



COMPARATIVE STUDY BETWEEN THE EFFECTS OF SITAGLIPTIN, AND VILDAGLIPTIN AS ORAL HYPOGLYCEMIC DRUGS IN UNCONTROLLED TYPE 2 DIABETES MELLITUS

Najim Abdullah Abdulwahid, Eman Abdulrahman Sheshah
Diabetes Center, King Salman Hospital, Riyadh, Saudi Arabia

ABSTRACT

Saudi Arabia has one of the highest percentages of Diabetes in the world, accounting to IDF 2013 for 24% of the population. The study's objective was to assess the efficacy, and safety of Sitagliptin, and Vildagliptin as Oral Hypoglycemic drugs, and to compare between the actions of both drugs. An observational prospective study carried out on 189 Type 2 Diabetes Mellitus patients at King Salman Hospital's Diabetic Center in Riyadh, KSA between the 1st of January 2013, and 30th of April 2013. This study was carried out over four months. The patients were grouped: Group 1 received Sitagliptin, and Group 2 received Vildagliptin. Both groups were receiving Sulphonylurea, Metformin 1000mg BID, Lipitor 10 mg, and Aspirin 81 mg prior to the study. Group 1: 158 patients, with mean age of 51.12 ±12.21 years. Group 2: 31 patients, with mean age of 44.6 ±13.2 years. Group 1: HbA1c dropped from 8.8%±2.1% to 7.9%±1.9%. LDL-C decreased from 2.9 ±1.0mmol/L to 2.7 ±0.9mmol/L, HDL-C increased from 1.1 ±0.3mmol/L to 1.3 ±1.1mmol/L, and Triglyceride decreased from 2.3±3.7mmol/L to 1.8±1.0mmol/L. Group 2: HbA1c decreased from 8.9%±1.71% to 7.8% ±1.7%, LDL-C decreased from 3.5±0.6mmol/L to 2.7 ±0.9mmol/L, HDL-C increased from 1.05±0.18mmol/L to 1.09±0.24mmol/L, and Triglyceride increased from 2.65 ±2.2mmol/L to 2.71 ±3.2 mol/d. Addition of Sitagliptin, or Vildagliptin improves equally DM Control, and lipid profile in previously uncontrolled Diabetic patients; Except Vildagliptin is superior in lowering LDL-C. Both drugs are safe on the kidney.

KEYWORDS: Sitagliptin, Vildagliptin, Type 2 Diabetes Mellitus and Oral Hypoglycemic drugs.

INTRODUCTION

Diabetes mellitus (DM) is a chronic disease that requires life-long pharmacological, and non-pharmacological management to prevent complications such as cardiovascular disease, retinopathy, nephropathy, and neuropathy, which all have inevitable debilitating sequelae: congestive heart failure, lost eyesight, the need for frequent hemodialysis, and foot amputation, or debridement^[1,2]. Mortality-wise, diabetes took the lives of approximately 3.4 million people in 2004, with more than 80% of these deaths occurring in low- and middle income countries^[3]. Nationally, according to the International Diabetes Federation, Saudi Arabia has one of the highest percentages of Diabetes in the world, with an estimated number of 2,065,300 people diagnosed with the disease in 2010, which is 16.8% of the population. In the United States, 10% of the population were expected to have had diabetes in 2010, 7.8% in India, and 4.2% in China. The Kingdom of Saudi Arabia (KSA) is a rapidly evolving country with a change that influenced the lifestyle of the people towards urbanization, particularly over the past 3 decades. Previous surveys from KSA suggested that diabetes is present in epidemic proportions throughout the country with exceedingly high rates concentrated in urban areas^[4]. Existing guidelines for management of Diabetes Mellitus in Saudi Arabia were directed to Primary Health Care (PHC) physicians, and other PHC team members. They were developed in 1988 to be used in a health center at King Saud University hospitals. These guidelines were later updated, and modified to be used in the Quality

Assurance (QA) Program in Primary Health Care developed jointly by the Saudi Ministry of Health, and World Health Organization (WHO). As per such guidelines, Saudi patients are prescribed combinations of Sulphonylurea, and Metformin, for non-obese, and obese patients respectively, as first line therapy^[5]. This is usually coupled with exercise; dieting, and monthly follow up, before proceeding to considering insulin. Since Gliptins have been proven to successfully provide an effective and safe alternative to the management of diabetes, in this study we aim to compare between Sitagliptin (Januvia), and Vildagliptin (Galvus) as oral hypoglycemic drugs, in uncontrolled Type 2 DM. This comparison will include efficacy (via studying FBG, and HbA1C). Since Patients with type 2 diabetes often have dyslipidemia, putting them at risk of cardiovascular disease, and are frequently treated with oral anti-hyperglycemic medications (OAMs) the comparison also considered Total Cholesterol, High Density Lipoprotein Cholesterol (HDL-C), Low Density Lipoprotein Cholesterol (LDL-C), and Triglycerides.^[6] Finally, to test drug safety; (Blood Urea Nitrogen, Serum (S.) Creatinine, S. Uric Acid level, and urine Albumin/Creatinine ratio) were also carried out to assess safety on the kidney.

METHODOLOGY

An observational prospective study was carried out on 189 Type 2 Diabetes Mellitus patients at King Salman Hospital's Diabetic Center in Riyadh, Saudi Arabia between the 1st of January 2013, and 30th of April 2013.

The 189 patients have been taking Sulphonyl urea and Metformin prior to the study. They were divided into 2 groups according to the added treatment; Group 1 were treated with Sitagliptin (100 mg once daily), and Group 2 were treated with Vildagliptin (50 mg twice daily). Group 1 consisted of 158 patients; 89 male (56.3%), and 69 female (43.7%), and their mean average age was 51.12 ±12.21 years. Group 2 consisted of 31 patients; 14 male (45.2%), and 17 female (54.8%), and their mean age was 44.6 ±13.2 years. Group 1 patients have had Type 2DM for a median of 6 years, ranging from 0.1 years to 32 years. Group 2 patients have had Type 2DM for a median of 4 years; ranging from 0.1 years to 20 years. There was no statistical significant difference between the 2 groups, regarding the DM duration.

In group 1 patients; the most common concomitant diseases among patients were Vitamin D deficiency, and dyslipidemia, 57%, and 52% respectively. Similarly, Vitamin D deficiency, and dyslipidemia were the most common diseases in Group 2 patients, 64.5%, and 48% respectively. 33% of group 1 patients, and 26% of Group 2 patients were hypertensive. 10% from Group 1 patients, and 16% from Group 2 patients had hypothyroidism. Only one patient in Group 1 was obese (0.6%), one was anemic (0.6%), one was hypocalcemic (0.6%), one suffered from Papillary Thyroid Carcinoma (0.6%), and one from Renal Failure (0.6%). In Group 2, one patient had nodular goiter (3.2%). From Group 1, in order of frequency the most common insulin form taken was Basal Insulin Lantus at 10.1% of the patients, 5.7% were treated with Humalog, Novomix, and Novorapid Aspart each, 3.8% took Detemer, or Levemir. The least prevalent insulin medications used were Mixtard, NPH Humulin Insulatard, and Humulin R Actrapid, with 1.9% (3 patients), 1.3% (2

patients), and 0.6% (1 patient) to each medication, respectively. Regarding the use of oral Hypoglycemic Drugs (OHD), group 1 patients used Metformin, Glimeperide, Pioglitazone, Gliclazide MR, and Glibinclamide at 82%, 35%, 9%, 8%, and 1% respectively. In Group 2, 6.5% were treated with Humalog, and Detemer, or Levemir each and 3.2% were treated with Novorapid Aspart, and NPH Humulin, each. Concerning the use of OHDs; Gavusmet was the most common at 52%, and unlike in Group 1, Metformin came second with 48%. Glimeperide, Gliclazide MR, and Pioglitazone MR's use was lower at 39%, 10%, and 10% respectively. Glibinclamide, and Sitagliptin were the least common OHD, at 3.2% (1 patient taking each).

Statistical Analysis

Descriptive statistics included frequency tables (n, mean, median, standard deviation, minimum, and maximum for continuous variables, and n, frequency, and percentage for categorical values). To test the differences between Sitagliptin, and Vildagliptin, paired t-test was performed.

RESULTS

HbA1C, and Fasting Blood Glucose were the parameters used to assess efficacy of Sitagliptin, and Vildagliptin. Values at the baseline visit, and the last visit were recorded, and compared as shown in table 1. Since Type 2DM is associated with lipid abnormalities, total cholesterol, LDL-cholesterol, HDL- cholesterol, and Triglycerides were monitored, and recorded between the first, and last visits as shown in table 2.

Albumin/Creatinine Ratio, Blood Urea Nitrogen (BUN), and S. Creatinine are all good indicators of kidney functions, and thus, were also recorded them to assess the drug safety, particularly on the kidney, as seen in table 3.

TABLE 1: The change in glycosylated Hemoglobin level, and Fasting Blood Glucose between the first visit, and the last visit

		Sitagliptin					Vildagliptin					p-value between groups
		Mean	SD	Mean Diff	% Change	p-value	Mean	SD	Mean Diff	% Change	p-value	
HbA1C	V1	8.8	2.1	-0.9	-9.8%	0.000	8.9	1.7	-1.1	-12.0%	0.003	0.572
	V2	7.9	1.9				7.8	1.7				
FBG	V1	9.9	3.8	-1.4	-14.2%	0.002	10.9	3.0	-1.4	-13.2%	0.251	0.976
	V2	8.5	3.3				9.5	3.5				

TABLE 2: The change in patients' lipid profile between the first, and second visits

		Sitagliptin					Vildagliptin					p-value between groups
		Mean	SD	Mean Diff	% Change	p-value	Mean	SD	Mean Diff	% Change	p-value	
Cholesterol	V1	4.86	1.44	-0.39	-7.9%	0.021	5.29	0.71	-0.65	-12.3%	0.189	0.542
	V2	4.48	1.07				4.64	1.65				
LDL-C	V1	2.90	0.99	-0.22	-7.6%	0.012	3.47	0.64	-0.79	-22.8%	0.041	0.027
	V2	2.68	0.9				2.68	0.9				
HDL-C	V1	1.07	0.26	0.18	16.9%	0.139	1.05	0.18	0.04	3.5%	0.518	0.613
	V2	1.25	1.08				1.09	0.24				
Triglyceride	V1	2.27	3.68	-0.52	-23.0%	0.197	2.65	2.16	0.06	2.3%	0.894	0.539
	V2	1.75	0.98				2.71	3.22				

TABLE 3: The change in kidney function tests between baseline visit, and at the end of the study

		Sitagliptin					Vildagliptin					p-value between groups
		Mean	SD	Mean Diff	% Change	p-value	Mean	SD	Mean Diff	% Change	p-value	
ALB / CRE	V1	16.57	47.53	3.89	23.5%	0.354	13.40	38.62	26.24	195.8%	0.373	0.155
RATIO	V2	20.46	75.84				39.65	155.04				
BUN	V1	6.05	3.31	-0.22	-3.7%	0.527	4.68	0.88	0.55	11.8%	0.375	0.318
	V2	5.82	2.65				5.23	2.01				
S. Creatinine	V1	78.60	29.34	-0.68	-0.9%	0.654	66.42	17.90	0.25	0.4%	0.913	0.782
	V2	77.92	27.36				66.67	18.02				

DISCUSSION

Studies have repeatedly shown that out-of-control diabetes results in complications from the disease; the goal for people with diabetes is an HbA1c less than 7% [6]. The higher the HbA1c, the higher the risks of developing complications related to diabetes [6]. In this study, HbA1c decreased between Visit 1, and Visit 2 by 9.8% in the group (1) treated with Sitagliptin with very highly statistical significance ($p=0.000$), and by 12% in the group (2) treated with Vildagliptin with highly statistical significance ($p=0.003$), but with no significant difference between results in the 2 groups. The Fasting Blood Glucose decreased between visits 1, and 2 by 14.2% in group 1 with highly statistically significant difference ($p=0.002$), and by 13.2% in group 2 but with no statistical significant difference ($p=0.251$).

Although both the HbA1c, and the FBG decreased, the difference between both groups, and consequently between the efficacy of Sitagliptin, and Vildagliptin was of no statistical significance, and so, there is no difference between both drugs in terms of efficacy as oral hypoglycemic drugs, in contrast to a similar study carried out in Japan. In a study assessing the comparative efficacy of Vildagliptin, and Sitagliptin in Japanese patients with Type 2DM, Vildagliptin 50 mg twice daily was associated with significantly greater HbA1c reduction than Sitagliptin 50 mg, or 100 mg once daily [7]. In a similar study, comparing Vildagliptin Twice Daily vs. Sitagliptin Once Daily Using Continuous Glucose Monitoring (CGM), the results concluded that the mean 24-hour blood glucose level was significantly lower in patients taking Vildagliptin than Sitagliptin, with no particular emphasis on Fasting Blood Glucose [8].

In a review focusing on the pharmacokinetics, pharmacodynamics, efficacy, and safety of gliptins (including Sitagliptin, and Vildagliptin), they were proved to provide an effective, and safe alternative to the management of diabetes. Shown to reduce HbA1c between 0.5% & 2% effectively, and safely, this new class of drugs demonstrated its market position. Even major diabetes management guidelines have acknowledged them for their safe adverse effect profile [9]. Other more thorough comparisons suggested that Sitagliptin, and Vildagliptin provide similar improvements in HbA1c when combined with metformin, a sulfonylurea, or a glitazone [10,11]. Type 2 diabetes is associated with a cluster of interrelated plasma lipid, and lipoprotein abnormalities, including reduced HDL- cholesterol, a predominance of (LDL-C) particles, and elevated triglycerides [12]. Total Cholesterol decreased between Visits 1, and 2 by 7.9% in Group 1, which was statistically significant ($p= 0.021$), and by 12.3% in Group

2, with no statistical significance. The difference between the 2 groups is of no statistical significance. Triglyceride level decreased in Group 1 by 23%, and increased in Group 2 by 2.3%, showing no statistical significance between the 2 groups. (p -value = 0.539). HDL-C increased by 16.9% in Group 1, and 3.5% in Group 2. (p -value = 0.613). Both Sitagliptin, and Vildagliptin were efficient enough to stop the reduction in HDL-Cholesterol, and in fact increased it; however the increase was non-statistically significant between both groups. Both drugs, on the other hand were very effective in lowering the LDL-C, as LDL-C decreased by 7.6% in Group 1, and 22.8% in Group 2, and both changes were statistically significant ($p=0.012$, and $p=0.041$ respectively). All the parameters used to assess kidney function, and consequently safety of the drugs (BUN, Serum Creatinine, and Serum Uric Acid levels, and Albumin/Creatinine ratio) were either minimally increased, or decreased, showing no statistical significance between before, and after treatment in the 2 treatment groups. BUN, serum Creatinine, and serum Uric Acid decreased in Group 1, and increased in Group 2, yet both changes, as previously mentioned were of no statistical significance. Albumin/Creatinine ratio increased in both groups. Similarly, the increase in both groups was of no statistical significance.

CONCLUSION

The addition of Sitagliptin, and Vildagliptin to Insulin, and/or Oral Hypoglycemic Drugs equally improves the control of Type 2DM. Both drugs are equally safe on the kidneys.

ACKNOWLEDGMENT

Najim. A. Abdulwahid conducted the study work, and collected data. Eman A. Sheshah wrote the manuscript, and contributed to the discussion.

REFERENCES

- [1]. American Diabetes Association. Standards of medical care in diabetes. Last updated:2012. Cited: 2015 Jan 13. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22187471> Suppl 1: S11-63.
- [2]. Qaseem, A., Qaseem, A., Humphrey, L. L., Sweet, D. E., Starkey, M., Shekelle, P. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*, 2012. 156(3): 218-31.
- [3]. Shlomo Melmed, Kenneth, S. Polonsky, M.D, P. Reed MD Larsen, and Henry M. Kronenberg, MD

- Williams textbook of endocrinology (12th ed.). Philadelphia: Elsevier/Saunders. 1371–1435.
- [4]. Alzaid, A. Time to declare war on diabetes. *Annals of Saudi Medicine* 1997; 17: 154-155.
 - [5]. Eiad A. Al-Faris, MRCGP (Lond). Guidelines For The Management of Diabetic Patients In The Health Centers Of Saudi Arabia. *J Family Community Med.* 1997 Jan-Jun; 4(1): 12–23.
 - [6]. Diabetes Health Center. “The Hemoglobin A1c (HbA1c) Test for Diabetes” Last updated 2012 May. Cited: 2015 Jan 13. Available from: <http://www.webmd.com/diabetes/guide/glycated-hemoglobin-test-hba1c>
 - [7]. Signorovitch, J.E., Wu E.Q., Swallow, E., Kantor, E., Fan, L., Gruenberger, J.B. “Comparative efficacy of vildagliptin, and sitagliptin in Japanese patients with type 2 diabetes mellitus: a matching-adjusted indirect comparison of randomized trials.” *Clin Drug Investig.* 2011; 31(9):665-74.
 - [8]. Masaya Sakamoto, Rimei Nishimura, Taiga Irako, Daisuke Tsujino, Kiyotaka, ando, Kazunori Utsunomiya. Comparison of Vildagliptin Twice Daily vs. Sitagliptin Once Daily Using Continuous Glucose Monitoring (CGM): Crossover Pilot Study (J-VICTORIA Study). *Cardiovasc Diabetol.* 2012 Aug 6; 11:92.
 - [9]. Vishal Gupta, and Sanjay Kalra. Choosing a Gliptin. *Indian J Endocrinol Metab.* v.15(4); Oct-Dec 2011
 - [10]. Chacra, A. R., Tan, G. H., Apanovitch, A., Ravichandran, S., List, J., Chen, R. Saxagliptin added to a submaximal dose of sulphonylurea improves glycaemic control compared with uptitration of sulphonylurea in patients with type 2 diabetes: A randomised controlled trial. *Int J Clin Pract* 2009;63:1395–406.
 - [11]. Chacra, A. R., Tan, G. H., Ravichandran, S., List, J., Chen, R. Safety, and efficacy of saxagliptin in combination with submaximal sulphonylurea versus up-titrated sulphonylurea over 76 weeks. *Diab Vasc Dis Res* 2011; 8:150–9.
 - [12]. American Diabetes Association: Management of dyslipidemia in adults with diabetes (Position Statement). *Diabetes Care* 26 (Suppl. 1):S83–S86, 2003