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Rechallenge with a Fixed Combination of Extended-Release Metformin plus Sitagliptin in Patients Labeled as Metformin-Intolerant is Well Tolerated and Reduces Albumin Excretion: The Memory Trial

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Abstract

Objective: To assess the tolerability of extended-release metformin in patients with type 2 diabetes mellitus labeled as metformin-intolerant and treated with a dipeptidyl-peptidase-4 inhibitor, and if its use can result in an improvement in renal function, particularly in reduction of albumin excretion.

Material and Methods: We recruited patients with type 2 diabetes mellitus and gastrointestinal metformin intolerance treated with a dipeptidyl-peptidase-4 inhibitor (excluding those with glomerular filtration rate <45 mL/min/1.73 m^2). It was switched to a single-pill combination of extended-release metformin and sitagliptin in 1000/50 mg pills, initially one daily, and two daily after one month if tolerance was acceptable. At baseline and after 3-4 months, fasting glucose, HbA1c, blood pressure and albuminuria in a morning urine sample were measured. The satisfaction of the patients was assessed by a Likert scale and their quality of life by EuroQoL-5D-3L.

Results: Of 72 recruited patients (62% women, age 55 ± 8 years), 60 (83%) tolerated 1 pill and 52 (72%) 2 pills. Fasting glycaemia dropped from 175 ± 34 to 127 ± 37 mg/dL (p <0.01). HbA1c dropped from 8.3 ± 1.0% to 7.6 ± 0.9% (p <0.01). The reported satisfaction was: Very High, High, Indifferent, Low, Very Low or No Response in 55.7%, 20.0%, 12.6%, 5.7%, 2.9% and 2.9% of the patients, respectively. The EuroQoL-5D-3L index improved from 0.759 ± 0.120 to 0.866 ± 0.132 (p=0.008). The glomerular filtration rate was unchanged but the albumin/creatinine ratio was reduced from 39 (17-78) to 31 (14-63) mg/gr (p=0.029). There was a strong positive correlation between the changes in the albumin/creatinine quotient and in HbA1c (r=0.473, p <0.001).

Conclusions: A large majority of our patients with type 2 diabetes mellitus and metformin intolerance treated with a dipeptidyl-peptidase-4 inhibitor tolerated extended-release metformin, with significant improvement of their metabolic control and their albumin excretion, reporting a high degree of satisfaction and improved quality of life.

Keywords: Extended-Release Metformin; Type 2 diabetes mellitus; Metformin intolerance; Sitagliptin; Albuminuria; Satisfaction; Quality of life; Rechallenge

Introduction

It is well recognized that changes in albumin excretion are predictors of cardiovascular and renal outcomes and can be used as surrogate endpoints [1-3]. Although the focus of treatment in patients with type 2 diabetes mellitus (T2DM) has shifted to new drugs such as SGLT2 inhibitors and GLP-1 receptor agonists [4,5], metformin is still a mainstay of therapy in these patients and is recommended as first-line treatment in most present guidelines [6-8]. Many trials have shown that intensive glucose control has a favorable effect on microvascular diabetic complications such as diabetic nephropathy [9-11]. Metformin has been shown to reduce albuminuria in patients with T2DM [10,12,13], and nephroprotective effects of metformin beyond its well-known glucose-lowering effects have been described [14-17].

Metformin is effective, inexpensive and largely devoid of severe side effects [18]. However, gastrointestinal disturbances, such as diarrhea, bloating, meteorism, nausea, and abdominal pain are very frequent [18]. In most patients they subside after a few weeks or months, but in a sizable minority of the patients (typically between 10 and 25% in different trials) [18,19] they remain indefinitely, disturbing the patients' well-being and quality of life [20], reducing adherence and compliance [18], and leading to poorer outcomes [21].

Conventional, immediate-release metformin, has a short duration of action, with a marked plasmatic peak 2.5 hours after ingestion, but since 2003 extended-release formulations of metformin are widely available, with a delayed and much less marked peak of action about 7 hours after ingestion and an effective duration of action nearing 24 hours [22-24]. The use of this extended-release metformin (XRM) in associated in several trials to a marked improvement in gastrointestinal tolerance vs. conventional metformin [24-28], even in patients previously labeled as metformin-intolerant [25]: it can improve the patients' adherence and compliance [26-28], enhance their quality of life [28] and the achievement of glycemic targets [26-28]. Since 2005 the British NICE guidelines for treatment of type 2 diabetes in adults (NG28) recommend offering XRM to patients who complain of gastrointestinal disturbances with the use of conventional metformin [6].

However, in the Spanish market, due to economic issues, XRM is still not available as a monotherapy. Only since 2022, when the patent of sitagliptin expired, many fixed combinations of generic metformin plus sitagliptin suddenly became available, most of them based on conventional metformin but some on XRM, in pills containing 1000 mg of XRM + 50 mg of sitagliptin. Thus we were able to prescribe XRM in patients previously labeled as metformin-intolerant, provided that the use of sitagliptin was also adequate. Favorable experiences in our first patients induced us to design an open-label, investigator-promoted assay in order to assess the tolerability and effectiveness the XRM/sitagliptin single-pill combination in patients with T2DM labeled as metformin-intolerant and treated with a DPP4 inhibitor but insufficiently controlled, and if the use of this combination can result in an improvement in renal function, particularly in reduction of albumin excretion.

Methods

For this study, consecutive unselected patients were recruited except for the following inclusion and exclusion criteria:

Inclusion

- Both sexes
- Aged 40 - 69 years
- Clinically diagnosed T2DM
- Insufficient blood glucose control (HbA1c > 7%, in the last 2 available visits)
- Gastrointestinal intolerance to metformin
- Pharmacologic treatment of T2DM including full-dose of a DPP4 inhibitor
- Informed consent

Exclusion

- Clinical suspicion of T1DM
- Very poor blood glucose control (HbA1c >9%)
- Concomitant severe disease
- Cardiovascular event in the 3 previous months
- Alcoholism or addictions
- Known poor adherence to medication or to scheduled clinical visits
- Present or planned pregnancy
- Stage III obesity (BMI >40 kg/m^2)
- Chronic kidney disease stage IIIb, IV o V (estimated GFR < 45 mL/min/1.73 m^2)
- Metformin intolerance or contraindication due to non-gastrointestinal causes (allergy, etc.)

Protocol

In the first visit and after having checked the compliance with the inclusion and exclusion criteria and obtained informed consent, weight and height were measured by standard clinical procedures; blood pressure and heart rate were obtained according to the present European Society of Hypertension guidelines [29].

Fasting blood glucose, HbA1c, creatinine, lipids (total cholesterol, HDL-cholesterol, non-HDL cholesterol and triglycerides), and the albumin/creatinine ratio in a morning urine sample were measured by routine laboratory methods. The GFR was estimated by the CKD-EPI equation [30], and the risk of progression or renal disease was classified according to the 2012 KDIGO categories [31]. The health-related quality of life was estimated by the well-validated EuroQol-5D-3L questionnaire [32] which includes five dimensions ("Mobility", "Self-Care", "Usual Activities", "Pain/Discomfort", and "Anxiety/Depression"), and three levels for each dimension (good, mediocre or bad), and also an analog visual scale (AVS) or "health thermometer" [32].

The DPP4 inhibitor which the patient was taking was withdrawn and switched to the single-pill combination of XRM/sitagliptin (1000/50 mg), one pill once a day (preferably with dinner) during the first month. After one month, if the tolerance was adequate, the dose was increased to two pills (preferably taken together). In case that the patient was taking additional medication for diabetes control it was not modified, but further recommendations on lifestyle and drug treatment for control of hypertension and dyslipidemia were given, according to the present Guidelines for Cardiovascular Prevention in Clinical Practice of the European Society of Cardiology [33].

The follow-up visit was scheduled after 3-4 months; the body weight, blood pressure and heart rate were measured again, the labs tests and the EuroQol-5D-3L questionnaire were repeated, and a simple Likert scale [34] questionnaire (selection of one of five smiley-type icons conventionally associated to "Very High", "High", "Indifferent", "Low" or "Very Low" satisfaction; with the additional option of "No Opinion") was offered. In order to avoid bias, the questionnaires were never administered to the patients by their responsible physician. Data on medication compliance and tolerance were obtained by an ad-hoc questionnaire.

Statistical Analysis

The normality of the studied parametric variables was assessed by the Kolmogorov-Smirnov test. Those normally distributed (Gaussian) were compared by the Student's paired t-test, and the non-Gaussian by the Mann-Whitney's U-test. In order to compare non-parametric variables in 2 x 2 tables, the Fischer's exact test was used, and the chi-square test in larger tables. For bivariate correlation Pearson's R was used, and for multivariate correlation analysis, a backwards logistic step-by-step analysis was performed. All analyses were done by intention to treat, except where specifically indicated. Calculations were performed by the IBM SPSS 28.0.1.1 for MS-Windows software package. For normally distributed parametric variables, values are given as mean ± standard deviation; median (interquartile range) is used for non-normal ones.

Ethical aspects

The present study has been performed according to the local applicable regulations (European Community Directive 2001/83/EC) and with the ethical principles established by the Helsinki Declaration, updated in Fortaleza, Brazil (2013) [35]. It was submitted for approval in the Ethics Institutional Committee of the Hospital Universitario San Roque of Las Palmas de Gran Canaria, Spain, and for registry in the webpage htpps://clinicaltrials.gov.

Results

A total 72 patients were recruited, 45 (62%) were women, aged 55 ± 8 years, and the known duration of T2DM was 7.5 ± 3.2 years. The main data on the patients at baseline and at the follow-up visit are shown in Table 1. All the analyzed parametric variables were normally distributed except for plasma triglycerides and the albumin/creatinine quotient.

Of 72 patients, 60 (83%) tolerated 1 pill of XRM/sitagliptin 1000/50 mg, although 17 of them (28%) reported mild gastrointestinal symptoms that subsided along the first months and did not cause withdrawal. 52 (72%) of the patients tolerated 2 pills, although 11 of them (21%) reported mild gastrointestinal symptoms after the dose increase. 12 patients (17%) did not tolerate the combination.

Of the 20 patients that did not tolerate 1 or 2 pills, 14 (19.4%) reported diarrhea, 7 (9.7%) flatulence, 4 (5.6%) nausea, 2 (2.8%) dyspepsia, y 1 (1.4%) abdominal pain.

In the 8 patients who tolerated only 1 pill of XRM/sitagliptin, the self-reported compliance by questionnaire was 89.2 ± 6.3% and never < 75%. In the 52 patients who tolerated 2 pills, compliance was 82.3 ± 7.9%, and < 75% in only one patient who reported 72.5% compliance and was not excluded from analysis.

There were no changes in the weight or BMI of the patients. Fasting glycemia dropped from 175 ± 34 mg/dL to 129 ± 23 mg/dL ($p < 0.05$) in the patients who tolerated 1 pill, and to 121 ± 21 ($p < 0.01$) in those who tolerated 2 pills. HbA1c dropped from 8.3 ± 1.0% to 7.7 ± 0.8% ($p < 0.01$) with one pill, and to 7.4 ± 0.7% ($p < 0.01$) with 2 pills. Data on lipid profile, blood pressure and heart rate of the patients were similar in patients who tolerated 1, 2 or no pills and are shown in Table 1.

There were no significant changes in the estimated GFR (CKD-EPI, 57±16 mL/min/1.73 m^2 in the first visit and 59±16 mL/min/1.73 m^2 in the follow-up visit), but the albumin/creatinine quotient (morning urine sample) dropped from 39 (17-78) mg/g to 29 (14-66) mg/g ($p = 0.029$) (Figure 1). In none of the 7 patients who had a baseline quotient ≥ 300 mg/g did it drop to < 300 mg/g, but in 3 of 11 patients (27.3%) with a

baseline quotient ≥ 30 mg/g it dropped to < 30 mg/g (regression to normal albuminuria). No patient had an increase in the quotient from < 30 mg/g to ≥ 30 mg/g, or from < 300 mg/g to ≥ 300 mg/g. No patients had their estimated GFR reduced to < 45 mL/min/1.73 m^2 in the follow-up visit. The distribution of the risk of renal disease progression (2012 KDIGO categories) was: low in 27 patients (38%), moderate in 31 (43%), high in 9 (12%) and very high in 5 (7%) at baseline, which changed to low in 29 patients (40%), moderate in 30 (42%), high in 8 (11%) and very high in 5 (7%) at the follow-up visit. Although there seemed to be a favorable trend, this change was not statistically significant (p = 0.147).

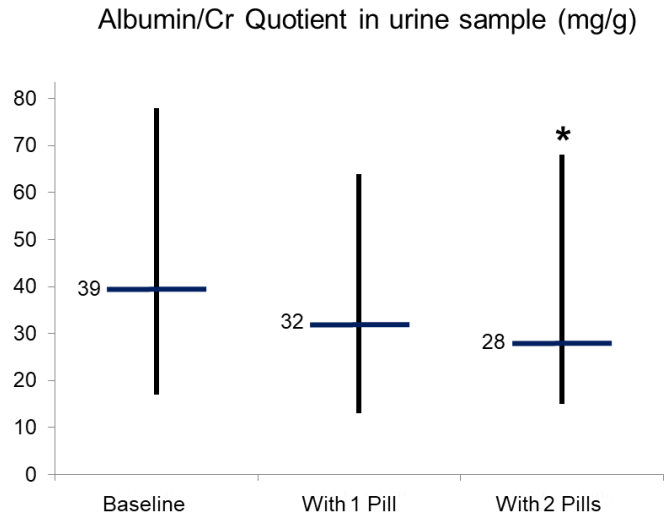

Figure 1: *Changes in the albumin/creatinine quotient in 72 patients with type 2 diabetes mellitus labeled as metformin-intolerant and switched from a DPP4 inhibitor to a single-pill combination of extended-release metformin/sitagliptin (1 or 2 1000/50 mg pills when tolerated), at baseline and 3-4 months after the switch. Because the distribution of this variable is non-Gaussian, values are given as median (interquartile range) and compared by Mann-Whitney U-test. *p= 0.0032 vs. Baseline.*

Table 1: *Parametric Variables analyzed in the Memory study. Parametric variables analyzed in 72 patients with type 2 diabetes mellitus labeled as metformin-intolerant and switched from a DPP4 inhibitor to a single-pill combination of extended-release metformin/sitagliptin (1 or 2 1000/50 mg pills when tolerated), at baseline and 3-4 months after the switch. Normally distributed (Gaussian) variables are given as mean ± standard deviation and compared by paired t-test; and non-Gaussian variables are given as median (interquartile range) and compared by Mann-Whitney U-test. *p < 0.05, **p < 0.01; ***p < 0.001.*

Variable	Baseline	3-4 months
BMI (kg/m^2)	31.5 ± 3.8	30.9 ± 4.1
Systolic Blood Pressure (mmHg)	142 ± 21	132 ± 17***
Diastolic Blood Pressure (mmHg)	175 ± 34	175 ± 34***
Heart Rate (bpm)	78 ± 16	73 ± 15
Fasting Glycemia (mg/dL)	175 ± 34	127 ± 37**
HbA1c (%)	8.3 ± 1.0	7.6 ± 0.9**
Total Cholesterol (mg/dL)	217 ± 33	197 ± 31**
HDL-Cholesterol (mg/dL)	50 ± 15	57 ± 16*
Non-HDL-Cholesterol (mg/dL)	167 ± 34	140 ± 33**
Triglycerides (mg/dL)	190 (154 - 238)	158 (127 – 214)*
Estimated GFR (mL/min/1.73 m^2)	57 ± 16	59 ± 17
Albumin/Creatinine Quotient (mg/g)	39 (17 - 78)	31 (14 – 63)*
EuroQoL-5D-3L Global Score	0.759 ± 0.120	0.866 ± 0.132**
EuroQol-5D-3L AVS Score	68.3 ± 13.9	82.5 ±14.1**
EuroQoL Mobility Score	0.785 ± 0.047	0.801 ± 0.067

EuroQoL Self-Care Score	0.812 ± 0.053	0.824 ± 0.065
EuroQoL Usual Activities Score	0.735 ± 0.067	0.769 ± 0.063
EuroQoL Pain/Discomfort Score	0.625 ± 0.056	0.831 ± 0.057**
EuroQoL Anxiety/Depression Score	0.674 ± 0.071	0.723 ± 0.079

There was a strong positive correlation between the changes in the albumin/creatinine quotient and the changes in HbA1c (Pearson's R = 0.473, p < 0.001), and also with the changes in systolic blood pressure (Pearson's R = 0.212, p < 0.01). The logistic regression analysis showed that both these variables were able to independently predict changes in albumin/creatinine quotient (P-value = 0.005 for HbA1c changes and 0.016 por systolic blood pressure changes) but the rest of the available variables did not predict changes in the quotient.

We were able to obtain the satisfaction report (short Likert scale questionnaire) with the change from the DPP4 inhibitor to the XRM/sitagliptin combination in 70 of the 72 patients. 39 (55.7%) of them reported "Very High" satisfaction, 14 (20.0%) "High", 9 (12.6%) "Indifferent", 4 (5.7%) "Low", 2 (2.9%) "Very Low", and 2 (2.9%) "No Opinion". Logistic regression analysis identified the lack of adverse effects as the only significant predictor of "High" or "Very High" satisfaction (P-value = 0.029), while changes in fasting glucose, HbA1c, BMI, blood pressure, hearggt rate, lipid profile, estimated GFR or the albumin/creatinine quotient did not independently predict satisfaction.

From the total 72 patients, 69 completed the EuroQol-5D-3L questionnaire in both visits. The Quality of Life global score was significantly enhanced, without significant differences between patients who tolerated 1 *vs.* 2 pills of the XRM/sitagliptin combination; the "health thermometer" AVS score was also significantly improved (Table 1). Of the 5 dimensions of the questionnaire, only the "Pain/Discomfort" one was significantly improved, without changes in the "Mobility, "Self Care", "Usual activities" or "Anxiety/Depression" dimensions (Table 1).

Discussion

Albuminuria is a well-established risk factor for the development of renal and cardiovascular complications in diabetic patients [36,37], moreover, there is ample evidence that reductions in albuminuria in these patients with drugs from many different therapeutic groups predict improved cardiovascular and renal outcomes [1-3,38-40]. This was already shown three decades ago with older antihypertensive drugs such as metoprolol and diuretics [41], and also with angiotensin converting enzyme inhibitors [42], angiotensin receptor blockers [43], GLP-1 receptor agonists [44], SGLT2 inhibitors [45], or the new endothelin receptor antagonists [46].

Intensive glucose control protects against the development of albuminuria and progression of diabetic kidney disease [9-11,47], and in particular metformin does reduce albuminuria in patients with T2DM [10,12,13]. Basic research with metformin has shown nephroprotective effects beyond glucose reduction, [12,13,16] such as podocyte preservation [14,15,48,49], and attenuation of albumin-induced alterations in renal tubular cells [17].

Gastrointestinal metformin intolerance is a major therapeutic issue in patients with T2DM [18,19], conducting to poor compliance or withdrawal [18], deteriorated quality of life [20] and greater risk of complications and death [21] besides increased number of hospital and emergency room admissions and higher medical and societal costs [21]. The tolerance of XRM has been compared in many studies with that of conventional (immediate release) metformin and is consistently better [24-28]. An Italian double-blinded randomized trial [28] including 253 patients showed significant benefits in fasting and postprandial glycemia, HbA1c, total and LDL-cholesterol, improved insulin resistance and adipokines, besides a much improved gastrointestinal tolerance and better results in general health perception, impact of diabetes in the quality of life and satisfaction with the treatment [28]. In the only study we were able to find in which metformin-intolerant patients were rechallenged with XRM, only 20% of the patients were still intolerant [25]. Both studies partially corroborate our data, but in none of them a DPP4 inhibitor was associated, while there is some evidence that this association can improve the tolerance on conventional metformin [50]. Also, in none of these studies the effects on albuminuria of renal function of extended-release metformin were assessed.

Most patients with T2DM need a combination of drugs for glycemic control [4-8] and some clinical guidelines recommend the early use of combinations [4,5,8], even in newly diagnosed patients when their HbA1C is > 7.5% [8]. Single-pill combinations have obvious advantages, particularly in polymedicated patients, simplifying their treatment schedule, improving adherence and resulting in better long-term outcomes [51]. They are particularly useful for treatment intensification, which is often delayed in patients with T2DM, exposing then to a higher risk of complications and mortality [52,53]. Several studies have shown that early combination with conventional metformin and a DPP4 inhibitor can improve the glycemic control of patients with newly diagnosed T2DM and maintain it for longer time than conventional stepped therapy [54,55]. A recent expert review [56] concluded that the early use of a single-pill combination of metformin and sitagliptin may be considered a first-line initial combination therapy, considering its safety, effectiveness and low cost. Our experience suggests that the XRM/sitagliptin single-pill

combination is also very well tolerated and accepted by the patients, even when they have been previously labeled as metformin-intolerant, with the potential to overcome inertia and improve compliance. Moreover, this combination may also result in a significant reduction in albuminuria, which could translate in long-term renal and cardiovascular protection.

The limitations of our study are obvious, being open and uncontrolled, thus our results need to be confirmed in a controlled, randomized double-blind study. We do not comment on the improvements in lipid profile and blood pressure, as they seem to be largely attributable to the additional medication offered to the patients and not to XRM. Also, the reduction in albuminuria cannot be attributed only to the addition of XRM, since the added antihypertensive medication is also known to have this effect. However our correlation studies show that although the blood pressure reduction contributed to the improvement in albuminuria, the dominant factor was the reduction in HbA1c. Finally, the recommended changes in lifestyle may have contributed to any or all of our favorable results, but in that case we would have expected a significant body weight reduction, which did not occur. On the whole, our findings are in line with the available evidence, and may contribute to recover for metformin use a very significant fraction of the patients with T2DM who are intolerant to conventional metformin and thus deprived of the long-term benefits of this remarkable drug.

Conclusions

In this open study in patients with T2DM and gastrointestinal intolerance to conventional metformin, the switch from a DPP4 inhibitor to the single-pill combination of XRM/sitagliptin was well tolerated by a large majority of the patients and resulted in a significant improvement in their glycemic control; the patients reported a high level of satisfaction with the treatment and improved their health related quality of life. Moreover, there was a significant reduction in the patients' albumin excretion, suggesting improvement in their long-term renal and cardiovascular risk (although this result is partly attributable also to the reduction in blood pressure by the addition of antihypertensive drugs to the patient's treatment). These results open a new therapeutic window in this group of patients with T2DM who are intolerant to conventional metformin.

Conflicts of Interest

This study was investigator-promoted and has not received funding from any public or private entity. The first author (FJMM) has received honoraria as an expert speaker from ADAMED (maker of the XRM/sitagliptin single-pill combination). No other conflicts of interest are present.

Abbreviations

AVS: Analog Visual Scale; BMI: Body Mass Index; CI: Confidence Interval; CKD-EPI: Chronic Kidney Disease EPIdemiology collaboration; DPP4i: DiPeptidyl-Peptidase type 4 inhibitor; GFR: Glomerular Filtration Rate; GLP-1: Glucagon-Like Peptide type 1; IQR: Inter-Quartile Range; SGLT2i: Sodium-Glucose Transport protein type 2 inhibitor; T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; UKPDS: United Kingdom Prospective Diabetes Study; XRM: eXtended-Release Metformin

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