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Editorial

Adding a DPP-4 inhibitor to metformin therapy may be safer than you think

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Type 2 diabetes mellitus (T2DM) is a chronic progressive metabolic disorder characterized by hyperglycemia due to insulin resistance and relative insulin deficiency. Recent International Diabetes Federation Guidelines have suggested that anti-diabetic treatment should be initiated with lifestyle interventions and, if glycemic control is not maintained, metformin should be started as first line[1]. In cases uncontrolled with metformin monotherapy, the addition of a sulfonylurea is recommended as the second line of treatment with the eventual introduction of insulin in patients uncontrolled with oral antidiabetes drugs (OADs)[1].

In spite of therapeutic interventions, glycemic control shows a slow but steady downwards trend with time. This is due to the fact that nearly half of β-cell function is lost at the time of diagnosis[2] and on top of that the number of β-cells gradually decreases over time. Hence preservation of β-cell function has now become one of the important focuses of treatment. Various in-vitro studies have been conducted to explore the effect of hyperglycemia on β-cell function and have revealed that the recovery of β-cell function is dependent on the duration of prior glucose toxicity[3] thereby indicating that therapeutic intervention can help in preserving β-cell function if started early in the course of the disease. Therefore, if better glycemic control is attained by initiating combination therapy in the early stages of T2DM, it will help in protecting β-cell function eventually resulting in better management of patients[4].

Treatment with OADs poses the risk of gastro-intestinal side effects, hypoglycemia, weight gain and edema[5]. Nausea and vomiting are generally well tolerated, but hypoglycemia and weight gain, which are usually associated with sulfonylurea use[6], are of major concern to patients. Hypoglycemia can be a distressing symptom for patients and understandably patients develop fear of hypoglycemia. The symptomatology of hypoglycemia varies among different patients and if hypoglycemic episodes occur repeatedly in a patient, a state of hypoglycemia unawareness arises[7] which can eventually result in brain dysfunction as suggested in the literature[8,9]. The risk of hypoglycemia particularly increases in the elderly[10], with the use of long acting drugs[11,12] and in patients with renal impairment[13,14]. With advancing age, elderly patients don't exhibit the typical signs and symptoms of hypoglycemia and neurological symptoms like drowsiness might go unnoticed[15]. Hypoglycemia has also been implicated in the prolongation of the QT interval, with the eventual increased risk of developing arrhythmias[16,17]. Also, in response to hypoglycemia, the autonomic nervous system gets activated and releases epinephrine which increases myocardial contractility thereby increasing cardiac output[17]. This increase in cardiac workload could have minimal impact on healthy individuals, but in the elderly or patients with compromised coronary blood flow it can have fatal outcomes and can even lead to myocardial infarction[18]. Hypoglycemic episodes can thus result in

increased morbidity/mortality, increased total cost of treatment and on a lesser scale can also lead to decreased patient compliance to the extent of treatment discontinuation because of the fear of hypoglycemia[19].

A number of studies have been conducted to assess the incidence of side effects of OADs. The United Kingdom Prospective Diabetes Study (UKPDS) was one of the first studies to assess hypoglycemia in T2DM patients. This 6 year follow up study reported the proportion of patients having at least one hypoglycemic episode as 45% among patients taking sulfonylureas and 3% in patients on metformin[20]. On the contrary, a recent meta-analysis has reported minimal incidence of hypoglycemic episodes with a newer class of OADs, the dipeptidyl peptidase-4 (DPP-4) inhibitors[21]. The UKPDS study reported that over a period of 6 years of treatment, subjects on sulfonylureas and diet therapy gained an average weight of 4 and 2 kg respectively, whereas the subjects on metformin did not gained weight[22]. Weight gain, which is associated with various OADs, may increase insulin resistance and eventually result in worsening of disease. The usage of the thiazolidinedione group of drugs is associated with the risk of patients developing edema[23], heart failure[24], increased risk of fractures[25] as well as bladder cancer[26]. Hence, the side effects of OADs form a big barrier to the optimal management of T2DM patients and managing hypoglycemia in particular, and put challenges in front of the patient and the physician on a daily basis.

The risk of hypoglycemia is minimal with metformin, but the medications added to it for combination purpose increase the incidence of hypoglycemia. This puts a physician in a difficult situation as there is a need to start the combination therapy early in the disease's course, but on the other hand the medications added to metformin either increase the incidence of hypoglycemia or gives rise to other side effects. The recently introduced DPP-4 inhibitors have shown effective glycemic control in randomized placebo controlled trials as add-on to metformin[27,28] and moreover they don't increase the risk of hypoglycemia[29,30]. A 52 week study made a head to head comparison between vildagliptin and glimepiride as an add-on therapy to metformin and showed similar efficacy in both groups with a better safety profile for vildagliptin in terms of no weight gain and significantly lower number of hypoglycemic episodes[31].

Hypoglycemia is not always due to iatrogenic interventions. Sometimes it may result from patients' activities and among them fasting is the most common reason for precipitating hypoglycemia. Especially during the holy month of Ramadan, Muslims from all over the world fast during the day and one study conducted on such a population, the EPIDIAR study, reported that a significantly higher number of hypoglycemic episodes (including severe hypoglycemia) was observed in the T2DM patients on various OADs during the fasting period[32]. The incidence of hypoglycemia during the fasting month has been noted to be particularly high in patients on sulfonylureas. A study conducted in five countries on Muslim patients ($N = 1378$) on sulfonylurea either alone or in combination with metformin, reported hypoglycemic episodes in approximately 20% of the enrolled population[33]. In contrast, DPP4 inhibitors have been found to have a relatively low incidence of hypoglycemic events. A recent prospective study conducted on a fasting Muslim population compared the incidence of hypoglycemia among patients on sitagliptin and sulfonylureas with or without metformin and showed significantly lower risk of hypoglycemia with sitagliptin (RR: 0.52; 95% CI 0.29–0.94; $p = 0.028$)[34]. Hence, DPP4 inhibitors are proving to be a better option for combination therapy with metformin.

Though randomized trials provide a wealth of information, a study conducted in a real clinical setting further strengthens such evidence. One such real life study, EDGE (Effectiveness of Diabetes control with vildagliptin and vildagliptin/mEtformin), was conducted in 27 countries and enrolled 45,868 patients[35], and a paper in which the post hoc analysis of patients from Germany was done has been presented in the current issue[36].

This paper compares the safety and efficacy of vildagliptin with sulfonylureas as an add-on to metformin among German patients who were uncontrolled with monotherapy. To avoid bias, the patients were enrolled in the study after the decision to prescribe either vildagliptin or another OAD was made. The primary endpoint of the study was the response to the treatment which was defined as a reduction of more than 0.3% in HbA1c levels without hypoglycemia, $\geq$5% weight gain, peripheral edema and discontinuations due to gastro-intestinal side effects. In addition, responder rate was defined as subjects achieving HbA1c <7.0% with no proven hypoglycemia and weight gain was also compared between the two groups.

The number of patients enrolled was 8887, out of them 6439 received vildagliptin/metformin (Vld/Met) and 971 were prescribed sulfonylurea/metformin (SU/Met). The response to treatment was achieved by 34.9% and 29.6% of Vld/Met and SU/Met group respectively (unadjusted OR of 1.27, 95% CI: 1.09, 1.47; $p = 0.001$). The responder rate was higher in the Vld/Met group (25.7%) compared to the SU/Met group (17.7%) with an unadjusted OR of 1.6 (95% CI: 1.31, 1.98; $p < 0.001$). Similar findings have been observed in another clinical practice based study[37]. Although the overall proportion of hypoglycemic episodes was low in both groups, the number was nearly four times higher in the SU/Met group (Vld/Met: 0.11%; SU/Met: 0.41%). A limitation of the study was an unequal distribution of patients in the treatment arms (Vld/Met group: 6439 patients, SU/Met group: 971 patients). This was due to the fact that the study design didn't restrict the physicians to allocate the patients to a particular group and the physicians prescribed the treatment as per their

routine practice and patients' preference. Still, a sincere effort was made to compare the efficacy and safety parameters of both groups.

One of the biggest issues a physician encounters while managing a type 2 diabetes patient is to manage the hypoglycemic events associated with the OADs. Therefore, there is lot of inertia on the part of the physicians to start any drug which can cause hypoglycemia as they have limited time to discuss the issues regarding hypoglycemia with patients. The task of the physicians becomes easy when they don't have to worry about hypoglycemia and any drug providing this freedom will eventually help both patients and physicians. Patients on the other hand also fear hypoglycemia and most wish to avoid it at any cost. Most patients fear death as a result of hypoglycemia, a misbelief which is hard to erase with the best of education! By providing a favorable safety profile, DPP4 inhibitors have solved the problem of hypoglycemia to a great extent along with weight gain that causes a lot of problems with sulfonylureas. With the findings of the SAVOR-TIMI 53 showing increased hospitalization of patients with heart failure in the saxagliptin group, the last word on cardiac safety is awaited. This aside, the long-term safety data coming in, along with the possibility of beta-cell preservation, indicate that DPP4 inhibitors will play a role in the management of T2DM patients for a long time to come.

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References

1. International Diabetes Federation, 2012 Clinical Guidelines Task Force. Global Guideline for Type 2 Diabetes. Available at: http://www.idf.org/sites/default/files/IDF%20T2DM%20Guideline.pdf [Last accessed 27 November 2013]
2. Garber AJ. Incretin effects on β-cell function, replication, and mass: the human perspective. Diabetes Care 2011;34:S258-63
3. Gleason CE, Gonzalez M, Harmon JS, et al. Determinants of glucose toxicity and its reversibility in the pancreatic islet β-cell line, HIT-T15. Am J Physiol Endocrinol Metabol 2000;279:E997-1002
4. Hanefeld M. Pioglitazone and sulfonylureas: effectively treating type 2 diabetes. Int J Clin Pract Suppl 2007;61(s153):20-7
5. Bolen S, Feldman L, Vassy J, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. Ann Intern Med 2007;147:386-99
6. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009;32:193-203
7. Bakatselos SO. Hypoglycemia unawareness. Diabetes Res Clin Pract 2011;93(Suppl 1):S92-6
8. Desouza CV, Bolli GB, Fonseca V. Hypoglycemia, diabetes, and cardiovascular events. Diabetes Care 2010;33:1389-94
9. Fanelli CG, Pampanelli S, Porcellati F. Cognitive function in hypoglycaemia. Diabetes Nutr Metabol 2002;15:367-72
10. Bremer JP, Jauch-Chara K, Hallschmid M, et al. Hypoglycemia unawareness in older compared with middle-aged patients with type 2 diabetes. Diabetes Care 2009;32:1513-17
11. Holstein A, Egberts EH. Risk of hypoglycaemia with oral antidiabetic agents in patients with Type 2 diabetes. Exp Clin Endocrinol Diabetes 2003;111:405-14
12. van Staa T, Abenhaim L, Monette J. Rates of hypoglycemia in users of sulfonylureas. J Clin Epidemiol 1997;50:735-41
13. Moen MF, Zhan M, Hsu VD, et al. Frequency of hypoglycemia and its significance in chronic kidney disease. Clin J Am Soc Nephrol 2009;4:1121-7
14. Yale JF. Oral antihyperglycemic agents and renal disease: new agents, new concepts. J Am Soc Nephrol 2005;16(Suppl 1):S7-10
15. Veitch PC, Clifton-Bligh RJ. Long-acting sulfonylureas – long-acting hypoglycaemia. Med J Aust 2004;180:84-5
16. Marques JL, George E, Peacey SR, et al. Altered ventricular repolarization during hypoglycaemia in patients with diabetes. Diab Med 1997;14:648-54
17. Landstedt-Hallin L, Englund A, Adamson U, et al. Increased QT dispersion during hypoglycaemia in patients with type 2 diabetes mellitus. J Intern Med 1999;246:299-307
18. Frier BM, Schernthaner G, Heller SR. Hypoglycemia and cardiovascular risks. Diabetes Care 2011;34(Suppl 2):S132-7
19. Bron M, Marynchenko M, Yang H, et al. Hypoglycemia, treatment discontinuation, and costs in patients with type 2 diabetes mellitus on oral antidiabetic drugs. Postgrad Med 2012;124:124-32
20. Turner RC. The U.K. Prospective Diabetes Study. A review. Diabetes Care 1998;21(Suppl 3):C35-8
21. Karagiannis T, Paschos P, Paletas K, et al. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. BMJ 2012;344:e1369
22. Group UKPDS. U.K. Prospective Diabetes Study 16: overview of 6 years' therapy of type II diabetes: a progressive disease. Diabetes 1995;44:1249-58
23. Nesto RW, Bell D, Bonow RO, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. Circulation 2003;108:2941-8
24. Hernandez AV, Usmani A, Rajamanickam A, et al. Thiazolidinediones and risk of heart failure in patients with or at high risk of type 2 diabetes mellitus: a meta-analysis and meta-regression analysis of placebo-controlled randomized clinical trials. Am J Cardiovasc Drugs 2011;11:115-28
25. Meier C, Kraenzlin ME, Bodmer M, et al. Use of thiazolidinediones and fracture risk. Arch Intern Med 2008;168:820-5
26. Colmers IN, Bowker SL, Majumdar SR, et al. Use of thiazolidinediones and the risk of bladder cancer among people with type 2 diabetes: a meta-analysis. Can Med Assoc J 2012;184:E675-83
27. Ahren B, Gomis R, Standl E, et al. Twelve- and 52-week efficacy of the dipeptidyl peptidase IV inhibitor LAF237 in metformin-treated patients with type 2 diabetes. Diabetes Care 2004;27:2874-80
28. Bosi E, Camisasca RP, Collober C, et al. Effects of vildagliptin on glucose control over 24 weeks in patients with type 2 diabetes inadequately controlled with metformin. Diabetes Care 2007;30:890-5
29. Karasik ACB, Liu J, Wu M, et al. Sitagliptin added to ongoing metformin therapy enhanced glycemic control and beta-cell function in patients with type 2 diabetes. Poster 501-P presented at the American Diabetes Association 66th Annual Meeting and Scientific Sessions in Washington DC, June 2006
30. Rosenstock JBR, Andryuk PJ, Lu K, et al. Addition of sitagliptin to pioglitazone improved glycemic control with neutral weight effect over 24 weeks in

inadequately controlled type 2 diabetes (T2DM). Poster 556-P presented at the American Diabetes Association 66th Annual Meeting and Scientific Sessions in Washington DC, June 2006
31. Ferrannini E, Fonseca V, Zinman B, et al. Fifty-two-week efficacy and safety of vildagliptin vs. glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy. Diabetes Obes Metabol 2009;11:157-66
32. Salti I, Bénard E, Detournay B, et al. A population-based study of diabetes and its characteristics during the fasting month of Ramadan in 13 Countries: Results of the Epidemiology of Diabetes and Ramadan 1422/2001 (EPIDIAR) study. Diabetes Care 2004;27:2306-11
33. Aravind SR, Al Tayeb K, Ismail SB, et al. Hypoglycaemia in sulphonylurea-treated subjects with type 2 diabetes undergoing Ramadan fasting: a five-country observational study. Curr Med Res Opin 2011;27:1237-42
34. Aravind SR, Ismail SB, Balamurugan R, et al. Hypoglycemia in patients with type 2 diabetes from India and Malaysia treated with sitagliptin or a sulfonylurea during Ramadan: a randomized, pragmatic study. Curr Med Res Opin 2012;28:1289-96
35. Mathieu C, Barnett AH, Brath H, et al. Effectiveness and tolerability of second-line therapy with vildagliptin vs. other oral agents in type 2 diabetes: a real-life worldwide observational study (EDGE). Int J Clin Pract 2013;67:947-56
36. Göke R, Gruenberger JB, Bader G, Dworak M. Real-life efficacy and safety of vildagliptin compared with sulfonylureas as add-on to metformin in patients with type 2 diabetes mellitus in Germany. Curr Med Res Opin 2014;30:785-9
37. Bluher M, Kurz I, Dannenmaier S, et al. Efficacy and safety of vildagliptin in clinical practice – results of the PROVIL-study. World J Diabetes 2012;3:161-9

