics committee.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

References

[1] Rada FH. Association of lipid fractions levels with cardiovascular disease. Asian Journal of Pharmaceutical and Clinical Research.2017,10 (3):180–182.

[2] Nauck MA.Incretin-based therapies for type 2 diabetes mellitus: properties, functions, and clinical implications. American Journal of Medicine.2011,124:S3–S18.

[3] Opinto G, Natalicchio A, and Marchetti P.Physiology of incretins and loss of incretin effect in type 2 diabetes and obesity. Archives of Physiology and Biochemistry.2013, 119:170–178.

[4] Koole C, Pabreja K, Savage EE, Wootten D, Furness SGB, Miller LJ, et al. Recent advances in understanding GLP-1R (glucagon-like peptide-1 receptor) function. Biochemical Society Transactions.2013,41(1):172–179.

[5] Sell H,Blüher M,Klöting N,Schlich R,Willems M,Ruppe F, et al. Adipose dipeptidyl peptidase-4 and obesity: correlation with insulin resistance and depot specific release from adipose tissue in vivo and in vitro. Diabetes Care.2013,36 (12):4083–4090.

[6] Rada FH. Peroxisome proliferator- activated receptors family overview. European Journal of Pharmaceutical and Medical Research.2019,6(1):167–170.

[7] Inzucchi SE,Matthews DR, Bergenstal RM, Buse JB, Peters AL, Wender R, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care.2012 , 35(6):1364–1379.

[8] Frederich R, McNeill R, Berglind N, Fleming D, Chen R.The efficacy and safety of the dipeptidyl peptidase-4 inhibitor Saxagliptin in treatment naive patients with type 2 diabetes mellitus: a randomized controlled trial. Diabetology and Metabolic Syndrome.2012, 4(1):36.

[9] DeFronzo R A, Hissa MN, Garber AJ, Gross JL,Duan RY, Ravichandran S, et al. The efficacy and safety of Saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. Diabetes Care. 2009,32(9) :1649–1655.

[10] Barnett AH,Charbonnel B,Donovan M,Fleming D.Effect of Saxagliptin as add-on therapy in patients with poorly controlled type 2 diabetes on insulin alone or insulin combined with metformin. Current Medical Research and Opinion.2012, 28:513–523.

[11] Rada FH. Adequacy of Olmesartan monotherapy versus cotherapy in patients with essential hypertension. International Journal of Research in Pharmaceutical Sciences. 2020,11(2):1649–1654.

[12] Turer AT,Scherer PE.Adiponectin: mechanistic in sights and clinical implications. Diabetologia.2012,55:2319–2326.

[13] Rada FH. Effect of Angiotensin II receptor blocker treatment on adipokine of corpulence. Biomedical and Pharmacology Journal.2020,13(2): 957–963.

[14] Yoshino J,Mills KF,Yoon MJ,Imai S.Nicotinamide mononucleotide ,a key NAD (þ) intermediate, treats the pathophysiology of diet- and age induced diabetes in mice. Cell Metabolism.2011,14(4):528–536.

[15] Rada FH. Oxidative stress assessment in patients with diabetic nephropathy. European Journal of Pharmaceutical and Medical Research.2018,5(1): 44–47.

[16] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clinical Chemistry.1972,18(6):499–502.

[17] Matthews DR, Hosker JP, Rudenski AS,Naylor BA,Treacher DF,Turner RC.Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia.1985,28(7):412–419.

[18] Scheen AJ, Charpentier G, Ostgren CJ, Hellqvist A,Gause-Nilsson I. Efficacy and safety of Saxagliptin in combination with metformin compared with sitagliptin in combination with metformin in adult patients with type 2 diabetes mellitus. Diabetes Metabolism Research and Reviews.2010,26:540–549.

[19] Russell-Jones D, Gough S.Recent advances in incretin based therapies. Clinical Endocrinology.2012, 77:489–499.

[20] Ali S, Fonseca V. Saxagliptin overview: special focus on safety and adverse effects. Expert Opinion on Drug Safety.2013,12:103–109.

[21] Leibowitz G, Cahn A, Bhatt DL, Hirshberg B, Mosenzon O, Wei C,et al.Impact of treatment with Saxagliptin on glycaemic stability and beta-cell function in the SAVOR-TIMI 53 study. Diabetes, Obesity and Metabolism.2015,17(5): 487– 494.

[22] Garber AJ,Abrahamson MJ,Barzilay JI,Blonde L, Bloomgarden ZT,Bush MA, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm -Executive Summary. Endocrine Practice.2016,22:84–113.

[23] Hirshberg B,Bryzinski B, Xu J,Iqbal N.A pooled analysis of the efficacy and safety of Saxagliptin as monotherapy in patients with type 2 diabetes. Journal of Diabetes and Metabolism.2015,6:524.

[24] Monami M,Ragghianti B, Zannoni S, Vitale V, Nreu B, Mannucci E. Identification of predictors of response to basal insulin and DPP4 inhibitors in patients with type 2 diabetes failing to other therapies. Acta Diabetologica.2016,53:35–40.

[25] Pratley R,Nauck M, Bailey T, Montanya E, Cuddihy R, Filetti S, et al. One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes: a randomised, parallel-group, open-label trial. International Journal of Clinical Practice.2011,65(4):397–407.

[26] Kamatani N,Katoh T, Sawai Y, Kanayama H, Katada N, Itoh M. Comparison between the clinical efficacy of linagliptin and sitagliptin . Journal of Diabetes and Endocrinology.2013,4(4):51–54.

[27] Asti A, D'Alessandro A, Zito FP, Nardi S, Sarnelli G,Maresca G, et al. Sitagliptin versus Saxagliptin in decompensated type 2 diabetes mellitus patients. Italian Journal of Medicine.2016,10(1):36–41.

[28] Li S, Li H, Wang R,Zhang JP.The effect of sitagliptin on obese patients with insulin treatment-induced diabetes mellitus. European Review for Medical and Pharmacological Sciences.2017,21:3490–3495.

[29] Pagano C,Pilon C, Olivieri M, Mason P, Fabris R, Serra R ,et al. Reduced plasma visfatin/pre-B cell colony-enhancing factor in obesity is not related to insulin resistance in humans. Journal of Clinical Endocrinology &Metabolism.2006,91(8):3165–3170