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Impact of Reduction in Pill Load Upon Use of a Once Weekly DPP-4 Inhibitor in 2 Cases of Type 2 Diabetes

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Abstract

Introduction: DPP-4 inhibitors are an integral part of the treatment of type 2 diabetes mellitus in Kenya. Most diabetics suffer from a lack of adherence due to a high pill burden due to multiple co-morbidities and the stigma of dependence on medication. Trelagliptin is a unique DPP-4 inhibitor due to its long biological half-life making it acceptable to be taken as a once-a-week dose. It was first accepted for use in Japan in 2015 and only got into the Kenyan market about 3 years ago. Here we have examined the effects of introducing this molecule into the regimen of a diabetic with extremely poor adherence due to a busy schedule and another diabetic who had multiple co-morbidities and subsequently a high pill load – with the benefits of its use in each case over a period of 6 months of observation.

Methods: These cases reported are the first of a 39-year-old female businessperson with a busy schedule and known to have mild hypothyroidism – yet always missing her medication. She was not confident in her consistency of medication uptake and always slacked in coming in for her tests because of the same. She is diagnosed to have diabetes with strong family history and thereafter she declined to add to her medication with daily metformin. She improved tremendously upon commencing trelaglyptin. The other is of an elderly woman who also had diabetes mellitus type 2, dyslipidemia, BPPV, and hypertension. She was unhappy about her results for diabetes and due to inconsistency in taking her medication but agreed to start on the trelaglyptin since it was once a week. Her outcomes were also very good from the same.

Conclusion: The use of trelaglyptin with the patients in Kenya could potentially lead to reduced stigma and inertia toward commencing medication and improved adherence to medication regimens in diabetes.

Keywords

DPP-4 Inhibitors, Adherence, Diabetes Mellitus Type 2, Pill Load, Glycated Hemoglobin, End-Organ Damage

Case Report

Case #1:

A 65-year-old diabetic female with BPPV, allergic rhinitis, dyslipidemia, osteoarthritis, and hypertension presented with undue fatigue due to her diabetes not being well controlled. She admitted to not being able to comply with her medication timings as required due to living with only her 70-year-old husband and not having anyone to take care of them. On average her fasting blood sugar readings would range between 10.0 and 13mmol/l while having to take metformin 1000mg twice a day and vildagliptin 50mg twice a day together

with telmisartan 80mg once, amlodipine 5mg once, betahistine 8mg two times a day, rosuvastatin 5mg once, calcium with vitamin D twice a day, and fluticasone nasal spray. She had a good understanding of her chronicity of medical conditions and her harm from non-compliance with medication. She had been diabetic for slightly more than 5 years and her educational background was that of a university graduate. She had not been admitted to the hospital in her life apart from giving birth two times. Her family history was significant for Diabetes Mellitus type 2, but nothing else.

She had tried using pill boxes to organize her medication and ensure that she does not skip any tablets but sometimes she admitted she just forgot to take them. She further expressed in her consultation that she would be much happier if there was a possibility of reducing her pill load to comply better with the medication. Sometimes she would purposely not take the medication because she would be "fed up" with taking so many tablets in a day. The blood test results taken during her first consultation are in **Table-1**.

Table-1: Case-1 blood test results

Test	Initial Result (ref range in brackets)	Result in 6 Months
HbA1c	8.9% (<6.5)	7.5% (<6.5)
Kidney Function	NORMAL – e GFR 69 ml/min/1.73 m 2 (>60)	NORMAL – e GFR 67 ml/min/1.73 m2 (>60)
Random Lipid Profile	Total Chol- 3.9 mmol/l (<5.16)	Total Chol- 3.5 mmol/l (<5.16)
	Triglyceride- 1.5 mmol/l(<1.8)	Triglyceride- 1.3mmol/l (<1.8)
	LDL Chol- 2.0 mmol/l((<3.8)	LDL Chol-2.2 mmol/l (<3.8)
	HDL Chol-0.8 mmol/l(>1.4)	HDL Chol-0.6 mmol/l (>1.4)
Thyroid Function	FREE T3- 1.3 ng/ml (0.8-2.0)	FREE T3- 0.9 ng/ml (0.8-2.0)
	FREE T4- 4.7 ug/dl (4.66-9.32)	FREE T4- 5.5ug/dl (4.66-9.32)
	TSH – 3.5 uIU/ml (0.25-5.0)	TSH – 2.9 uIU/ml (0.25-5)
Random Serum Insulin Levels	11.0 U/ml (2.6-24.9)	Not done

There was slight stage I related retinopathic changes in the right eye, but no other clinical signs of end-organ damage. Insulin levels were tested initially to identify the need for supplementary insulin and measure its depletion but this was not necessary to repeat in 6 months.

After counseling the patient, we agreed that the reason for her sugars not being well controlled was her non-compliance with medication. A shared decision was made to switch her to a regimen that had a much lower pill burden to attempt to improve compliance with the medication regimen she was on.

We gave a fixed-dose combination for the telmisartan and amlodipine and made the metformin extended release once a day. She was particularly impressed with the fact that her DPP4 inhibitor we chose was to be taken once a week – trelaglyptin 100mg. For the betahistine, an ENT specialist involved was able to confirm she only needed one 8mg pill a day until a further review in about 3 months. Exercise was also advised on a consistent basis at 30 minutes of brisk walking daily.

When she attended my clinic for a review in 3 months, she reported much improvement in her compliance with medication since the initiation of the reduced pill regimen. Her fasting sugars would on average be around seven. She felt much better in terms of her energy levels as well. HbA1c had reduced to 7.1%, while her kidney function remained normal, and her triglyceride levels also normalized.

***Case #2*:**

A 39-year-old female hypothyroid single

businessperson who was getting difficulty, due to her busy schedule, to comply with her medication for hypothyroidism now presented with new onset diabetes. She was sure she would not be able to adhere to the medication consistently after seeing her inconsistency in taking her thyroid medication. She declined to take metformin due to this reason despite being counselled on the potential harm it could cause. She has a strong family history of Diabetes with her father having progressed to insulin dependency.

Her remaining examination and history were normal. She had no past medical history of note. Lab test results are in **Table-2**.

After discussing with her on methods that she would use to remember to take her medication on time, she claimed to have attempted all of them in her efforts to comply. She was advised on keeping an alarm and ensuring better compliance to her thyroid medication and her exercise regime. For initiation of therapy regarding the diabetes, she agreed to taking a tablet a week due to its frequency of being taken being very convenient for her.

The results of her complying with medication has been seen in her lab results below with reductions in Hba1c, and improvement in her thyroid function results as well.

Table-2: Case-2 blood test results

Test	Initial Result (ref range in brackets)	Result in 6 Months
HbA1c	7.2% (<6.5)	6.5% (<6.5)
Kidney Function	NORMAL – e GFR 95 ml/min/1.73 m 2 (>60)	NORMAL – eGFR 105 ml/min/1.73m 2 (>60)
Random Lipid Profile	Total Chol- 4.7 mmol/l (<5.16)	Total Chol- 5.0 mmol/l(<5.16)
	Triglyceride- 1.7 mmol/l(<1.8)	Triglyceride- 1.2mmol/l(<1.8)
	LDL Chol- 3.5 mmol/l((<3.8)	LDL Chol-3.2 mmol/l((<3.8)
	HDL Chol-0.5 mmol/l(>1.4)	HDL Chol-0.8 mmol/l(>1.4)
Thyroid Function	FREE T3- 1.0 ng/ml (0.8-2.0)	FREE T3- 0.9 ng/ml (0.8-2.0)
	FREE T4- 5 ug/dl (4.66-9.32)	FREE T4- 7 ug/dl (4.66-9.32)
	TSH - 6.2 uIU/ml (0.25-5.0)	TSH - 5.5 uIU/ml (0.25-5)
Random Serum Insulin Levels	15.0 U/ml (2.6-24.9)	NOT DONE

Discussion

Diabetes Mellitus type 2 has a large prevalence globally and the chronic nature of the condition has implications for inducing mood disorders and stigma in the affected patients [1]. Due to these reasons people hide their condition and are sometimes not able to comply with requirements for control of diabetes through lifestyle and dietary modification. Their attitude toward disease is also negatively impacted by the fact that they will require to take large amounts of medication regularly. The pill burden is well known to have a negative impact socially and mentally as well as forming a barrier to adherence to medication. This was both significantly felt in patients who were above and those below the age of 65 years [2].

The impact of the lack of adherence due to the above is very large globally. Meta-Analysis studies of more than one hundred global studies have shown a poor adherence to medication in patients with hypertension, diabetes, and dyslipidemia. The measure of medication possession ratio over 12 months was mostly around 60%. That means about 40% of the doses would not be complied with [3].

Trelagliptin is a unique oral hypoglycemic that belongs to the dipeptidyl peptidase-4 (DPP-4) inhibitors group. It was first approved for use in Japan in the year 2015 where it showed clear non-inferiority

in diabetes control versus alogliptin that was given daily [4]. It conforms to the characteristics of other DPP-4 inhibitors in the increased safety profile against hypoglycemic events in comparison to sulphonyl urea's (except gliclazide), which have made the class an exceedingly popular solution to Diabetes mellitus type 2 [5]. Even with severe renal impairment of CrCl <30, trelagliptin has shown no major safety concerns in a study after adjusting the dose to 25mg once a week [6].

There is no doubt from the literature that after metformin therapy is not able to control diabetes, DPP-4 inhibitors are much more appropriate to add on that sulphonyl urea's. There was also a clear decrease in incidence of cardiovascular events and all-cause mortality when this was implemented [5]. In fact, there have even been studies showing DPP-4 inhibitor monotherapy, though inferior to metformin as a first line, may be considered for use in cases with HbA1c levels of between 6.5% and 7.5%, where metformin monotherapy is contra-indicated or not feasible [7].

Trelagliptins introduction into the Kenyan market over the last 2 years has a potential to significantly improve our patient's adherence to medication. It has shown an incredibly positive change in both the attitude to taking medication consistently and reduction in the stigma to the disease for both these cases. DPP-4 inhibitors have also been used in conjunction with insulin therapy [8], and it may be a particularly good option to be considered in the Kenyan population who would benefit from the pill burden reduction. The beneficial consistency in sugar control would further curb our incidence of end organ damage and both macro- and microvascular complications from the disease [9]. A good example can be found in the case studies afore mentioned.

Conclusion

Trelagliptin has shown efficacy in action while being administered on a weekly basis, thereby reducing the pill burden in diabetes management. This has shown benefit in improving adherence and reducing the stigma related to the chronic disease. It would a make viable choice for clinicians to consider in Kenya since it has been introduced in our country over the last few years.

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Conflict of Interest

The author has read and approved the final version of the manuscript. The author has no conflicts of interest to declare.

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