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Editorial Board of *World Journal of Diabetes*
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381892
Fax: +86-10-85381893
E-mail: wjd@wjgnet.com
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Fax: +86-10-85381893
E-mail: wjd@wjgnet.com
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Antidiabetic treatment: Though lovers be lost, love shall not

Nikolaos Papanas, Efstratios Maltezos

Nikolaos Papanas, Efstratios Maltezos, Outpatient Clinic of Obesity, Diabetes and Metabolism, Second Department of Internal Medicine, Democritus University of Thrace, Alexandroupolis 68100, Greece
Author contributions: Papanas N conceived and wrote the manuscript; Maltezos E finalised and provided useful insight throughout the process.
Correspondence to: Nikolaos Papanas, MD, Outpatient Clinic of Obesity, Diabetes and Metabolism, Second Department of Internal Medicine, Democritus University of Thrace, G Kondyli 22, Alexandroupolis 68100, Greece. papanasnikos@yahoo.gr
Telephone: +30-25-51084972 Fax: +30-25-51074723
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Abstract

The new position statement of the American Diabetes Association and the European Association for the Study of Diabetes on the management of type 2 diabetes mellitus represents a paradigm shift in our understanding of antidiabetic treatment. It emphasises the necessity to individualise management based on patient needs. Glycaemic targets should also be pursued on an individualised basis. New therapeutic combinations are discussed, and the uncertainty surrounding the ideal choice is acknowledged. Above all, it is the mindful and experienced clinician who will implement the best available evidence towards flexible and efficacious treatment. Some areas of uncertainty may ensue, but it is expected that the new position statement will improve patient healthcare and treatment satisfaction. This now remains to be seen in practice.

Key words: Diabetes mellitus; Guidelines; Insulin; Oral agents; Treatment

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INVITED COMMENTARY ON HOT ARTICLES

We read with great interest the recent article by Inzucchi *et al*[1] providing the new position statement of the American Diabetes Association and the European Association for the Study of Diabetes on the management of type 2 diabetes mellitus (T2DM). This new consensus statement is very important, because it represents a paradigm shift in seven issues and is, thereby, anticipated to induce considerable progress in these areas.

This the first, to the very best of our knowledge, consensus statement emphasising the need to individualise treatment, based on patient preferences and characteristics. The pivotal role of individualisation is characteristically expressed in the title describing this approach as "patient-centered"[1]. For example, in patients less willing to perform multiple daily blood glucose monitoring at home, the clinician may consider a slightly less intensive regimen, which is, at the same time, safer in terms of hypoglycemia. Similarly, patients with virtually no meals during daytime and a large dinner may respond well to meglitinide or an injection of premixed insulin at dinner. Individualised therapeutic decisions should also pay attention to age, weight, comorbidities, and, possibly, gender and racial/ethnic differences[1]. In this way, the need for improved guidelines incorporating patient characteristics[2] is realised at last. Such individualised approach would also ensure improved patient empowerment, in accordance with the chronic care model[3]. Arguably, the closer collaboration between patient and physician may be expected to achieve optimal results in a fashion similar to that shown for type 1 diabetes[4].

Secondly, in close relationship with individualised healthcare, comes the choice of glycaemic targets[1]. Indeed, it has now been realised that caution is needed to

avoid too precipitous glycaemic control in subjects with established cardiovascular disease[5]. Likewise, prudence is needed in patients with long diabetes duration, poor life expectancy and/or a heavy burden of comorbidities[1]. In this context, the new position statement provides clear suggestions as to which patients should be more intensively and which less stringently treated. Specifically, stricter glycaemic control is advised, among others, for patients with short diabetes duration, longer life expectancy, as well as absence of unrelated comorbidities and/or vascular complications, whereas less stringent control is advocated for those with the opposite profile[1]. More importantly, the clinician is encouraged to assess every patient on an individualised basis and, dependent on his characteristics as outlined above, place him on a scale between the strictest and least stringent therapeutic targets[1]. At the end of the day, this new approach emerges as the most clinically wise, because it pays tribute to patient uniqueness, and guides patient and physician alike towards treatment flexibility.

Impressively, the new consensus acknowledges that very little is known in terms of which oral agent is the best add-on treatment to metformin[1]. Likewise, in the event of metformin intolerance, it is unknown which agent had best be used as monotherapy[1]. This recognition has duly replaced the older distinction between better and less well studied therapeutic alternatives[6] and provides freedom of choice to the clinician. Certainly, in everyday clinical practice it is not always easy to predict which antidiabetic drug will be the most efficacious in the individual patient, and randomised trials are no safe guide in this endeavour, because they provide general truths that do not necessarily apply to the patient in question[7].

Moreover, the new statement suggests that triple oral combination therapy may be attempted in some patients[1]. This is important because it corresponds to therapeutic choices commonly used in clinical routine, especially in patients reluctant to embark on insulin. The treatment alternative based on three oral agents had hitherto not been approved by existing guidelines, and so its suggestion can be viewed with relief.

A fifth change is that pre-mixed insulin is mentioned as an acceptable, more convenient but less flexible, treatment modality[1]. The premixed insulin regimen may suit patients who eat regularly and cannot easily cope with a more complex regimen[1]. Again, such treatment scheme had not been proposed at all by the prior version[6], and this represents important progress in our understanding of the complexity and suppleness inherent in insulin therapy. As stated in the consensus, any insulin is efficacious in reducing plasma glucose and HbA_{1c} and may, to a variable degree depending on insulin type, be related with some weight gain and/or hypoglycemia[1]. Initiation of basal insulin analogues with subsequent addition of rapid-acting insulin analogues at mealtimes is by far the safest and the most precise and flexible regimen[1] to be widely used, but there is some evidence that one may, in selected patients, start and intensify treatment with premixed insulins as well[8], which should not be entirely ignored.

In addition, the new combination therapy including injectable GLP-1 agonists and basal insulin is now described as a meaningful option[1]. This regime has the advantages of adequate basal coverage by insulin with simultaneous post-prandial effect by the GLP-1 agonist, as well as the potential for some weight loss[9], and it merits further clinical exploration.

Finally, this document clearly emphasises the increasing complexity of antidiabetic treatment options with the ever-rising role of thoughtful clinicians in their implementation[1]. The authors acknowledge that the new position statement is less prescriptive and algorithmic than the previous one. Current evidence must be thoroughly evaluated, and its limitations should not be overlooked. Clinicians are given freedom to judge on their own what is best in every single patient, and their expertise is called upon as an aid in this enterprise[1]. This is a clinical message of vast importance. Indeed, some medications may be withdrawn and others come to the market, but expert clinical judgement will triumphantly survive such changes. What should by all means prevail is the inspiration to combine the best available evidence with clinical judgement suited to every situation, so that patients benefit, or, as the poet Dylan Thomas wrote, "Though lovers be lost, love shall not"[10].

Given these inspiring changes, it now remains to see how they will translate into practice. Will the diabetes community respond to this challenge and seize the opportunity to improve treatment? It is likely that some uncertainty may arise, granted that no absolute therapeutic suggestion is offered. This uncertainty needs to be overcome by carefully examining the potential of therapeutic alternatives in everyday clinical situations. Every experienced clinician should be encouraged to pursue the new approach in order to find out its strengths and limitations. Of further concern, the new position statement may not be very helpful in primary healthcare. At this healthcare level, a more concrete guide to antidiabetic treatment might be appropriate. Nonetheless, primary care physicians should also comprehend the fundamental principles of the new approach and realise that treatment should, ideally, be tailored to patients' attributes and needs. If a more explanatory algorithm based on the new principles is needed, there will be time to write it.

In conclusion, the new position statement of the American Diabetes Association and the European Association for the Study of Diabetes on the management of T2DM reflects important progress in our understanding. Therefore, the authors expect that it will encourage more flexible and efficacious patient healthcare, thereby contributing to improved treatment satisfaction. The beneficial effect of these promising improvements remains to be seen in the near future.

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BRIEF ARTICLE

Efficacy and safety of vildagliptin in clinical practice-results of the PROVIL-study

Matthias Blüher, Ira Kurz, Simone Dannenmaier, Markus Dworak

Matthias Blüher, Department of Medicine, University of Leipzig, 04103 Leipzig, Germany
Ira Kurz, Kantar Health GmbH, 80687 Munich, Germany
Simone Dannenmaier, Markus Dworak, Clinical and Regulatory Affairs, Novartis Pharma GmbH, 90429 Nuremberg, Germany
Author contributions: Blüher M, Dannenmaier S and Dworak M designed research; Blüher M and Dworak M performed research; Dannenmaier S, Kurz I and Dworak M analyzed data; Blüher M, Kurz I and Dworak M wrote the paper.
Supported by Novartis Pharma GmbH
Correspondence to: Dr. Markus Dworak, MSc, Clinical and Regulatory Affairs, Novartis Pharma GmbH, Roonstr. 25, 90429 Nürnberg, Germany. markus.dworak@novartis.com
Telephone: +49-911-27313093 Fax: +49-911-27317093
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Abstract

AIM: To investigate efficacy and safety of vildagliptin compared to other oral antidiabetics in clinical practice in Germany.

METHODS: In this prospective, open, observational study, patients with type 2 diabetes mellitus (T2DM) previously on oral monotherapy were selected by their treating physician to receive either vildagliptin add-on to metformin (cohort 1), vildagliptin + metformin single-pill combination (SPC) (cohort 2) or another dual combination therapy with oral antidiabetic drugs (OADs) (cohort 3). According to routine clinical practice, interim examinations occurred every 3 mo: at baseline, after approximately 3 mo and after approximately 6 mo. Parameters documented in the study included demographic and diagnostic data, history of T2DM, data on diabetes control, vital signs, relevant prior and concomitant medication and disease history. Efficacy was assessed by changes in HbA1c and fasting plasma glucose (FPG) 3 mo and 6 mo after initiation of dual combination therapy. Safety was assessed by adverse event reporting and measurement of specific laboratory values (serum creatinine, total bilirubin, alanine aminotransferase, aspartate aminotransferase, creatine kinase).

RESULTS: Between October 2009 and January 2011, a total of 3881 patients were enrolled in this study. Since 47 patients were withdrawn due to protocol violations, 3834 patients were included in the statistical analysis. There were no relevant differences between the three cohorts concerning age, body weight and body mass index. Average diabetes duration was approximately 6 years and mean HbA1c was between 7.6% and 7.9% at baseline. Antidiabetic treatment was recorded in 3648 patients. Patients were treated with vildagliptin add-on to metformin (n = 603), vildagliptin + metformin (SPC) (n = 2198), and other oral OADs including combinations of metformin with sulfonylurea (n = 370), with glitazones (n = 123), other dipeptidyl peptidase-4 inhibitors (n = 99). After 6 mo of treatment, the absolute decrease in HbA1c (mean ± SE) was significantly more pronounced in patients receiving vildagliptin add-on to metformin (-0.9% ± 0.04%) and vildagliptin + metformin (SPC) (-0.9% ± 0.03%) than in patients receiving other OADs (-0.6% ± 0.04%; P < 0.0001). In addition, significant cohort differences were observed for the improvement in FPG after 6 mo treatment (vildagliptin add-on to metformin: -291 mg/L ± 18.3 mg/L; vildagliptin +metformin (SPC): -305 mg/L ± 9.6 mg/L; other antidiabetic drugs: -209 mg/L ± 14.0 mg/L for (P < 0.0001). Moderate decreases in body weight (absolute difference between last control and baseline: mean ± SE) were observed for patients in all cohorts (vildagliptin add-on to metformin: -1.4 kg ± 0.17 kg; vildagliptin + metformin (SPC): -1.7 kg ± 0.09 kg; other OADs: -0.8 kg ± 0.13 kg). No significant differences in adverse events (AEs) and other safety measures were observed between the cohorts. When performing an additional analysis by age (patients < 65 years *vs* patients ⩾ 65 years), there was no relevant difference in the most common AEs between the two age groups and the AE profile was similar to that of the overall patient population.

CONCLUSION: Clinical practice confirms that vildagliptin is an effective and well-tolerated treatment in combination with metformin in T2DM patients.

Key words: Observational study; Combination therapy; Vildagliptin; Metformin; Type 2 diabetes

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most common non-communicable diseases worldwide and will be one of the most challenging health problems in the 21st century[1]. It is estimated that the world prevalence of diabetes among adults (aged 20-79 years) will be 7.7%, affecting 439 million adults, by 2030[2]. Thus, in addition to preventive measures such as lifestyle changes, effective and safe treatments are necessary to manage T2DM.

So far, metformin has been recommended by the American Diabetes Association[3] and is widely used as the first-line antidiabetic drug of choice[4]. However, progression of the underlying pathogenetic factors despite metformin treatment in T2DM patients frequently requires additional glucose lowering drugs[5]. Thus, the treatment of T2DM has moved towards combining metformin with other drugs with a different mechanism of action. Oral antidiabetic medications which can be used in combination with metformin or alone include dipeptidyl peptidase-4 (DPP-4) inhibitors, which act by improving α- and β-cell sensitivity to glucose *via* increasing concentrations of active GLP-1[6]. Vildagliptin is a DPP-4 inhibitor which has been shown to improve glycemic control (without the weight gain and hypoglycemia) in combination with metformin[7]. In an extensive clinical study program, vildagliptin has been shown to be an efficacious and safe treatment both as monotherapy and in combination with metformin[8-11]. When studied in comparison to the respective monotherapy treatments, combinations of vildagliptin and metformin provided superior efficacy while still showing a comparable overall tolerability profile and a low risk of hypoglycemia[12,13].

Evidence on the efficacy and safety of vildagliptin has been obtained from clinical studies, which were usually conducted in a restricted and highly regulated environment and may, thus, not necessarily reflect the everyday reality of diabetes management. Observational studies have been suggested as a tool complementing randomized controlled trials to investigate efficacy and safety of treatment strategies under conditions of clinical practice[14]. Observational studies are important for the detection of rare or late adverse effects of treatments or insights into the efficacy in daily medical practice[14,15].

To gain more information about the real-life situation in the treatment of type 2 diabetes with vildagliptin in Germany, we have performed this large observational study "Pill burden and compliance in type-2 diabetic patients treated with vildagliptin" (PROVIL). The aim of this study was to investigate the therapeutic efficacy, safety and the pill burden of a combination therapy of vildagliptin with metformin (vildagliptin add-on to metformin, GALVUS®, referred to as "vildagliptin add-on to metformin") or a fixed combination therapy of vildagliptin and metformin [EUCREAS®, referred to as "vildagliptin + metformin single-pill combination (SPC)"] compared to other oral antidiabetic drugs (OADs) in routine medical practice.

MATERIALS AND METHODS

Study design

The PROVIL study was conducted as open, observational multi-center study between October 2009 and January 2011 in practices of 867 general practitioners and internists in Germany. The study was registered in accordance with § 67 (6) German Drug Law (Arzneimittelgesetz, AMG) and conducted according to the applicable regulatory requirements and recommendations. As far as possible within the setting of an observational, non-interventional trial, this study was conducted in accordance with ICH-GCP. For all included patients written informed consent for documentation was obtained. The participating physicians received a compensation for the documentation of each patient in accordance with the official scale of physicians' fees(Gebührenordnung für Ärzte, GOÄ). The study was approved by the Ethics committee at the University of Leipzig. Participation in this study did not affect individual treatment according to medical needs of the patients. The procedures and decisions of the physicians were not influenced and the frequency and scope of examinations was to be according to practice routine. Additional examinations exceeding the usual scope were not required.

Study population

A total of 3881 patients were enrolled in 867 practices (Figure 1). Patients of either sex with T2DM who had the following criteria were included into this non-interventional study: patients who had received oral monotherapy, whose T2DM was considered inadequately controlled by this therapy by the physician and for whom the physician, thus, decided a therapy with vildagliptin add-on to metformin, vildagliptin + metformin SPC or another dual combination therapy with OADs. Since this was an observational study, all patients were treated based on routine clinical practice. No specific exclusion criteria did apply. To obtain a sufficient number of patients for the individual treatment cohorts, this study aimed to document patients on vildagliptin add-on to metformin (cohort 1) and vildagliptin + metformin SPC (cohort 2) *vs* other OADs (cohort 3).

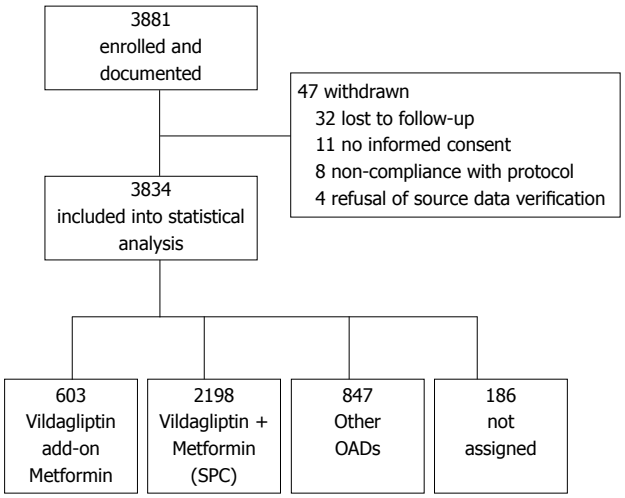

Figure 1 Study flow chart. Patient flow throughout the study. In total 3881 patients fulfilled the in- and exclusion criteria and were enrolled into the study. 3834 patients completed the study and were included into the statistical analysis. OADs: Oral antidiabetic drugs; SPC: Single pill combination.

Study design and assessments

The study duration was about 6 mo. According to routine practice, interim examinations were expected so that patients were evaluated three times: at baseline (first visit), after approximately 3 mo and after approximately 6 mo. Parameters documented in the study included demographic and diagnostic data, history of T2DM, data on diabetes control independent of this study and according to the summary of product characteristics (SmPC) and laboratory parameters [HbA1c, fasting plasma glucose (FPG), serum creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase], vital signs, relevant prior and concomitant medication and diseases were documented. After 3 and 6 mo weight, measurements on diabetes control and laboratory parameters independent of this study and according to the SmPC, as well as vital signs were repeated. In addition, changes in antidiabetic therapy, premature discontinuation, and occurrence of adverse events (AEs) were documented. After 6 mo, efficacy and tolerability of the oral dual antidiabetic combination therapy was assessed by the treating physician and continuation of oral dual antidiabetic therapy was recorded.

Since only OADs were allowed in this trial, no daily blood glucose measurement was needed based on the SmPC. We did not include additional blood glucose measurements in this observational study setting to reflect real life clinical practice.

The data in all documentation forms were examined for their plausibility by the data management department. Additionally, for a defined percentage (2%, i.e., 28 centers in line with common practice in Germany[16]) randomly chosen study centers, the documentation forms were compared with the source documents during on-site monitoring.

Statistical analysis

According to the predefined statistical analysis plan, the statistical evaluation was carried out using basic descriptive statistical methods and was interpreted in an explorative way. The difference in AE incidences between the cohorts was tested by a Chi-square test and the changes in HbA1c and fasting blood glucose were tested by a Kruskal Wallis test. Insofar as statistical procedures were used their results are to be understood as being descriptive not confirmatory. The statistical evaluation was carried out using SAS® Version 9.2 for Windows, (SAS Institute, Cary, NC). Patients who discontinued treatment for any reason and for whom no further data were available after the baseline visit were not included in the analysis.

RESULTS

Exposure

A total of 3881 patients were enrolled into this study. Of these, 3834 were included in the statistical analysis as 47 patients were withdrawn (Figure 1). About 2801 patients received vildagliptin either as vildagliptin add-on to metformin (n = 603) or vildagliptin + metformin (SPC) (n = 2198). 847 patients had received other OAD combination therapies. For 186 patients assignment to one of these three cohorts was not possible, due to inconsistent cohort information documented by the treating physician.

The most common daily dose in the vildagliptin add-on to metformin cohort was 100 mg (50 mg bid) vildagliptin and 2000 mg metformin (20.2% of patients), followed by 50 mg (50 mg qd) vildagliptin and 1000 mg metformin (15.6%) and 50 mg (50 mg qd) vildagliptin and 2000 mg metformin (13.1%). The vildagliptin + metformin (SPC) cohort daily dose at the initial visit was 50 mg/850 mg twice a day in 31.8% of the patients and 50 mg/1000 mg twice a day in 63.9% of patients.

Demography

There were no significant differences between the 3 treatment cohorts concerning age, body weight and BMI (Table 1). On average, patients had been diagnosed with T2DM for about 6 years and the mean HbA1c was between 7.6% and 7.9% at baseline.

In all three cohorts, the most common concomitant medication given at baseline in addition to any anti-diabetic medication was medication for the cardiovascular system (in 66.2% to 73.2%) followed by medication for the musculoskeletal system (in 23.1% to 24.6% of patients), for the alimentary tract and metabolism (in 20.3% to 25.6% of patients), for the blood and blood forming organs (in 19.2% to 21.2% of patients), and for the nervous system (in 19.0% to 22.9% of patients).

The OAD therapy used during the study course is summarized in Table 2. Apart from vildagliptin add-on to metformin and vildagliptin + metformin (SPC), patients in this study received combinations of metformin with sulfonylurea (n = 370), with glitazones (n = 123) or other DPP-4 inhibitors (n = 99).

Efficacy

The efficacy of vildagliptin add-on to metformin, vilda-

Table 1 Baseline demographic and clinical characteristics

	Vildagliptin add-on to metformin		Vildagliptin + metformin (SPC)		Other OADs	
	n	mean ± SD or *n* (%)	*n*	mean ± SD or *n* (%)	*n*	mean ± SD or *n* (%)
Sex						
Male		338 (56.1)		1247 (56.7)		436 (51.5)
Female		263 (43.6)		938 (42.7)		404 (47.7)
Age (yr)						
Total	578	63.0 ± 11.1	2115	62.4 ± 10.6	819	63.2 ± 11.0
Male	324	62.1 ± 10.8	1200	61.4 ± 10.2	422	62.5 ± 11.0
Female	252	64.1 ± 11.5	902	63.7 ± 11.0	392	64.0 ± 11.0
Weight (kg)						
Total	601	89.3 ± 16.8	2183	90.6 ± 17.5	836	87.9 ± 16.5
Male	337	93.7 ± 16.3	1239	95.1 ± 17.0	432	92.3 ± 15.6
Female	262	83.7 ± 15.7	931	84.6 ± 16.3	397	83.0 ± 16.0
BMI (kg/m²)						
Total	601	30.6 ± 5.3	2181	31.1 ± 5.5	836	30.3 ± 5.2
Male	337	30.4 ± 5.0	1239	30.7 ± 5.1	432	29.8 ± 4.7
Female	262	30.9 ± 5.6	929	31.6 ± 6.0	397	30.8 ± 5.6
Underweight/normal weight (BMI < 25)		70 (11.6)		174 (8.0)		90 (10.8)
Overweight/obese (BMI ≥ 25)		531 (88.4)		2007 (92.0)		746 (89.2)
Mean (Median) duration of type Ⅱ diabetes mellitus (yr)	556	6.2 ± 5.3 (median: 5.0)	2010	6.2 ± 5.1 (median: 5.0)	588	5.9 ± 5.2 (median: 4.5)
< 1		78 (14.0)		235 (11.7)		93 (15.8)
≥ 1 and < 5		197 (35.4)		771 (38.4)		215 (36.6)
≥ 5		281 (50.5)		1004 (50.0)		280 (47.6)
HbA1c (%)	597	7.8 ± 1.2	2186	7.9 ± 1.3	832	7.6 ± 1.2
< 6.5		43 (7.2)		150 (6.9)		91 (10.9)
≥ 6.5 and < 7.5		222 (37.2)		747 (34.2)		357 (42.9)
≥ 7.5 and < 10		300 (50.3)		1119 (51.2)		353 (42.4)
≥ 10		32 (5.4)		167 (7.6)		31 (3.7)
Fasting plasma glucose (mg/dL)	560	158.6 ± 47.2	2091	160.4 ± 49.0	797	151.3 ± 46.5
Serum creatinine (μmol/L)	552	82.4 ± 21.4	2053	82.2 ± 19.0	769	84.4 ± 22.8

The number of patients (*n*) given in this table constitutes the number of patients who had data available for the respective parameters and thus differ from the number of patients in the cohorts given in Figure 1. BMI: Body mass index; HbA1c: Glycosylated hemoglobin; OADs: Oral antidiabetic drugs; SPC: Single pill combination.

gliptin + metformin (SPC) and other antidiabetic drugs was assessed by changes in HbA1c and FPG.

HbA1c values significantly decreased in all 3 treatment cohorts after 3 and 6 mo of treatment [mean ± SE after 6 mo: vildagliptin add-on to metformin -0.9% ± 0.04%; vildagliptin + metformin (SPC): -0.9% ± 0.03%; other OAD -0.6% ± 0.04% (Figure 2A)]. Using a Kruskal-Wallis test, pairwise cohort comparisons showed statistically significant differences comparing vildagliptin add-on to metformin and vildagliptin + metformin (SPC) to the other OADs cohort both at 3 mo and at 6 mo (all $P < 0.0001$).

FPG concentrations decreased significantly in all 3 cohorts after 3 and 6 mo of treatment compared to baseline [mean ± SE after 6 mo: vildagliptin add-on to metformin: -291 mg/L ± 18.3 mg/L; vildagliptin +metformin (SPC): -305 mg/L ± 9.6 mg/L; other OADs: -209 mg/L ± 14.0 mg/L (Figure 2B)]. Patients receiving vildagliptin add-on to metformin and vildagliptin + metformin (SPC) showed a significantly greater reduction in FPG both after 3 and 6 mo than patients receiving another dual combination therapy with OADs (all $P < 0.0001$).

The absolute changes in HbA1c between baseline at 6 mo were more pronounced for vildagliptin add-on to metformin and vildagliptin + metformin (SPC) than for the other OADs (Figure 2C). A Kruskal-Wallis test showed that the differences between vildagliptin add-on to metformin and metformin in combination with the respective other substance were statistically significant at 6 mo (sulfonylureas: $P < 0.0001$; glitazone: $P < 0.0001$; other incretin-based therapies: $P = 0.0327$; and other substances: $P = 0.0020$). Similar differences were observed for the comparison between vildagliptin + metformin (SPC) and metformin in combination with other substances (sulfonylureas: $P < 0.0001$; glitazone: $P < 0.0001$; other incretin-based therapies: $P = 0.0046$; and other substances: $P < 0.0001$).

Decrease in FPG was more pronounced in the cohorts treated with vildagliptin add-on to metformin and vildagliptin + metformin (SPC) compared to other OADs (Figure 2D). After 6 mo, statistically significant differences compared to metformin in combination with the respective other substances were seen for both vildagliptin add-on to metformin (*P*: sulfonylureas: $P < 0.0001$; glitazone: $P = 0.0219$; other incretin-based therapies: $P = 0.0203$; other: $P = 0.0078$; Kruskal-Wallis test) and vildagliptin + metformin (SPC) (sulfonylureas; $P < 0.0001$; glitazone: $P = 0.0054$; other incretin-based therapies: $P = 0.0048$; other: $P = 0.0004$; Kruskal-Wallis test).

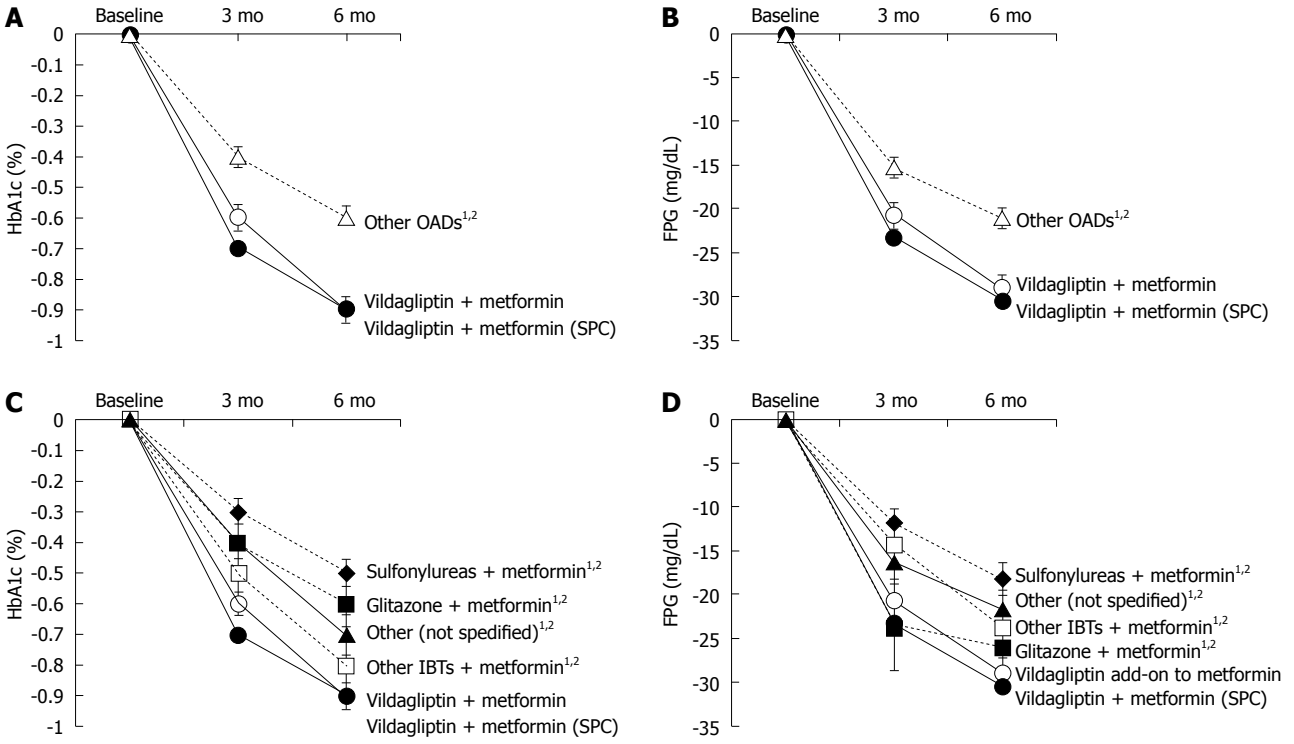

Figure 2 Difference in HbA1c and fasting plasma glucose after 3 and 6 mo of treatment. A: Changes in HbA1c in the vildagliptin add-on to metformin groups and combined other oral antidiabetic drugs (OADs); B: Changes in fasting plasma glucose (FPG) in the vildagliptin add-on to metformin groups and other OADs; C: Difference in HbA1c during treatment-vildagliptin add-on to metformin, vildagliptin + metformin [single-pill combination (SPC)] and other antidiabetics (individual substance classes); D: Difference in FPG during treatment-vildagliptin add-on to metformin, vildagliptin + metformin (SPC) and other antidiabetics (individual substance classes). [1]Statistically significant difference to vildagliptin add-on to metformin at 6 mo; [2]Statistically significant difference to vildagliptin + metformin (SPC) at 6 mo. IBTs: Incretin-based therapies.

Table 2 Oral antidiabetic therapy

Type of therapy	*n* (%)
Total number of patients	3648
Metformin + vildagliptin	603 (16.5)
Metformin + vildagliptin (SPC)	2198 (60.3)
Metformin + sulfonylureas	370 (10.1)
Glibenclamide/metformin	96 (2.6)
Glimepiride/metformin	241 (6.6)
Gliquidone/metformin	1 (< 0.1)
Nateglinide/metformin	2 (0.1)
Repaglinide/metformin	30 (0.8)
Metformin + glitazones	123 (3.4)
Pioglitazone/metformin	99 (2.7)
Rosiglitazone/metformin	24 (0.7)
Metformin + other DPP-4 inhibitors	99 (2.7)
Saxagliptin/metformin	7 (0.2)
Sitagliptin/metformin	92 (2.5)
Other[1]	255 (7.0)

[1]The group "other" also included patients for whom data were documented in this observational study without the physician recording information on the medication given and patients for whom the physician recorded only one medication although only patients receiving dual therapy were to be documented in this study. SPC: Single pill combination; DPP-4: Dipeptidyl peptidase-4.

In a subgroup analysis of patients with an HbA1c ⩾ 6.5% at baseline, we found that in the vildagliptin add-on to metformin cohort 57.7% and in the vildagliptin+metformin (SPC) cohort 61.1% had an improvement at the last control visit, while only 45.3% of the patients in the other antidiabetics drugs cohort had an improvement at this time (Table 3). A total of 25.3% in the vildagliptin add-on to metformin cohort, 23.5% in the vildagliptin + metformin (SPC) and 19.8% in the other OAD cohort even reached an HbA1c of < 6.5% at the last control visit.

Table 3 Change in HbA1c in patients with an HbA1c-value of ⩾ 6.5% at initial visit *n* (%)

Changes	Vildagliptin add-on to metformin	Vildagliptin + metformin (SPC)	Other OADs
Patients with an HbA1c-value of ⩾ 6.5% at initial visit	*n* = 553	*n* = 2033	*n* = 741
Patients with improvement in HbA1c at the last control visit compared to baseline	319 (57.7)	1242 (61.1)	336 (45.3)
Of these, patients with HbA1c value of < 6.5% at the last control visit	140 (25.3)	477 (23.5)	147 (19.8)

OADs: Oral antidiabetic drugs; SPC: Single pill combination.

In elderly patients (⩾ 65 years), both HbA1c and FPG decreased compared to baseline in all three treatment cohorts. For HbA1c, absolute differences between last control and baseline were greater in the vildagliptin add-on to metformin (-0.7% ± 0.06%) and the vildagliptin + metfor-

Table 4 Summary of adverse events *n* (%)

	Events		
	Vildagliptin add-on to metformin	Vildagliptin + metformin (SPC)	Other OADs
Total adverse events	77 (100.0)	336 (100.0)	77 (100.0)
Adverse events with suspected causal relationship[1]	34 (44.2)	151 (44.9)	31 (40.3)
Serious adverse events	20 (26.0)	118 (35.1)	16 (20.8)
Serious adverse events with suspected causal relationship[1]	1 (1.3)	22 (6.5)	6 (7.8)
Most common adverse events (preferred terms)			
Glycosylated haemoglobin increased	18 (23.4)	102 (30.4)	26 (33.8)
Blood glucose increased	11 (14.3)	34 (10.1)	6 (7.8)
Blood pressure increased	5 (6.5)	16 (4.8)	9 (11.7)
Blood pressure systolic increased	5 (6.5)	16 (4.8)	7 (9.1)
Treatment noncompliance	4 (5.2)	18 (5.4)	1 (1.3)
Hypertension	3 (3.9)	13 (3.9)	7 (9.1)
Selected hepatic adverse events (preferred terms)			
Transaminases increased	0 (0.0)	2 (0.6)	1 (1.3)
Alanine aminotransferase increased	0 (0.0)	1 (0.3)	0 (0.0)
Aspartate aminotransferase increased	1 (1.3)	1 (0.3)	0 (0.0)

[1]Following a conservative approach, in addition to events with definite, likely and possible causal relationship all events with missing causality assessments or causality indicated as "not assessable" were also classified as events with suspected causal relationship. OADs: Oral antidiabetic drugs; SPC: Single pill combination.

min (SPC) cohort (-0.8% ± 0.04%) than for other antidiabetic drugs (-0.5% ± 0.04%) in elderly patients. Similarly, the absolute changes in FPG (mean ± SE) were also greater in the vildagliptin add-on to metformin (-274 mg/L ± 26.5 mg/L) and the vildagliptin + metformin (SPC) cohort (-268 mg/L ± 14.3 mg/L) than in the other antidiabetics cohort (-157 mg/L ± 21.6 mg/L). SAEs and AEs did not differ from the younger population. There was only one reported mild hypoglycemic event in the vildagliptin/metformin SPC cohort.

Moderate decreases in body weight (absolute difference between last control and baseline: mean ± SE) were observed for patients in all cohorts [vildagliptin add-on to metformin: -1.4 kg ± 0.17 kg; median: -1.0 kg; vildagliptin + metformin (SPC): -1.7 kg ± 0.09 kg; median: -1.0 kg; other OADs: -0.8 kg ± 0.13 kg; median: 0.0 kg]. There was no difference in body weight fluctuations between younger and older patients across all cohorts.

Safety and tolerability

A total of 50 patients (8.3%) in the vildagliptin add-on to metformin cohort reported 77 AEs, 209 patients (9.5%) in the vildagliptin + metformin (SPC) cohort experienced 336 AEs and 67 patients (7.9%) in the other antidiabetics cohort experienced 77 AEs. For the comparison of AE incidence between the 3 cohorts a χ^2 test was performed: there was no statistically significant difference between the 3 cohorts (*P*: 0.3185) (Table 4). Only 3 cases of hypoglycemic events were reported: "hypoglycemia" in one patient in the vildagliptin + metformin (SPC) cohort and "blood glucose decreased" for one patient in the vildagliptin + metformin (SPC) cohort and one patient in the other antidiabetics cohort.

To assess hepatic safety of the treatments, we examined the time courses of specified liver laboratory parameters (total bilirubin, ALT, AST) and evaluated the reported hepatic AEs and SAEs. For total bilirubin, ALT, and AST no relevant changes during the study were seen. However, laboratory values were missing for a considerable percentage of patients (ranging from about 35% of patients to about 70% of patients depending on cohort and laboratory value). A total of 129 of 3834 patients (3.4%) discontinued therapy: 31 of 603 patients (5.1%) in the vildagliptin add-on to metformin cohort, 73 of 2198 patients (3.3%) in the vildagliptin + metformin (SPC) cohort and 21 of 847 patients in the other oral antidiabetics cohort (2.5%). In the vildagliptin add-on to metformin and vildagliptin + metformin (SPC) cohort, the most frequent reason for discontinuation was inadequate blood sugar control (45.2% and 34.2% of patients, respectively), followed by change of therapy in the vildagliptin add-on to metformin cohort (38.7% of patients) and by AE in the vildagliptin + metformin (SPC) cohort (31.5%). In the other OADs cohort, the most frequent reason for discontinuation was change of therapy (57.1% of patients) followed by inadequate blood sugar control (38.1% of patients).

During the observation period, 4 patients died: 1 patient in the vildagliptin add-on to metformin cohort (event: lung neoplasm malignant; not related to treatment) and 3 patients in the vildagliptin + metformin (SPC) cohort (events: convulsion and brain neoplasm, not related to treatment; cardiac failure, bile duct cancer and cardiac arrest, not related to treatment; and death, relationship to treatment not assessable).

When performing an additional analysis by age (patients younger than 65 years *vs* patients aged 65 years and older), there was no relevant difference in the most common AEs between the two age groups and the AE profile was similar to that of the overall population.

DISCUSSION

The present study was conducted to provide real-life data regarding the safety and efficacy of vildagliptin compared to other OADs in combination with metformin in the treatment of T2DM. Vildagliptin in a free or fixed combination with metformin decreased HbA1c and FPG concentrations to a greater extent than other OAD-metformin combinations after 3 and 6 mo of therapy without increasing any AEs or safety parameters. The results support previous observations from randomized clinical trials (RCTs) and provide important information about the use of vildagliptin and other antidiabetic agents in clinical practice.

About 3881 patients with T2DM were enrolled into this study, without triaging the patients by other inclusion and exclusion criteria, thus reflecting a heterogeneous patient population as observed in routine clinical practice. The observed reductions in HbA1c and FPG with vildagliptine are comparable with data from RCTs[7] and support previous evidence that vildagliptin is effective and well-tolerated in combination with metformin in T2DM patients.

The decrease in HbA1c at 6 mo compared to baseline (-0.9% ± 0.03%) was slightly less in magnitude than that reported from a large randomized, double-blind, active-controlled study (-1.1% ± 0.1%) employing similar doses of vildagliptin and metformin[8]. Apart from the different study design, patients in this RCT had higher baseline HbA1c values (8.4% ± 1.0%) than patients in the present study population [vildagliptin + metformin: 7.8% ± 1.2%; vildagliptin + metformin (SPC): 7.9% ± 1.3%]. Also, treatment compliance is maximized in clinical trials, since patients have to follow strict treatment protocols with frequent follow-up visits and additional patient support[17,18] providing another explanation for lower efficacy outcomes between RCTs and observational studies. Also, the observed superior reduction in HbA1c and FPG with vildagliptin when compared to other oral antidiabetic agents is in agreement with recently published observational and clinical data[7,19].

The overall safety and tolerability of vildagliptin and the other antidiabetic agents was assessed by AE monitoring and specific laboratory parameters. Especially hepatic safety has been an area of concern in DDP4-inhibitors[11]. To assess hepatic safety in the present study, the time course of specified liver laboratory parameters was examined (total bilirubin, ALT, AST). No relevant differences in hepatic safety parameters were observed during the study. However, a limitation is that laboratory values were not available for a considerable percentage of patients due to the non-interventional nature of this study.

The present safety data are consistent with the results from a meta-analysis of phase Ⅱ and Ⅲ clinical studies which indicated that vildagliptin was not associated with increased risk of hepatic events or hepatic enzyme elevations indicative of drug-induced liver injury[10]. Similar results were also seen in a pooled analysis of clinical trials[20].

Hypoglycemia is often the limiting factor in the glycemic management of diabetes. Reported rates of severe hypoglycemic events in clinical studies vary between 0.4% (ADVANCE)[21] and 3.1% per year (ACCORD)[22]. In UKPDS the rates of hypoglycemic episodes per year varied between 0.7% and 2.0% for major hypoglycemic episodes and between 7.9% and 25.5% for any hypoglycemic episode with the highest incidence in patients treated with sulfonylureas and insulin[23]. Especially in patients who receive sulfonylureas, the incidence of hypoglycemic events increases significantly when compared to incretin-based therapies[24]. Hypoglycemia can be considered a serious patient safety event with severe health complications, including dizziness, disorientation, slurred speech, convulsions, and death[25,26]. Unfortunately, the reporting rate of hypoglycemic events in clinical practice appears to be a major problem[27-29]. In the present observational study with 3834 analyzed patients only 3 hypoglycemic events were reported. Since 10.1% of the patients in this study received sulfonylureas (Table 2), the occurrence of a higher number of hypoglycemic events should have been expected in this study. A potential reason for this may be that many patients in routine practice are unaware of symptoms of hypoglycemia. Especially older patients over 65 years of age do not fully recognize the symptoms of hypoglycemia[27], an age group that displays 42% of the current study population. Also, recent data suggest that despite the risks of untreated hypoglycemia, nearly a third of patients with T2DM acknowledge that they do not routinely discuss the condition with their physician[29]. The high risk of hypoglycemia in T2DM patients and the low awareness of such events requires anti hyperglycemic treatments with a low risk of hypoglycemic events. Therefore, the selection of antidiabetic agents by physicians should consider also other factors beside blood sugar lowering such as weight gain as well as the potential to induce severe or frequent hypoglycemic events-especially in patients at a high risk, such as elderly or renally impaired patients[30].

In general, the majority of the evidence on the efficacy and safety of antidiabetic therapies stems from RCTs, which are generally recognized as "gold standard" for data evaluation. RCTs are fundamentally important in establishing the efficacy of new agents under optimal controlled conditions in carefully selected patients; however they are less informative in determining the effectiveness of a therapy under real-life conditions[31,32]. Since RCTs do not include many practical treatment issues encountered by the clinician in daily practice and the selected participants may not be representative for patients seen in the real-world clinical environment[31], the results may have limited applicability to patients in everyday reality of diabetes management. However, these limitations of RCTs are often ignored[14]. Therefore, observational studies can serve as an important addition to the clinician's resources by complementing RCT data with information on treatment safety, efficacy, and treatment compliance in patients under real-life conditions[31,32]. Especially the larger sample

size, the broad representation of many heterogeneous patients and the detection of rare or late adverse effects represent advantages of observational studies[14,15].

In summary, the data from the current observational study show that vildagliptin in combination with metformin is a safe and effective antidiabetic treatment for T2DM patients.

As other studies, also observational studies have inherent limitations[32]. First, observational studies have the risk of main selection bias. There were no strictly defined in- and exclusion criteria beside the contraindications mentioned in the SmPC of the respective medications. Therefore, confounding variables such as co-morbid diseases, treatment compliance and lifestyle interventions could affect the results. Also, subjects in the OAD cohort may have used varying doses of their oral antidiabetic agents which could affect treatment efficacy. Treatment compliance could have also been a variable between the different cohorts with impact on efficacy, whereas treatment compliance is maximized in clinical trials, since patients have to follow strict treatment protocols. However, it could be assumed that this compliance issue was similar among the study cohort. Furthermore, the low reporting rate of hypoglycemic events in this observational trial could be improved by better patient education, to make patients aware of the potential implications of hypoglycemic events. Another often discussed weakness of an observational study and in fact of every non-randomized study is that there may be a selection bias because the treating physician chooses which patients will be treated with which medication. A major strength of the PROVIL study is the determination of safety and efficacy parameters in T2DM patients under real-life conditions. Therapy was administered in routine practice and in accordance with the German SmPC. This allowed us to collect data in a real-life situation which provides information on typical patient characteristics and current treatment approaches and to obtain information on what is achieved in daily medical practice in the management of diabetes[14,15].

In conclusion, the present data suggest that vildagliptin in combination with metformin is a safe and effective antidiabetic treatment in daily medical practice by significantly reducing HbA1c and FPG without an increased incidence of AEs.

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COMMENTS

Background

Type 2 diabetes mellitus (T2DM) is one of the most common diseases worldwide and will be one of the most challenging health problems in the 21st century. In previous clinical trials it was shown that the dipeptidyl peptidase-4 (DPP-4) inhibitor vildagliptin with and without metfomin can significantly reduce HbA1c without significant hypoglycemic events and weight gain. However, evidence on the efficacy and safety of vildagliptin has been obtained from clinical studies, which were usually conducted in a restricted and highly regulated environment and may, thus, not necessarily reflect the everyday reality of diabetes management. Observational studies have been suggested as a tool complementing randomized controlled trials to investigate efficacy and safety of treatment strategies under conditions of clinical practice.

Research frontiers

DPP-4 inhibitors are an established treatment for T2DM. Numerous clinical studies showed that DPP-4 inhibitors are efficacious in treating hyperglycemia and well tolerated without hypoglycemia and weight gain. However, data from real clinical practice are lacking.

Innovations and breakthroughs

This is the first observational multi-center study that examines safety and efficacy of vildagliptin in combination with metformin in real life clinical practice in Germany.

Applications

This study confirms that vildagliptin in combination with metformin is a safe and efficacious antidiabetic treatment in daily medical practice by significantly reducing HbA1c and fasting plasma glucose without an increased incidence of adverse events.

Terminology

HbA1c: Glycated hemoglobin is a form of hemoglobin that is measured primarily to identify the average plasma glucose concentration over prolonged periods of time. It is formed in a non-enzymatic glycation pathway by hemoglobin's exposure to plasma glucose. The 2010 American Diabetes Association Standards of Medical Care in Diabetes added the A1c $\geqslant$ 48 mmol/mol ($\geqslant$ 6.5%) as another criterion for the diagnosis of diabetes.

Peer review

This is a very nice report of an observational study with vildagliptin in combination with metformin for the management of T2DM.

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CASE REPORT

Severe insulin resistance treatment with intravenous chromium in septic shock patient

Salim R Surani, Iqbal Ratnani, Bharath Guntupalli, Swetha Bopparaju

Salim R Surani, Texas A and M University, Corpus Christi, TX 78366, United States
Iqbal Ratnani, DeBakey Heart and Vascular Center, Houston, TX 77030, United States
Bharath Guntupalli, Swetha Bopparaju, Pulmonary Associates of Corpus Christi, Texas 78413, United States
Author contributions: All authors contributed in preparation and review of manuscript; all authors have reviewed the final draft.
Correspondence to: Salim R Surani, MD, MPH, MSHM, FACP, FCCP, FAASM, Associate Professor, Texas A and M University, Corpus Christi, 1177 Wheeler Avenue, suite 1, Aransas Pass, TX 78366, United States. srsurani@hotmail.com
Telephone: +1-361-8857722 Fax: +1-361-8507563
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Abstract

Insulin resistance has been well documented in critically ill patients. Adequate blood sugar control has been associated with better wound healing, and better outcomes in selected patient populations. Chromium is an essential component of human diet. It is believed to affect changes in glucose uptake. Several studies have shown beneficial effects of oral chromium in diabetic patients with insulin resistance, but role of intravenous chromium infusion has not been completely evaluated. We present a case of extreme insulin resistance in a 62-year-old woman with history of diabetes who suffered a cardiac arrest and respiratory failure, leading to aspiration pneumonia and septic shock requiring greater than 7000 units of insulin over a period of 12 h which was successfully treated with intravenous chromium replacement.

Key words: Insulin resistance; Chromium; Septic shock; Sepsis; Nutrition

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INTRODUCTION

Hyperglycemia and insulin resistance has been described in the critical care literature[1-5]. Evidence has suggested tight blood sugar control in the critically ill patients, specifically surgical intensive care unit (ICU) patients, may improve outcomes in these patients[6]. Hyperglycemia has been associated with increase in cytokines and counter-regulatory hormones which, in turn, lead to insulin resistance[2]. An increase in insulin resistance has also been described in patients with sepsis, renal failure, and a variety of critical illnesses[4,7,8].

Chromium is a trace element which plays an important role in carbohydrate, protein and lipid metabolism[9,10]. There have been several studies which have shown improvement in blood sugar control with the addition of extrinsic chromium[11-18]. In addition, chromium has shown to improve the insulin sensitivity. This agent's resulting decrease in insulin resistance, increases low density lipoprotein cholesterol, decreases high density lipoprotein cholesterol, increases body fat mass, and decrease in lean body mass. We present a case of a patient with septic shock and severe insulin resistance, in whom intravenous chromium was utilized with good clinical results.

CASE REPORT

A 62-year-old Caucasian woman with a past medical history of diabetes mellitus, coronary artery disease and hypercholesterolemia was brought to the emergency department after suffering a witnessed cardiac arrest. Initial

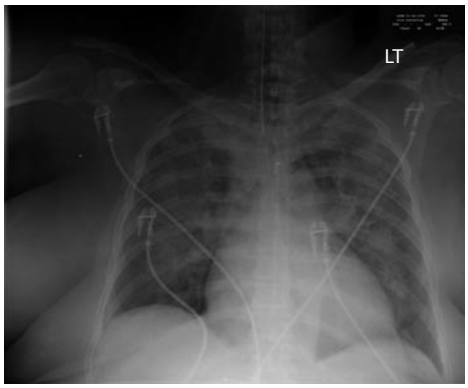

Figure 1 Chest X-ray showing bilateral lung infiltrates.

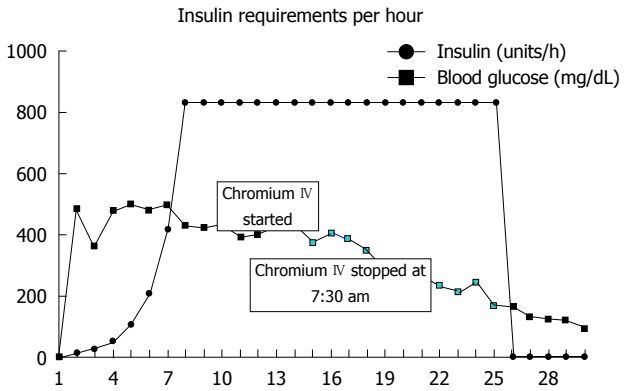

Figure 2 Insulin requirements and corresponding blood sugar levels.

bystander cardiopulmonary resuscitation was initiated. The patient was found to be in ventricular fibrillation and underwent electroshock into normal sinus rhythm and was then intubated. She was awake and able to follow simple commands in the ICU while on assisted mechanical ventilation. Chest X-ray revealed bilateral pulmonary infiltrates and increased vascular markings suggesting a combination of pulmonary edema and possible aspiration pneumonia (Figure 1). The patient was observed over the the next several hours where, despite adequate volume resuscitation, the patient's blood pressure would decline, requiring norepinephrine to keep the systolic blood pressure above 90 mmHg. A pulmonary artery catheter was placed revealing a cardiac output of 8.2 L/min, a calculated systemic vascular resistance (SVR) of 424 dynes/cm^2, and a pulmonary capillary wedge pressure of 16 torr. The findings of high cardiac output and low SVR were consistent with septic shock. Patient white blood cell count was recorded as 21.4 × 10^3 cells/mm^3. Approximately 24 h later, the patient's blood sugar began to increase above 1500 mg/L, which required initiation of intravenous insulin therapy. After 4 h of insulin administration, the patient was found to still require 832 units of insulin per hour with blood sugar levels above 4000 mg/L. After 7 h on an insulin drip administered at 832 units/h, the patient's blood sugar was still above 4000 mg/L. The patient was then started on chromium chloride at 3 μg/h intravenous infusion for 5 h. By the fifth hour of chromium infusion, the patient's blood sugar was less than 2000 mg/L, and by the sixth hour of the patient was off insulin, the blood sugar having been determined to be within normal values (Figure 2).

DISCUSSION

Resistance to insulin has been well documented in the literature[1-5]. The gold standard for measuring insulin resistance is by the insulin clamp test[1]. Saberi and coworkers studied the prevalence, incidence and clinical resolution of insulin resistance in critically-ill patients[5]. They found that on admission to an ICU, 67% of patients demonstrated overt insulin resistance, 9.4% of patients had non-overt insulin resistance, and 24% of patients were insulin sensitive. During the course of ICU stay, an additional 16% developed overt insulin resistance, leaving only 10% of critically-ill patients insulin sensitive. These observations in of themselves highlight the importance of insulin resistance in critically-ill patients. The ICU stay is complicated by renal insufficiency in almost 3%-16% of ICU patients, depending on the population studied[19]. Basi and co-investigators found that glucose concentrations among survivors were significantly lower than among non-survivors throughout the 5-wk study period ($P = 0.013$)[7].

The mechanism by which chromium is believed to affect changes in glucose uptake has been posited by various sources. Chromium (Ⅲ), the trivalent form of the element, is the elemental form in question, as chromium demonstrates six (Ⅰ-Ⅵ) naturally occurring valences, the number of which determines subsequent molecular forms found in nature. Chromium (Ⅲ) circulates in the blood bound to transferrin, a transport metal binding protein usually associated with iron. Four steps characterize the autoamplification that characterizes chromium (Ⅲ) effects on insulin bound insulin receptors. Insulin, binding to insulin sensitive cells, stimulates autophosphorylation of intracellular β-subunit tyrosine residues, an autocatalytic pathway constituting the first step in the classical cell signaling pathway of insulin. Increased insulin plasma concentrations are postulated to simultaneously activate a transient permeability of the cell membrane to chromium (Ⅲ) which dissociates from transferrin to enter the cell. The flux of chromium (Ⅲ) into the cell is captured by pre-synthesized apocalmodulin proteins present intracellularly. Calmodulin, also referred to in the literature as low molecular weight chromium binding protein, strongly binds the free form of chromium (Ⅲ), in a ratio of 4:1. The calmodulin-chromium complex binds to the β-subunit intracellular portion of the insulin receptor and further enhances autophosphorylation. The end-result of the traditionally understood insulin-mediated uptake of glucose in insulin sensitive cells follows. Following increase in intracellular glucose concentration, insulin concentration drops. The affinity for the calmodulin-chromium complex for the insulin receptor is dependent directly to the concentration of insulin, and calmodulin dissociates from the insulin receptor. It is then released from the

cell; however, this loss is of the calmodulin-chromium complex, rather than of chromium or calmodulin individually. This may be understood by the magnitude of the association constant K_f of approximately 10^{21} M^{-1}[20].

Chromium is an essential component of the human diet. The Food and Drug Administration proposes a reference dietary intake of 120 μg/d, whereas the National Academy of Science has proposed a daily intake of 20 μg/d for females and 30 μg/d for males. This, in contrast to the calculated reference dose of 70 mg/d, represents an almost 350 fold difference between the recommended and the safety dose[21,22]. There have been several studies suggesting a beneficial effect of chromium[11-18]. For example, supplementation with chromium picolinate, a stable and highly bio-available form of chromium, has been shown to reduce the risk of cardiovascular disease and type 2 diabetes[23]. Existing data suggests using chromium picolinate supplementation of at least 200 μg/d. Other studies have suggested higher doses. Anderson *et al*[14], suggests that a dose of chromium of 1000 μg/d has a more pronounced effect during a 4 mo trial. Administering a 1000 μg/d of chromium also lead to a significant decrease in the HbA1c (glycosylated hemoglobin) after the second month of treatment. A follow-up study demonstrated that the effect of chromium supplementation was long lasting[24]. The long lasting beneficial effects were also seen with a 500 μg/d dose of chromium picolinate.

In addition to oral supplementation, chromium supplementation has been a part of multi-trace element formulation in total parental nutrition (TPN), which provides on average only 10 μg/d. Some authors have suggested that the high glucose content in TPN also increases the renal excretion of chromium[25]. Wongseelashote *et al*[26] did an observational study on patients with parental chromium supplementation. They found a mixed response to parental chromium supplementation.

A case of extreme insulin resistance in a cardiothoracic ICU patient treated with chromium infusion has previously been described[27]. That particular patient developed severe insulin resistance following surgical repair of the thoracic aorta. Post-operatively, the patient required 2110 units of insulin over 40 h while receiving vasopressors and glucocorticoids. After administration of intravenous chromium at a rate of 3 μg/h (100 μg elemental chromium chloride in 1 L of normal saline infused at 30 mL/h) the patient had a significant response. The insulin infusion rate was decreased and 12 h later insulin infusion was stopped.

In the case of our patient, an even more significant response to chromium intravenous infusion was noted. Our patient demonstrated an extreme insulin resistance which responded well to intravenous chromium. This case also served as a learning model and led us to reassess our protocols for insulin as well as several other protocols, and emphasizes the need of placing a ceiling on amount of insulin which a patient can receive. Chromium has been used orally to improve insulin sensitivity. Its role in parental infusion has not been evaluated. Our case represents the second successful case of improving insulin sensitivity in a patient with extreme insulin resistance. In view of an excellent response to blood sugar control with the addition of chromium, we suggest that future studies be conducted to study the effect of chromium on insulin resistance in critically-ill patients.

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Science, 465 Kajii-cho, Hirokoji, Kawaramachi, Kamikyo-ku, Kyoto 602-8566, Japan

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February 8-11, 2012
5th International Conference on Advanced Technologies and Treatments for Diabetes
Barcelona, Spain

February 9-10, 2012
EC Conference on Diabetes and Obesity Research - Save the Date
Brussels, Belgium

February 21, 2012
Association of Children's Diabetes Clinicians 6th Annual Meeting
Coventry, United Kingdom

February 23, 2012
Diabetes and kidney disease: advances and controversies
Birmingham, United Kingdom

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Paris, France

March 7-9, 2012
Diabetes UK Annual Professional Conference 2012
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Monogenic Disorders of Insulin Secretion: Congenital Hyperinsulinism and Neonatal Diabetes
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March 29-April 1, 2012
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Ocho Rios, Jamaica

April 2-6, 2012
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April 4-7, 2012
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Athens, Greece

April 11-13, 2012
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April 11-13, 2012
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Chaoyang District, Beijing 100025, China
E-mail: wjd@wjgnet.com
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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 200201 03498. 2002 Aug 1

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