

# **Influence of DPP-4 Inhibitors on Weight in Newly Diagnosed Type-2 Diabetic Patients in Egypt**

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## **Abstract**

**Background:** The prevalence of type-2 diabetes mellitus (T2DM) is rapidly increasing and the majority of diabetics are obese. Many of the therapeutic options for T2DM can cause further weight gain. Concerns about weight gain adversely affect patients' willingness to begin and continue treatment with glucose-lowering medications, such as thiazolidinediones insulin, and sulfonylureas. **The aim of this work** was to study the influence of DPP-4 inhibitors on weight of newly diagnosed T2DM patients in Egypt. **Subjects and methods:** This study included 357 newly diagnosed T2DM patients from the private sector of Cairo & Fayoum. They were divided into three groups according to the treatment strategy. **Results:** patients treated with DPP4-1 +/- metformin achieved a reduction of A1c by 1.2 -1.7 gm % and weight loss of 3.2-4.6 kgs in one year compared to the control group who achieved greater HbA1c (1.5 -2.2 gm% p < 0.05) and weight gain(2.2 – 3.5 kgs p < 0.0001) the weight changes started within the first month, reached its maximum in 6 months then followed by a slight rebound weight gain **Conclusion:** Dipeptidyl peptidase-4 (DPP-4) inhibitors were effective in improving glycemic control with significant weight reduction in newly diagnosed Egyptian T2DM patients specially when combined with metformin

**Keywords:** Diabetes; Obesity; BMI ; Incretin; DPP4-I; Weight;

## **1 Introduction**

The prevalence of type-2 diabetes mellitus (T2DM) is rapidly increasing worldwide. The International Diabetes Federation (IDF) estimates the current prevalence of diabetes at around 382 million which is estimated to increase to 552 million cases of diabetes and 398 million cases of impaired glucose tolerance (IGT) by 2030 [1]. The majority of patients with T2DM are obese [2] and many of the current therapeutic options for

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management of T2DM can cause further weight gain [3]. Concerns about weight gain adversely affect patients' willingness to begin and continue treatment with glucose-lowering medications, such as thiazolidinediones (TZDs), insulin, and sulfonylureas (SU) [4]. The dipeptidyl peptidase-4 inhibitors (DPP-4 I) are a newer class of oral drugs that increase the incretin effect in patients with type 2 diabetes. In clinical practice they are associated with significant reductions in HbA1c, no weight gain and a low risk of hypoglycemia [5]. Studies on the influence of DPP-4 inhibitors on patient weight demonstrated variable results but are generally considered to be neutral [6,7].

## 2 Aim of the Work

The aim of this work was to study the influence of DPP-4 inhibitors on the weight in newly diagnosed type-2 diabetic patients in Egypt.

## 3 Subjects and Methods

This study included 357 newly diagnosed type 2- diabetic patients (169 males and 188 females ) aged 25 – 55 years old divided into three groups.

**Group -1** included 114 patients, fifty nine of them [ P-1] were treated with DPP-4 inhibitors (100 mg of Sitagliptin or Vildagliptin) and fifty five patients treated with sulfonylureas (SU) glimipride up to 6 mg or gliclazide up to 120 mg as a control group [C-1].

**Group -2** included 108 patients, fifty seven of them [ P-2] were treated with DPP-4 inhibitors ((as P-1) plus one gram of metformin and fifty one patients treated with SUs (as C-1) plus one gram of metformin as a control group [C-2].

**Group -3** included 125 patients, sixty four of them [ P-3] were treated with DPP-4 inhibitors (as P-1) plus two grams of metformin, and sixty one patients treated with SUs ( as C-1) plus two grams of metformin as a control group [C-3]

All patients were subjected to thorough medical history and examination. weight, height. BMI, waist circumference were recorded initially, after one month and then quarterly together with measuring the HbA1c for total of 52 weeks. Patients in whom the liver or the kidney functions were excluded from the study

All the patients were subjected to a diabetes structured educational session for 2 hours focusing on the diabetes burden, causes types, symptoms, and how to live better with diabetes through life style changes, adherence to treatment and regular follow up. also acute complications as hypoglycemia was specifically discussed concentrating on how to avoid and how to diagnose and how to deal with if happened.

The patients were instructed to record and give immediate information for any drug side effect.

### **Ethical consideration**

The whole research process was explained to all patients and a written consent was obtained from all the participants. This study was approval by the ethical committee of Fayoum university

## **4 Main Results**

This study included 357 (169 males and 188 females ) newly diagnosed type-2 diabetic patients aged 25 – 55 years old, recruited from the private sector of Cairo, Giza and Fayoum areas from June 2012 to Feb. 2014.

The patients were divided into three groups according to the treatment regimen

Patients treated with DPP4-I ( P-1) showed reduction of weight by a mean of  $3.2 \pm 0.73$  kgs and waist circumference (WC) by  $1.6 \pm 0.45$  cms from the baseline readings compared to weight gain by  $2.2 \pm 0.33$  kgs and increase in WC by  $0.6 \pm 0.32$  in their control group ( C-1) that received SUs and the difference was statistically significant ( $p = 0.01$ ). (Table 1)

Patients treated with DPP4-I plus one gram of metformin (P-2) showed weight reduction by 4.2 kgs and decrease in WC by 2.3 cms from the baseline readings compared to weight gain by 3.1 kgs and increase in WC by 1.8 cms from the baseline readings in their control group ( C-2) who received SUs plus one gram of metformin and the difference was statistically significant( $p = 0.0001$ ). (Table 1 and fig 1)

Table 1: Weight, BMI, Waist and HbA1c changes in different study groups

	Group 1			P-value	Group 2			P-value	Group 3			P-value
	Base line	AT THE END			Base line	AT THE END			Base line	AT THE END		
		P-1	C-1			P-2	C-2			P-3	C-3	
Weight (kg)	92.5±5.5	89.3±4.9	94.8±5.7	0.01	95.±6.2	91.4±7.2	98.7±8.6	0.0001	98.3±8.9	93.9±7.3	101.8±11.2	0.0001
BMI (Kg/m <sup>2</sup> )	29.3±2.3	28.1±2.5	30.1±2.9	0.07	31.4±3.2	30.2±3.5	32.3±4.8	0.08	32.7±5.7	31.3±4.7	33.5±4.7	0.06
Waist (cms)	99.1±6.7	97.6±6.2	99.7±6.2	0.07	103.8±6.1	101.5±5.9	105.6±6.2	0.04	105.5±7.1	102.9±6.7	107.6±8.7	0.02
HbA1C (gm%)	8.7±0.73	7.6±0.65	7.2±0.82	0.03	8.9±0.73	7.7± 0.20	7.3±0.69	0.04	9.2±0.82	7.5±0.80	7.0±0.79	0.01

P-1= patients of group 1, P-2= patients of group 1, p-3= patients of group 3 C-1 = Control of group 1  
 C-1 = Control of group 1, C-2= Control of group 2, C-3 = Control of group 3, BMI= Body mass index  
 HbA1c = Glycated hemoglobin P – Value of > 0.05 was considered significant.

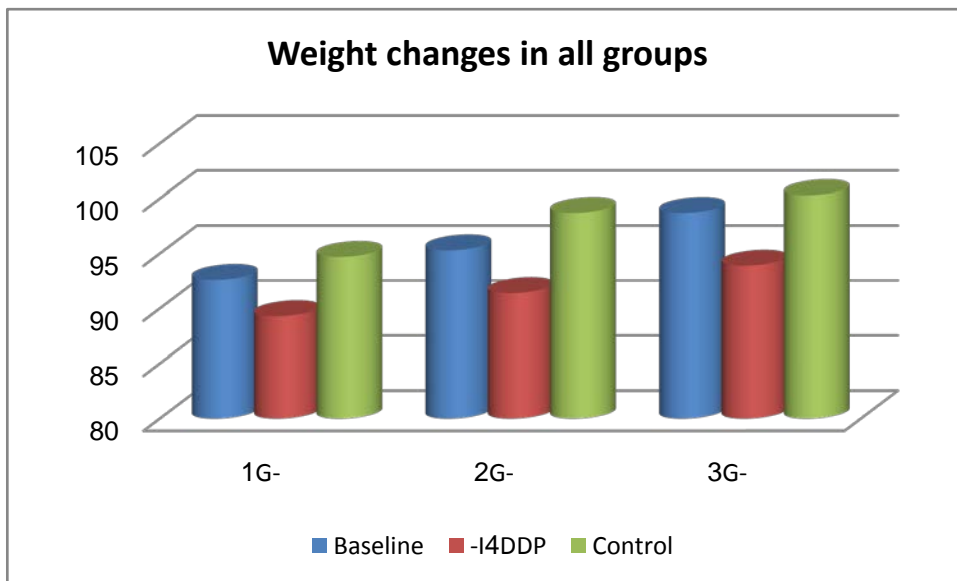


Figure 1: Weight changes in all groups

G-1 =Group-1, G-2 =Group-2, G-3 =Group-3, DPP4-I= dipeptidylpeptidase- 4 inhibitor

Patients treated with DPP4-I plus 2 gram of metformin ( P-3) showed reduction of weight by 4.4 kgs and WC by 2.6 cms from the baseline readings compared to weight gain 3.5 kgs and increase in WC by 2.1 cms in their control group ( C-3) that received SUs plus 2 grams of metformin and the difference was statistically significant( $p = 0.0001$ ). (Table 1). Weight changes started in the early weeks following treatment, reached its maximum after six months and then there was a rebound weight gain in some patients but at the end of the study (52 weeks) weight changes are still significant fig 2.

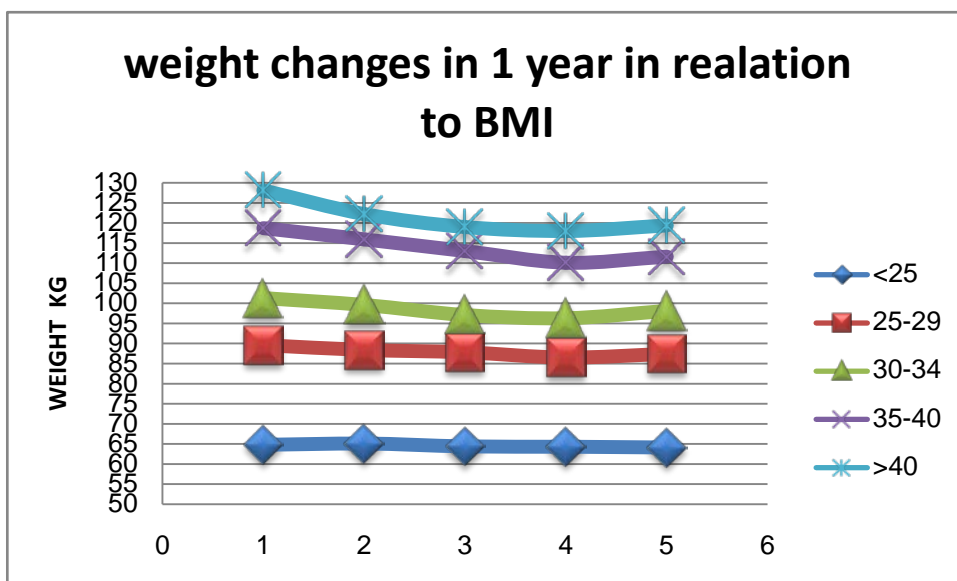


Figure 2: Weight changes in I year in relation to BMI (body mass index)

Younger patients (below 40 years old) achieved a greater weight reduction (4.2 kgs) compared to older patients (2.9 kgs ) and the differences were statistically significant (  $p = 0.02$ ) (Table 2)

It was found that there was a significant correlation between the degree of weight loss and the base line weight( $p = 0.007$ ), Patients with higher BMI showed significant reduction of weight and WC compared to others of lower BMI , the greatest reduction of weight was observed in obese patients with BMI greater than 35 kg/m<sup>2</sup> where the weight loss ranged from 7-16 kgs & the lowest reduction of weight was observed in patients with BMI less than 25 kg/m<sup>2</sup> where the weight changes ranged from +2 to -3 kgs (Table 2 and fig-2). Males receiving DPP-4 inhibitors showed greater weight reduction of body weight and WC compared to females receiving the same medications but the differences were statistically insignificant ( $p = 0.06$ ) (Table 2 ).

Table 2: Demographic data of patients treated with DPP4-1 at baseline and after 1 year

		Number 180	Weight		P value	Waist Circumference		P value
			Baseline Mean $\pm$ SD	1 yea Mean $\pm$ SD		Baseline Mean $\pm$ SD	1 yea Mean $\pm$ SD	
Age	< 40	86	92.3 $\pm$ 4.53	88.1 $\pm$ 4.22	0.02	102.2 $\pm$ 4.8	100.2 $\pm$ 5.5	0.08
	>40	94	93.4 $\pm$ 5.67	90.5 $\pm$ 4.87		104.2 $\pm$ 5.3	101.9 $\pm$ 5.8	
Gender	male	83	93.1 $\pm$ 6.1	89.2 $\pm$ 4.6	0.0001	101.2 $\pm$ 4.8	99.6 $\pm$ 4.7	0.06
	female	97	92.1 $\pm$ 5.2	90.8 $\pm$ 4.7		103.8 $\pm$ 5.5	102.7 $\pm$ 5.9	
HbA1c	<7.5	88	93.2 $\pm$ 4.53	88.3 $\pm$ 4.22	0.03	102.8 $\pm$ 4.8	100.7 $\pm$ 5.5	0.08
	>7.6	92	92.7 $\pm$ 5.67	89.2 $\pm$ 4.87		103.2 $\pm$ 5.3	101.9 $\pm$ 5.8	
DPP4-I	Sitagl	96	91.9 $\pm$ 4.65	88.8 $\pm$ 4.62	0.06	101.7 $\pm$ 4.8	100.1 $\pm$ 5.5	0.08
	Vildagl	84	92.8 $\pm$ 5.45	89.9 $\pm$ 4.87		102.5 $\pm$ 5.9	100.8 $\pm$ 5.8	
BMI	<25	44	64.8 $\pm$ 3.5	64.2 $\pm$ 3.2	0.6	72.4 $\pm$ 3.8	72.2 $\pm$ 3.2	0.9
	26 -34.9	120	101.4 $\pm$ 6.4	98.8 $\pm$ 6.1	0.0001	111.9 $\pm$ 6.8	108.6 $\pm$ 6.9	0.04
	>35	16	126.3 $\pm$ 9.6	117.4 $\pm$ 8.4		136 $\pm$ 10.7	127 $\pm$ 9.5	0.03
Group	P-1	59	92.5 $\pm$ 5.5	89.3 $\pm$ 4.9	0.0001	99.1 $\pm$ 6.7	97.6 $\pm$ 6.2	0.06
	P-2	57	95. $\pm$ 6.2	91.4 $\pm$ 7.2		103.8 $\pm$ 6.1	101.5 $\pm$ 5.9	
	P-3	64	98.3 $\pm$ 8.9	93.9 $\pm$ 7.3		105.5 $\pm$ 7.1	102.9 $\pm$ 6.7	

HbA1c = Glycated hemoglobin. P – Value of  $> 0.05$  was considered significant

DPP4-I = dipeptidyl peptidase-4 inhibitors BMI= Body mass index

There was no significant differences between Sitagliptin and Vildagliptin regarding their weight reducing effect. (Table 2). Patients treated with SUs either alone or combined with metformin up to 2 grams showed greater reduction of HbA1c compared to those treated with DPP4-inhibitors either alone or combined with metformin and the differences were statistically significant. ( fig. 3 )

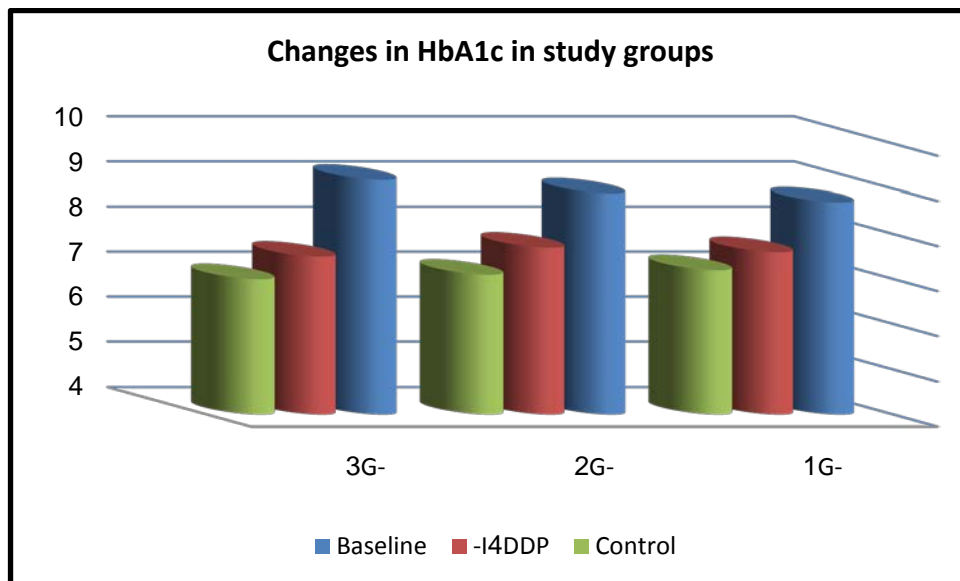


Figure 3 Changes in HbA1c in the study group  
G-1 =Group-1, G-2 =Group-2, G-3 =Group-3, DPP4-1= dipeptidylpeptidase- 4 inhibitor

## 5 Discussion

The clinical management of patients with type 2 diabetes has to balance the potential benefits of controlling hyperglycemia on micro vascular and macro vascular complications, [8] with possible side effects of treatment and possible harm from over intensive control of glycemia.[9] From the perspective of the patient with diabetes, weight gain and hypoglycemia are undesirable and unwanted side effects. Of the older therapies, sulfonylureas, insulin and glitazones are all associated with significant weight gain, whereas metformin is associated with slight weight loss [10]. As a class, the DPP-4 inhibitors are weight neutral, causing neither weight gain nor weight loss. As the majority of patients with type 2 diabetes are overweight or obese this offers a potential advantage over older, established therapies, and DPP-4 inhibitors are being used in clinical practice as second-line therapy in addition to metformin in overweight and obese patients who fail to reach glycemic targets with metformin monotherapy. The very low rates of hypoglycemia are an additional advantage in vulnerable patients, such as the elderly or patients who live alone [6,7].

In this study Patients treated with DPP4-I ( P-1) showed reduction of weight by a mean of  $3.2 \pm 0.73$  kgs and waist circumference (WC) by  $1.6 \pm 0.45$  cms from the baseline readings compared to weight gain by  $2.2 \pm 0.33$  kgs and increase in WC by  $0.6 \pm 0.32$  in their control group ( C-1) that received SUs and the difference was statistically significant. ( $p = 0.02$ )

Patients treated with DPP4-I plus one gram of metformin ( P-2) showed weight reduction by 4.2 kgs and decrease in WC by 2.3 cms from the baseline readings compared to weight gain by 3.1 kgs and increase in WC by 1.8 cms from the baseline readings in their control group ( C-2) who received SUs plus one gram of metformin and the difference was statistically significant. ( $p = 0.0001$ )

Patients treated with DPP4-I plus 2 gram of metformin ( P-3) showed reduction of weight by 4.4 kgs and WC by 2.6 cms from the baseline readings compared to weight gain 3.5 kgs and increase in WC by 2.1 cms in their control group ( C-3) that received SUs plus 2 grams of metformin and the difference was statistically significant ( $p = 0.0001$ ) Previous studies on the influence of DPP-4 inhibitors on patient weight demonstrated variable results but are generally considered to be neutral. Studies regarding treatment with sitagliptin showed variability between 1.5 kg of weight loss in 52 weeks of therapy to 1.8 kg of weight gain in 24 weeks of therapy. Studies regarding treatment with Vildagliptin showed variability between 1.8 kg of weight loss to 1.3 kg of weight gain in 24 weeks of therapy. Similar studies regarding saxagliptin showed variability between 1.8 kg of weight loss to 0.7 kg of weight gain in 24 weeks of therapy. In a meta-analysis of 13 studies regarding the treatment of all three DPP-4 inhibitors, the effect of this group of drugs on weight was neutral [6,7]

Also in the DURATION 2 trial patients on sitagliptin 100 mg once daily achieved a weight reduction by a mean of 0.8 kg in 26 weeks [12].

In this study it was found that Weight changes started in the early weeks following treatment, reached its maximum after six months and then there was a rebound weight gain in some patients but at the end of the study (52 weeks ) weight changes are still significant.

Similar to our findings was in the DURATION 2 trial, the differences in weight loss became apparent by 4 weeks [12]. Also during the 1860-Lira DPP4 extension phase, weight loss achieved during the first 26 weeks was sustained at 52 weeks [13]. In our study DPP4-1 produced a significant weight loss compared to previously published data, this could be explained the high carbohydrate high fat diet of Egyptians, lack of physical activity and the high prevalence of obesity in Egypt. Also this study was conducted on newly diagnosed T2DM patients.

In this study Patients treated with SUs either alone or combined with metformin showed reduction of the HbA1c by 1.6 -2.2 gm % compared to those treated with DPP4-inhibitors alone or combined with metformin) reduced it by 1.2 -1.7 mg% (and the differences was statistically significant ( $p < 0.05$ ) fig 3.

Regarding the efficacy of DPP4-1 the results of previous studies showed different results. Monami and colleagues, published in 2010.[6] In the meta-analysis they included 32 published trials and nine unpublished trials with a duration greater than 12 weeks. They confirmed that, compared with placebo, the DPP-4 inhibitors reduced HbA1c by around 0.7%. The efficacy was similar in monotherapy and in combination with other agents. When comparisons were made with other oral drugs used in type 2 diabetes, the reductions in HbA1c were comparable with glitazones, but slightly less than with metformin or sulfonylureas. There was no weight gain and a very low risk of hypoglycemia.

In the 1860-Lira-DPP-4 study, mean baseline HbA1c was 8.4%. A greater reduction in HbA1c was seen with liraglutide 1.2 mg (-1.24%; 95% CI, -1.37 to -1.11) and 1.8 mg (-1.5%; 95% CI, -1.63 to -1.37) compared with sitagliptin (-0.9%; 95% CI, -1.03 to -0.77). Estimated mean treatment differences for liraglutide at 1.2 mg and 1.8 mg doses compared to 100 mg sitagliptin were -0.34% for 1.2 mg ( $P < 0.0001$ ) and -0.6% for 1.8 mg ( $P = < 0.0001$ ). The reduction of 0.9% in HbA1c with sitagliptin in the 1860-Lira-DPP-4 study is one of the better results achieved in a trial with sitagliptin [11]. During the extension phase of the 1860-Lira-DPP-4 study, mean HbA1c improvement with liraglutide 1.8 mg and 1.2 mg, and sitagliptin at 52 weeks from



baseline was 1.29%, 1.51% and 0.88%, respectively. Thus liraglutide produced a significant and sustained reduction in HbA1c compared to sitagliptin at 52 weeks. The improvement in glycemic control with liraglutide was irrespective of baseline HbA1c [13].

In the DURATION-2 study, the mean baseline HbA1c was 8.6%. Exenatide therapy resulted in a significant reduction in HbA1c compared with sitagliptin (-1.5% versus -0.9%,  $P = <0.0001$ ). Significant HbA1c improvement was noted within four weeks of exenatide therapy and within six weeks of sitagliptin therapy. In a subgroup of patients with a basal HbA1c less than 9%, exenatide therapy resulted in significant improvements (mean baseline HbA1c 7.8%, change in HbA1c -1.1%) in comparison to sitagliptin (mean baseline HbA1c 7.7%, change in HbA1c -0.5%) [12].

Also in the T-emerge 4 Trial, taspoglutide 10 mg and 20 mg has been shown to improve HbA1c significantly more than that achieved with sitagliptin (-1.3%, -1.23% and -0.89% improvement from baseline with taspoglutide 20 mg, 10 mg and sitagliptin, respectively;  $P < 0.001$  for both doses of taspoglutide against sitagliptin) [14].

In the DURATION-4 trial 26 weeks monotherapy with exenatide reduced HbA1c by 1.5% from baseline as opposed to a 1.2% reduction with sitagliptin [15].

In our study the DPP4-I (sitagliptin or Vildagliptin) monotherapy had reduced the A1c by a mean of 1.2 mg percent and this is similar to work done by other researchers where monotherapy with 100 mg/200 mg sitagliptin significantly lowered mean HbA1c levels compared with placebo by 0.61/0.76% ( $P < 0.001$  for both doses) in a 24-week trial and by 0.48/0.36% ( $P < 0.001$  for both doses) in an 18-week study, whereas mean HbA1c level was decreased by 0.8/0.9% with 50 mg/100 mg Vildagliptin, respectively, after a 24-week intervention ( $P = 0.006/P < 0.001$ ) [16,17] A low-dose (2.5, 5, 10, 20, or 40 mg) intervention with saxagliptin for 12 weeks reduced HbA1c levels by 0.7–0.9% compared with placebo in all treatment arms, and a high-dose (100 mg) 6-week intervention decreased HbA1c levels by 1% [18].

In our study patients treated by a DPP4-I in combination with metformin, the reduction of A1c ranged from 1.3 to 1.7 gm % after 1 year and this is greater than the results of other colleagues in which Vildagliptin reduced mean HbA1c by 0.7% (100 mg,  $P < 0.0001$ ; 24-week trial) and sitagliptin by 0.5/0.9% compared with placebo (50 mg/100 mg,  $P < 0.001$ ; 24-week trial), while with 2.5 mg/5 mg/10 mg saxagliptin, the mean placebo-subtracted HbA1c was 0.73/0.83/0.72%, respectively ( $P < 0.0001$  for all doses; 24-week treatment) [16, 18].

A meta-analysis of data from randomized control trials longer than 12 weeks with DPP-4 inhibitors showed significantly lower HbA1c compared with placebo (weighted mean difference -0.74%; 95% CI -0.85 to -0.62); additionally, patients receiving a DPP-4 inhibitor were more likely to achieve HbA1c levels of  $<7.0\%$  compared with placebo [19].

Regarding drug side effects in our study 4 patients had skin allergy, 13 had gastrointestinal upset but all were self limited

In similar clinical studies, all DPP-4 inhibitors were well tolerated with low rates of side effects. Mild-to-moderate hypoglycemia occurred at a low frequency, and there was practically no difference between DPP-4 inhibitors and comparator groups (19). Among other side effects, headache, urinary tract infections, and nasopharyngitis appeared to be more frequent, whereas gastrointestinal adverse effects occurred rarely [19]

In this study only 19 patient out of 347 patients developed at least one attack of mild hypoglycemia per year, and out of those 19 patients only 3 were treated with DPP4-1 (one

as monotherapy and 2 combined with metformin )and no cases of sever hypoglycemia or nocturnal hypoglycemic attacks were reported in patients receiving DPP4-I  
In agreement with our findings, There was a low risk of hypoglycemia in clinical trials, and severe hypoglycemia occurred rarely with both drugs (this happened mainly when associated with a sulfonylurea) (19).

## 6 Conclusion

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a new class of oral drugs for type 2 diabetes that are effective in controlling hyperglycemia as they reduced the mean HbA1c by 1.2 if given as a first line therapy and when combined with metformin more HbA1c reduction (1.7gm%). Also weight reduction was found to be significantly more than the published data 3.2 kgs and if combined with metformin the mean weight loss reaches 4.6 kgs in 1 year compared to weight gain in patients who were given SUs.it was also noted that there was a statistically significant correlations between the baseline weight and the degree of weight loss.

Patients younger than 40 years old achieves a significant weight loss compared to patients older than 40 years old

Males receiving DPP-4 inhibitors showed greater weight reduction of body weight and WC compared to females receiving the same medications but the differences were statistically insignificant ( $p = 0.06$ )

There was no significant differences between Sitagliptin and Vildagliptin regarding their weight reducing effect. Patients treated with SUs either alone or combined with metformin up to 2 gms showed greater reduction of HbA1c compared to those treated with DPP4-inhibitors either alone or combined with metformin and the differences were statistically significant.

## 7 Recommendations

Further research is need to confirm our results specially weight changes in patients treated with DPP4- in different regions and different races as well as different age groups with larger sample size.Also further research is needed to look for the durability, sustainability of the glycemic control and other metabolic benefits of DPP4-I

## 8 Conflict of Interest

Mohamed Mashahit has no conflict of interest

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