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Case Reports

Effectiveness and Safety of Sitagliptin in Patients with Beta-thalassaemia Major and Diabetes Mellitus: A Case Series

Shahrzad Zonoozi[1], Maria Barnard[1], Emma Prescott[2], Romilla Jones[1], Farrukh T Shah[2] and Ploutarchos Tzoulis[1]

[1] Department of Diabetes, Whittington Hospital, Magdala Avenue, London, N19 5NF
[2] Department of Haematology, Whittington Hospital, Magdala Avenue, London, N19 5NF

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Abstract. Sitagliptin, a modern antidiabetic agent which is weight neutral and associated with low rate of hypoglycaemias, is being increasingly used in type 2 diabetes mellitus (DM). However, there is a paucity of data about its efficacy and safety in beta-thalassaemia major (β-TM).
This retrospective case series of five patients (mean age of 45 years) is the first study evaluating the use of sitagliptin in patients with β-TM and DM.
Four patients responded well to sitagliptin, as evidenced by a decrease in fructosamine by 77 and 96μmol/L (equivalent reduction in HbA1c of 1.5% and 1.9%) observed in two patients and reduction in the frequency of hypoglycaemia without worsening glycaemic control in two others. One patient did not respond to sitagliptin. No patients reported significant side effects.
This study provides evidence that sitagliptin may be considered, with caution, for use in patients with β-TM and DM, under the close monitoring of a Diabetologist.

Keywords: diabetes, beta thalassaemia, sitagliptin.

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Correspondence to: Ploutarchos Tzoulis, Department of Diabetes, Whittington Hospital, Magdala Avenue, London, N19 5NF. E-mail: ptzoulis@yahoo.co.uk

Introduction. The aetiology of diabetes mellitus (DM) in patients with β-TM is multifactorial. It has been predominantly attributed to transfusion-related pancreatic iron overload resulting in destruction of insulin secreting β cells of the pancreas and liver haemosiderosis leading to insulin resistance.[1] Other factors such as hepatitis C viral infection, autoimmunity, family history of DM and genetic factors also play an important role.[2] As life expectancy in patients with β-TM has risen substantially, optimal glycaemic control is becoming extremely important in order to reduce the risk of diabetic complications.

Sulfonylureas, traditionally considered second line glucose-lowering agents after metformin, are associated with a poor side-effect profile, including high risk of hypoglycaemia and weight gain. For these reasons, the 2015 position statement for type 2 DM recommends considering the use of dipeptidyl peptidase 4 (DPP-4) inhibitors or gliptins as second line agents when the first line agent, metformin, has not achieved optimal glycaemic control.[3] The most popular drug in this drug class, sitagliptin, inhibits DPP-4, the key enzyme which inactivates glucagon like peptide 1 (GLP-1),[4] leading to increased levels of GLP-1 in the plasma. GLP-1 is a gut hormone

which increases insulin secretion and suppresses glucagon secretion in a glucose-dependent manner. DPP-4 inhibitors have similar glucose-lowering efficacy as sulfonylureas, whilst associated with lower risk of hypoglycaemia and no weight gain.[5] In addition, some studies have suggested that sitagliptin may have greater durability of glucose control and better maintenance of beta-cell function in comparison with sulfonylureas.[6]

In patients with thalassaemia and DM there has been little to no published data supporting the efficacy of modern oral antidiabetic agents such as sitagliptin. The aim of this study was to evaluate the efficacy and safety of sitagliptin in patients with β-TM and DM in a Specialist Thalassaemia Centre in the UK.

Methods. Our study is a retrospective case series of patients with β-TM and DM at our institution treated with sitagliptin. All the participants attended the Joint Diabetes Thalassaemia Clinic at our Specialised Thalassaemia Centre serving the largest cohort of patients with thalassaemia in the UK.

There were no pre-specified criteria for the use of sitagliptin. For example, markers of pancreatic β-cell function, such as serum C-peptide, and of insulin resistance, such as homoeostasis model assessment of insulin resistance (HOMA-IR), were not evaluated prior to treatment initiation. They were not regarded as essential since sitagliptin is effective as an add-on glucose-lowering therapy even in patients with insulin deficiency by suppressing glucagon secretion in a glucose-dependent manner.[7]

Retrospective case notes and biochemical results review was performed in order to collect data on: demographic characteristics (age, gender, ethnic origin), duration of diabetes, smoking status, weight, antidiabetic treatment history, fructosamine, blood pressure, lipid profile, liver function tests and ferritin on a 6-monthly basis starting from the time point of sitagliptin initiation until most recent review or its discontinuation.

Since glycated haemoglobin (HbA1c) can be unreliable in patients with β-TM due to regular transfusions, fructosamine levels were regularly monitored as a surrogate marker of glycaemic control in the preceding 2-3 weeks.[8] Fructosamine was measured in the serum using a Roche Modular P800 system. A fructosamine level of 285 μmol/L was considered as being equivalent to HbA1c of 6.5% with every additional 50 μmol/L of fructosamine being calculated as equivalent to a rise of 1% in HbA1c.[9] Fructosamine and ferritin values were calculated as a mean of 2 or 3 results around the time point of interest.

Written informed consent was obtained from all five patients for publication of this case series.

Results. Amongst 36 patients with β-TM and DM at our institution, five patients (4 females, 1 male), all with strong family history of diabetes and aged between 44 and 50 years, were commenced on sitagliptin at a dose of 100 mg once daily, as shown in **Table 1**.

Sitagliptin was used as second line agent in one patient, as add-on to metformin. Among the other four patients on metformin and gliclazide combination therapy, sitagliptin was added as 3rd line agent in two cases with poor glycaemic control, while it replaced gliclazide in two cases with frequent hypoglycaemias.

Review of lipid profile and blood pressure during the time period of sitagliptin treatment did not demonstrate any significant changes.

Patient 1. A 50-year-old female with inadequate glycaemic control despite lifestyle modification and metformin monotherapy was started on sitagliptin. Fructosamine levels decreased from 340μmol/L to 323μmol/L at 6 months and 263μmol/L at 12 months (equivalent reduction in HbA1c of 0.3% and 1.2% respectively). Her weight increased by 1kg.

Table 1. Demographic characteristics and iron chelation therapy

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**
Gender	Female	Male	Female	Female	Female
Age (years)	50	44	44	44	45
Ethnic origin	Turkish	Iranian	Turkish	Bangladeshi	Cypriot
BMI (kg/m^2)	21.3	22.8	38.2	24.2	27.2
Smoking status	Non-smoker	Ex-smoker	Smoker	Non-smoker	Ex-smoker
Blood transfusion regime	2-3 units every 3 weeks	3 units every 4 weeks	3 units every 4 weeks	3 units every 4 weeks	3 units every 4 weeks
Iron chelation	Ferriprox and desferal	Ferriprox	Ferriprox and desferal	Ferriprox and desferal	Exjade

BMI: body mass index.

Patient 2. Sitagliptin replaced gliclazide in a 44-year-old male who had poor glycaemic control and frequent episodes of hypoglycaemia on dual combination therapy with metformin and gliclazide. Fructosamine levels initially decreased from 417µmol/L to 337µmol/L at 6 months (equivalent reduction in HbA1c of 1.6%), but then increased to 353µmol/L at 12 months (equivalent increase in HbA1c of 0.3%). Around this time point, gliclazide was reintroduced, resulting in fructosamine decrease to 343µmol/L at 24 months (equivalent HbA1c decrease of 0.2%). Episodes of hypoglycaemia were eliminated, while weight remained stable for the first 2 years, followed by an increase by 4kg in the final 6 months when gliclazide was reintroduced.

Patient 3. This 44-year-old female had frequent hypoglycaemias on dual combination therapy of metformin and gliclazide. For this reason, gliclazide was replaced with sitagliptin which resulted in an increase of fructosamine levels from 246µmol/L to 333µmol/L at 6 months (equivalent 1.7% increase in HbA1c). In light of poor response, sitagliptin was withdrawn and substituted by gliclazide.

Patient 4. This 44-year-old female had frequent hypoglycaemias on combination therapy of metformin and gliclazide. As a result, sitagliptin was initiated, and gliclazide dose was reduced. Six months after sitagliptin introduction, there was a significant reduction in frequency of hypoglycaemic episodes and a slight decrease of fructosamine levels from 265µmol/L to 255µmol/L (equivalent reduction in HbA1c of 0.2%). Her weight increased by 2.2 kg.

Patient 5. A 45-year-old female had suboptimal glycaemic control despite combination treatment with metformin and gliclazide. Sitagliptin was added as 3rd line agent, leading to significant fructosamine reduction from 354µmol/L to 258µmol/L (equivalent reduction in HbA1c of 1.9%) and weight loss of 6 kg over 6 months.

Overall, four out of the five patients were responders to sitagliptin therapy, as evidenced by a significant reduction in fructosamine in two patients by 77 and 96µmol/L (equivalent reduction in HbA1c of 1.5 and 1.9%). In the other two patients, there was a significant reduction in the frequency of hypoglycaemia with relatively stable glycaemic control. In one case sitagliptin did not result in glucose lowering and was appropriately stopped after 6 months. No patients exhibited signs/symptoms of pancreatitis or cholecystitis, while liver function tests did not change significantly after sitagliptin initiation. In total, no significant side effects were reported.

As seen in **Table 2**, there was no relationship between fructosamine and ferritin levels which could explain changes in glycaemic control.

Discussion. Our case series shows that the DDP-4 inhibitor sitagliptin is an effective glucose-lowering agent and is associated with low rate of hypoglycaemias in patients with β-TM. Four out of five patients initiated on sitagliptin were responders, either by achieving a reduction in fructosamine levels or by experiencing less

Table 2. Longitudinal changes in fructosamine, weight and ferritin

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Fructosamine (µmol/L)	**Baseline**	340	417	246	265	354
	6 months	323	337	333	255	258
	12 months	263	353			
	18 months		328			
	24 months		343			
	30 months		294.5			
Weight (kg)	**Baseline**	60.0	65.9	80.5	46.8	64.4
	6 months	61.1	65.8	86.7	49	58.4
	12 months	61.0	-			
	18 months		-			
	24 months		65.7			
	30 months		69.8			
Ferritin (µg/L)	**Baseline**	3843	754	1996	2694	991
	6 months	3319	782.5	806	1974	1201.5
	12 months	3109	973			
	18 months		590			
	24 months		665			
	30 months		496			

frequent hypoglycaemic episodes. These findings are in keeping with RCTs in patients with type 2 DM showing that sitagliptin improves glycaemic control and reduces the rate of hypoglycaemias. The lack of association between changes in fructosamine and ferritin indicates that intensification of glycaemic control could not be attributed, at least in our small cohort, to changes in iron chelation therapy.

Whilst previous studies have reported sitagliptin to be weight neutral in patients with DM, a mixed response was recorded in our cohort.[10] Two patient maintained stable weight, one achieved reduction and two others had weight gain. Besides the effect of sitagliptin, weight gain might be attributed to factors such as poor adherence to dietary advice, concomitant use of sulfonylureas and psychosocial factors.

Data review of this case series did not raise any safety concerns. Previous studies in participants with type 2 DM have shown possible association of DPP-4 inhibitors with pancreatitis, increased risk of infections and arthralgias,[11,12] although the overall incidence of serious adverse events is extremely low.[13] In view of conflicting evidence about whether sitagliptin increases the risk of pancreatitis,[14-16] current consensus is that DPP-4 inhibitors should be avoided in patients with a history of pancreatitis.[15] However gallstones, commonly seen in patients with β-TM, are not a contraindication for the use of sitagliptin. The European spontaneous reporting database recently published 65 reports of cholecystitis in patients with type 2 DM treated with sitagliptin, suggesting sitagliptin may increase the risk of cholecystitis.[17] However a large population-based study showed that DPP-4 inhibitors were not associated with an increased risk of bile duct and gallbladder disease.[18] In contrast to initial reports showing an increased incidence of nasopharyngeal and upper respiratory tract infections in association with sitagliptin, contemporary data do not suggest any increased risk of infection.[19] A recent FDA warning reported sitagliptin has been rarely associated with severe joint pain through an unknown mechanism.

The main strength of our study is that this is the first study ever conducted reporting real-life use of DPP-4 inhibitors in patients with β-TM. Limitations of this study include its retrospective nature, the very small number of patients and the lack of comparator group.

At present sitagliptin as well as other modern antidiabetic agents such as s GLP-1 agonists and SGLT-4 inhibitors are increasingly used with great success in patients with type 2 diabetes, offering optimal glycaemic control and reducing the rate of hypoglycaemic episodes without associated weight gain. However the lack of evidence on efficacy and safety of these agents in patients with thalassaemia restricts access of these patients to potentially valuable therapeutic options. While findings from studies in the general population may apply to patients with β-TM, these patients have a different pathophysiological basis of diabetes and also have multiple comorbidities and complex needs. These reasons highlight the urgency to generate high quality evidence in this field.

Whilst our data supports the potential for sitagliptin use as add-on therapy to metformin and sulfonylurea combination therapy in patients with β-TM, we recommend considering also the use of sitagliptin as second line agent to metformin in agreement with international guidelines for patients with type 2 DM.[3] The rationale behind this is that sulfonylureas, which are commonly used nowadays as second-line agents, are associated with high rate of hypoglycaemia and significant weight gain. Specifically, optimal candidates for switching from sulfonylurea to sitagliptin in order to decrease significantly symptomatic hypoglycaemia are patients with dominant insulin resistance.[20] Taking into account that very little to no data exist on sitagliptin use in patients with β-TM, the benefits and risks of therapy should be carefully considered and always discussed with the patient. If patient and doctor make a decision to start sitagliptin, they should specify the goals of this therapy. For example, sitagliptin should be usually discontinued if the patient does not achieve fructosamine reduction of at least 25μmol/L (equivalent HbA1c reduction of 0.5%) within 6 months of initiation or does not experience a significant reduction in the frequency of hypoglycaemic episodes. Finally, initiation of sitagliptin should take place only under the guidance, supervision and close monitoring of a Diabetologist with experience in management of patients with β-TM and DM.

Conclusion. Our study provides some evidence that sitagliptin could be considered for use in selected patients with β-TM and DM. To the best of our knowledge, this is the first study demonstrating the efficacy and safety of a modern oral antidiabetic agent in patients with β-TM and it could facilitate access of this population to sitagliptin.

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