

# ROLE OF DIPEPTIDYL PEPTIDASE-4 INHIBITOR IN GLYCEMIC CONTROL AND CARDIOVASCULAR MORTALITY AND MORBIDITY

**An Article Review By Dr. Shaikh Khalid Anwar, India**

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## SOURCE

Dror Dicker, MD, DPP-4 Inhibitors: Impact on glycemic control and cardiovascular risk factors, Diabetes care, volume 34, supplement 2 may 2011. care.diabetesjournals.org, Page : S276 –S278

## KEYWORDS

Glycemic cycle, DPP-4, Amori, inhibitors, hypoglycemia, diabetes

## REVIEW OF LITERATURE

DPP-4 inhibitors are one of the newer class drugs which have been claimed to have more efficacy and varied effect not only on the glycemic cycle but also on cardiovascular mortality and morbidity and weight control. There are many types of DPP-4 inhibitors but the commonly used ones are Sitagliptin, Vildagliptin and Saxagliptin each of them have different metabolism, dosage and excretion.

Studies have shown showed a variable reduction in HbA1c levels between 0.4 to 1.4 with different DPP-4 inhibitors. A study done by Amori et al showed a decrease of 0.74% in HbA1c with these drugs. This result proved that sulfonylureas were slightly more effective than DPP-4 inhibitors while being as effective as metformin and thiazolidinediones in reduction of blood glucose. In studies where DPP-4 inhibitors and metformin were used as a single tablet, the results were much better for two reasons, firstly, metformin has an positive regulating effect on the level of GLP-1, and hence it augments the effect of incretin on DPP-4 inhibitors. The second probable explanation for the positive results of the combined drug is that the patients are more compliant taking a single oral tablet instead of two.

Boschmann et al added that DPP-4 when inhibited accentuate the postprandial lipid causing it to be mobilized and oxidized it by activating the sympathetic system causing an indirect effect on the metabolic status. Matikainen et al explained that treatment with vildagliptin for 4 weeks improves the postprandial triglyceride and the apolipoprotein B-48 which contains triglyceride rich lipoprotein particle after taking a meal rich in fat in type 2 diabetes patients who were drug-naive patients.

Studies with DPP-4 inhibitors and its effect on patient weight showed variable results but in general they are weight neutral.

Commonly seen adverse effects in clinical trials were naso-pharyngitis, headache and upper respiratory tract infection. Pancreatitis is one suspected side effects of DPP-4 inhibitors. Sitagliptin causing pancreatitis has not been proved yet. Though, diabetes in itself is one of the risk factor for pancreatitis.

## **INTRODUCTION**

I shall review this article mainly for its action on blood glucose levels and the cardiovascular system. In this article the author has elaborated only on three drugs namely Sitagliptin, Saxagliptin, and Vildagliptin.

Saxagliptin, Vildagliptin and Sitagliptin are different in their metabolism (Saxagliptin and Vildagliptin are metabolized in the liver while Sitagliptin is not metabolised in liver) their recommended dosage, excretion, and the daily dosage for effective treatment. But when compared to their efficacy regarding lowering the safety of the drug its HBA1c lowering effect and patient tolerance, all are almost same.

I shall look into the different studies which the author has taken as references to impress the usefulness of DPP-4 inhibitors in not only influencing the glycemic cycle but also the cardiovascular system and the weight neutrality.

I shall look into the different studies used as references by the author to prove his point.

A study done by Hsieh et al showed that inhibition of DPP-4, or increasing of GLP-1 receptor (GLP-1R) signaling, causes a decrease in intestinal secretion of triacylglycerol, apolipoprotein B-48 and cholesterol. Further the endogenous GLP-1R signaling is required for the control of secretion and biosynthesis of intestinal lipoprotein.

These studies with other similar ongoing studies used by the author have impressed that the DPP-4 inhibitors group of drugs will have a beneficial effect not only on the glycemic control but also on cardiovascular system.

## **ARTICLE SUMMARY**

DPP-4 are few of the newer generation of drugs which are showing effectiveness in not only controlling blood sugars but also having reasonable effect on cardiovascular system, blood pressure and other metabolism of the body.

Management of diabetic patients with these drugs from the incretin family is one of the latest addition in the group of oral anti diabetic medication which is as efficient as the other oral anti diabetic drugs, it is safer to treat with a DPP-4 inhibitor rather than a sulfonylurea when compared to the incidences of hypoglycemia. It can be used as a single drug or in combination with metformin. When wanting to choose between the GLP-1 analogues and the DPP-4 inhibitors, the physician should take into consideration the patient's age, weight, compliance, the time from initial diagnosis of diabetes, and financial status.

In the older population the author has recommended the use of DPP-4 inhibitors for their confined effect in blood glucose lowering and no effect on caloric intake so less negative effect on the total body protein mass and the muscle. In young patients who have been newly diagnosed type 2 diabetes, abnormal metabolic profile, abdominal obesity, the physician should consider treating with a GLP-1 analogs as it will have a better effect in improving metabolic profile and weight reduction. DPP-4 inhibitors when used in low doses are safe for managing patients with moderate to severe renal failure, while GLP-1 analogs are contraindicated in these patients.

## **ARTICLE STRUCTURE**

The author has presented this article and its relevant references and study in a very simple and narrative manner though with not much of visual statistics like graphs tables etc. but he has managed to impress upon the beneficial use of the three drugs Sitagliptin, Vildagliptin and Saxagliptin.

The author introduces the drugs when they were introduced in different part of the world and touches upon the metabolism and excretion.

He further moves on to the effects of these three drugs on the glycemc cycle, cardiovascular action and weight reduction all of which he has authenticated by different studies.

The author has mentioned different studies which show the effect on HBA1c and that DPP-4 inhibitors are a little less effective than sulfonylureas but equally effective as thiazolidiones and metformin in reducing blood glucose. But in studies where a combination of DPP-4 inhibitors and metformin in one tablet were used, the results were better.

Studies with regard to weight, DPP-4 inhibitors showed variable results but are usually considered to be neutral though some studies have shown a loss of weight for almost up to 1.8 kilogram.

Mistry et al. showed that sitagliptin had small but significant reductions statistically in systolic blood pressure varying between 2–3 mmHg and diastolic between 1.6–1.8 mmHg in a 24-hour blood pressure measured acutely in ambulatory patients on day 1 and on day 5 it showed a steady state in non-diabetic patients with mild to moderate hypertension.

Boschmann et al explained that DPP-4 inhibition increases postprandial mobilization and oxidation of lipid by activating the sympathetic system but not by a direct effect on metabolic status.

He has concluded with a comparison between DPP-4 and GLP-1 analogs where he has proved that GLP-1 analogs are a drug of choice in younger patients especially newly diagnosed while DPP-4 inhibitors are better suited for older patients.

## **ARTICLE CRITIQUE**

### **AUTHORITY**

The author Dror Dicker is working in Tel Aviv, Israel with Hasharon Hospital.

This publication is influenced on the presentations discussed in the 3rd World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy).

The Congress itself and the publication were made in part by grants from Boehringer Ingelheim, Astra Zeneca, Daiichi Sankyo, Bristol-Myers Squibb, Eli Lilly, Ethicon Endo-Surgery, F. Hoffmann-La Roche, Janssen-Cilag, Genex Biotechnology, Johnson & Johnson, Medtronic, Pfizer and Novo Nordisk.

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Dror Dicker has published many papers few of them are:

1. Increased Epicardial Adipose Tissue Thickness as a Predictor for Hypertension: A Cross-Sectional Observational Study by Dror Dicker, Eli Ata et al
2. Metabolic Syndrome Controversy by Dror Dicker - ESIM 2011

## **ACCURACY**

The article has used different studies in the form meta-analysis, retrospective study, clinical trials and long-term prospective trial, this gives it substantial evidence based backup and enough weightage to be considered as an authentic article.

The author has used as references these studies from 2006-2009. The very fact that it is published in Diabetes Care which has a strong preview structure to publish any article in this journal. The authenticity is verified and only then it is published thus giving this article and the author a sort of authority on this topic.

So in conclusion it can be said the article is reasonably accurate.

## **WHETHER THE ARTICLE IS OLD / CURRENT**

This article was published in the diabetes care issue of 2, May 2011 which is around 2 and a half year from now. DPP-4 has become one of the most popular drugs used in diabetes for its multicentric action. Though much work has been done on DPP-4, the studies and references used by the author in his article still holds good and there is no denial that these are evidence based which are supporting this article to prove its point. In recent years the cost effectiveness of this drug compared to a sulfonylurea or other oral hypoglycemic agents have been matter of discussion.

## **RELEVANCY**

The title of DPP-4 Inhibitors and its Impact on glycemic control and cardiovascular risk factors does justify the information shared by the author. Though besides giving the different studies which have proved the actions and efficacy of DPP-4 inhibitors on glycemic control and cardiovascular effects he has also touched upon the weight loss or neutrality of these drugs.

He has compared DPP-4 inhibitors with GLP-1 analogs their effectiveness in different age groups ie younger and newly diagnosed show better response to GLP-1 analogs while older group benefit more with DPP-4 inhibitors and the reason behind their action which he has seconded by different studies. Though there is no reference of GLP-1 analogs in the title.

## **OBJECTIVITY**

The author has objectively used different studies to prove his point about DPP-4 inhibitors and to some extent GLP-1 analogs. He has proved the usefulness of DPP-4 inhibitors in the glycemic cycle, cardiovascular action and weight effects with the use of different studies. It does not appear to be biased article though as mentioned by the author that this publication “on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy)”, was based on the presentations at the 3rd World Congress. Grants were given to the Congress and also for the

publication of this supplement from different pharmacological companies which could have been an influence.

## **STABILITY**

The article has used recognised studies, references for describing DPP-4. He has mentioned that there is no conflicts of interest with regard to this article. Diabetes Care is one of the most respected journals in the field of diabetes and the article being published here gives it stability.

## **ANALYSIS OF GRAPH/IMAGE/TABLE**

Not applicable.

## **RECENT ADVANCES RELATED TO THE TOPIC**

An article published by Claire McDougall, Miles Fisher, Gerard A McKay Fisher, *Drugs for Diabetes: Part 5 DPP-4 Inhibitors in Medscape Br J Cardiol.* 2011;18(3):130-132 showed that managing patients having type II diabetes, needs balancing potential benefits of controlling hyperglycaemia on microvascular and macrovascular complications, with possible side effects of treatment and possible harm from over intensive control of glycaemia.

In diabetes hypoglycaemia and weight gain are the undesirable side effects. The adverse effects of drugs like sulphonylureas, glitazones and insulin are all associated with weight gain, while metformin is good with causing slight weight loss. Meanwhile the DPP-4 inhibitors are weight neutral, causing neither weight loss nor weight gain.

Usually patients with type 2 diabetes are overweight or obese, thus DPP-4 inhibitors has a potential advantage over other drugs, and now DPP-4 inhibitors are being used as a second-line therapy in addition to metformin in overweight and obese patients who are unable to achieve glycaemic control with metformin monotherapy. The negligible incidences of hypoglycaemia are an additional advantage in the elderly patients or patients living alone.

Another article published by Sell, Henrike et al titled: *Adipose Dipeptidyl Peptidase-4 and Obesity, Diabetes Care Issue: Volume 36(12), December 2013, p 4083–4090* showed a correlation with insulin resistance and depot-specific release from adipose tissue in vivo and in vitro has impressed upon DPP-4 an adipokine has a higher release from VAT that is particularly pronounced in obese and insulin resistant patients. The authors suggested that DPP4 maybe a marker for insulin resistance, visceral obesity and metabolic syndrome.

Most experts at the World Diabetes Congress 2013 have agreed that patients with type II diabetes who in the high risk for or who already have heart failure should not be precluded from receiving

DPP-4 inhibitor glucose-lowering agents, rather, they should be supervised closely for the initial 6 months of treatment, because the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus — TIMI 53(SAVOR-TIMI 53) trial, reported that heart-failure was associated with the use of saxagliptin, appeared to occur in the initial 6 months of use of the drug(3).

## CONCLUSION

This article brings home a very positive usefulness of DPP-4 inhibitors as one of the leading oral hypoglycemic agents available presently. The incretin family is choice in the management of diabetes. This treatment equally efficient as the other known oral anti diabetic drugs, further it is much safer than sulfonylurea with regard to hypoglycemia and hence can be used as a single drug therapy or in combination with metformin. When choosing a drug to between a GLP-1 analogs and a DPP-4 inhibitors, one must consider different parameters such as the age of the patient, body weight, the time lapse from initial diagnosis of diabetes, financial status and compliance. Also one should consider that DPP-4 inhibitors in low doses can be safely used in patients with renal failure - moderate to severe, while GLP-1 analogs should be avoided in these patients.

The author has compiled different studies which are a mix of meta-analysis, retrospective studies and other references to prove his point about the efficacy of DPP-4, but still there is scope for more research to actually see the benefit of this drug.

The GLP-1 analogs are another newer group of drugs which are almost equally effective though even these needs more research.

Further the cost-effectiveness of DPP-4 is still a topic of discussion.

## REFERENCE

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