

OBSERVATIONS

Is Metformin Safe in Patients With Mild Renal Insufficiency?

Among the first million patients who received metformin in the U.S., 47 patients developed metformin-associated lactic acidosis (MALA), with 43 having predisposing factors for lactic acidosis (including moderate to severe renal failure and congestive heart failure) (1). Although there was initial concern, studies have suggested that MALA is secondary to underlying conditions and represents a coincidental finding (2,3). While the current consensus is that the risk of lactic acidosis is negligible when metformin is used as labeled (4), we present a patient who developed MALA in the absence of currently recognized contraindications to metformin.

A 55-year-old man with hypertension, type 2 diabetes, and mild renal insufficiency (measured creatinine clearance 91 ml/min) presented with sudden onset of fatigue, vomiting, and altered mental status after performing strenuous yard work without sufficient hydration. His medications included nifedipine, captopril, hydrochlorothiazide, glyburide, and metformin.

The patient rapidly developed respiratory distress and hypotension necessitating intubation and vasoactive agents. Laboratory studies revealed a serum creatinine level of 9.4 mg/dl, pH 6.98, CO_2 <6 mmol/l, and lactic acid 27 mmol/l. Evaluation using a computed tomography scan and magnetic resonance angiography of the abdomen/pelvis, various cultures and cardiac echocardiogram could not reveal an etiology for lactic acidosis. Serum metformin level (ARUP Laboratories, Salt Lake City, UT) was 8 mg/l (therapeutic range 1–2). Continuous venovenous hemofiltration was initiated immediately. Conservative management was followed by rapid amelioration of his general status. He was extubated within 24 h, continuous venovenous hemofiltration was stopped after 36 h, and he was discharged 6 days after presentation without deficits.

This case is unique in that MALA developed in the absence of currently recognized risk factors or predisposing

conditions. Although this patient had mild impairment of kidney function, contraindication criteria for the use of metformin were not met (5). The patient was taking 2 g metformin per day, which is within the recommended therapeutic range.

In our opinion, a threshold serum creatinine level above normal range should not be considered safe for metformin use because renal function can rapidly deteriorate in patients with even mild underlying kidney disease, resulting in accumulation of metformin and development of MALA. We suggest that consideration be given to avoiding metformin in patients with any degree of renal dysfunction.

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Malignant Melanoma Misdiagnosed as a Diabetic Foot Ulcer

A male patient aged 48 years with type 2 diabetes presented with a painless nonhealing ulcer of 18 months duration under his right first metatarsal head. The ulcer was not a typical-appearing neuropathic foot ulcer and had mushrooming granulation tissue and areas of intact epidermis in a lenticular fashion over the wound bed (Fig. 1). The patient also complained of a “knot” in his right inguinal area. An incisional biopsy was taken from the foot lesion, which revealed a poorly differentiated melanoma covered by an intact epidermis and granulation tissue. The incisional biopsy was 0.8-cm thick, and melanoma extended to the deep margin. At presentation, the size and poor differentiation of the tumor made it impossible to assess the subtype of the original melanoma. The S-100 and HMB-45 stains (positive in melanoma cases) were strongly positive. A computed tomography of the chest, abdomen, and inguinal areas revealed metastasis to the inguinal lymph nodes and liver. The patient died 6 months later.

Although rare, melanomas can present as neuropathic foot ulcers in individuals with diabetes (1,2). Melanomas are located on the plantar surface in ~7% of cases (3) with the exception of Japanese patients, in whom the plantar surface is



Figure 1—Malignant melanoma tumor that was misdiagnosed as a neuropathic foot ulcer.

the most common location (4). Acral lentiginous melanoma is the most common melanoma type that presents on the plantar aspect of the foot (3). This type of melanoma is commonly amelanotic, frequently ulcerates (5), and does not exhibit the classic signs of malignant melanoma associated with the mnemonic aid "ABCD" (asymmetry, border, color, diameter). In a review (6) of 53 lower extremity melanomas, 11 of 18 (61%) misdiagnosed cases were on the plantar foot. All misdiagnosed lesions were histopathologically acral lentiginous melanomas. Initial misdiagnoses included nonhealing ulcer, wart, tinea pedis, and onychomycosis. Another retrospective review (7) of palmoplantar melanoma found that misdiagnosis led to a median delay of treatment for 12 months and was associated with increased tumor thickness (5.0 vs. 1.5 mm) and a lower 5-year survival rate (15.4 vs. 68.9%).

We are not supposing that plantar melanoma occurs more frequently in individuals with diabetes. However, we believe there is a greater chance of misdiagnosis given this population's predilection toward plantar ulceration. An individual with peripheral sensory neuropathy is more likely to unknowingly ambulate on a plantar foot lesion, and this increased pressure and trauma can cause a lesion to initially resemble a diabetic foot ulcer. This case and short review emphasizes the importance of performing biopsies on chronic and atypical wounds early in the treatment algorithm of diabetic foot ulcers.

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COMMENTS AND RESPONSES

An Open, Randomized, Parallel-Group Study to Compare the Efficacy and Safety Profile of Inhaled Human Insulin (Exubera) With Glibenclamide as Adjunctive Therapy in Patients With Type 2 Diabetes Poorly Controlled on Metformin

Response to Barnett et al.

In response to the interesting article by Barnett et al. (1), we would like to offer the following comments. Diabetes control has been shown to improve with diet and exercise regimens (2,3). The degree of study participants' compliance with diet and exercise regimens may have con-

founded the change in A1C reported in the study (1). Also, the independent effect of BMI on both diabetes control and response to therapy has been studied extensively (4). The effect of modification of baseline BMI on diabetes control among various strata of BMI in both study groups needs clarification.

The open-blinded design of the study (1), especially since it involves diabetes education and self monitoring, can significantly impact internal validity due to both performance bias of the subject with respect to compliance with lifestyle modifications as well as detection bias of the health care providers in ascertaining adverse outcomes (5). In addition, the non-inferiority design offers no protection against a predetermined idea of equivalence by the investigator, who could allocate similar scores to responses and events of all study subjects (6).

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An Open, Randomized, Parallel-Group Study to Compare the Efficacy and Safety Profile of Inhaled Human Insulin (Exubera) With Glibenclamide as Adjunctive Therapy in Patients With Type 2 Diabetes Poorly Controlled on Metformin

Response to Kanna and Abreu-Pacheco

We thank Kanna and Abreu-Pacheco (1) for their comments on our study (2). As Kanna and Abreu-Pacheco point out, overweight and obesity are strongly linked to the development of type 2 diabetes and can complicate its management. While most patients with type 2 diabetes are overweight (3), this study (2) included individuals with a range of BMI values typical of those seen in clinical practice; mean BMI in the inhaled insulin and glibenclamide groups was 31.8 (range 19–51) and 31.1 (22–47), respectively. When analyzed by baseline BMI values, the mean change from baseline A1C in the moderately high A1C arm (≥ 8 to $\leq 9.5\%$) was -1.6 , -1.3 , and -1.5% in patients with baseline BMI values of <30 , $30-35$, and ≥ 35 kg/m², respectively, compared with -1.5% for all subjects. In the very high A1C arm ($>9.5\%$), mean change from baseline A1C was -3.1 , -2.8 , and -2.8% in patients with baseline BMI values of <30 , $30-35$, and ≥ 35 kg/m², re-

spectively, compared with -2.9% for all subjects. The results show no meaningful differences between the BMI categories, and the authors therefore believe it to be unlikely that the baseline BMI values could have confounded the A1C results.

For the duration of the study, patients were required to follow an American Diabetes Association diet (with 30% fat and calories sufficient to maintain ideal body weight) and to perform 30 min of moderate exercise at least 3 days per week. There was no specific measure of compliance with diet and exercise regimens during the study, but patients were reminded of their importance at each clinic visit.

Finally, we would like to point out that our study was open label and not blinded. As highlighted in the article, a double-blind study, while desirable, was not possible for two principal reasons: 1) it was not possible to manufacture a suitable placebo for inhaled insulin, and 2) it is generally inappropriate to blind treatment when individualized flexible dose titration is needed for effective management with exogenous insulin.

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Hyperglycemia and Diabetes in Patients With Schizophrenia or Schizoaffective Disorders

Response to Cohen et al.

We commend Cohen et al. (1) on their report on hyperglycemia and diabetes in patients with schizophrenia and schizoaffective disorders. To our knowledge, this is the first large study of oral glucose tolerance tests in this population.

Cohen et al. found that the prevalence rate of diabetes was significantly higher in patients with schizophrenia and schizoaffective disorders than in the general population. They did not detect a differential effect of antipsychotic monotherapy in diabetogenic effects, and they consequently proposed a modification of the consensus statement on antipsychotic drugs, obesity, and diabetes, i.e., measurement of fasting glucose in all patients with schizophrenia irrespective of the prescribed antipsychotic drug. We argue that the differences in the metabolic effects of different antipsychotic agents are too clear in the literature to justify any notion that the antipsychotic agents are comparable in their metabolic effects.

Comparative studies of antipsychotic agents are limited in their scope by the difficulty in conducting randomized controlled trials of antipsychotic agents. For many patients, specific antipsychotic agents are indicated ahead of the others based on the information available at that time. For example, clozapine is difficult to study in comparative investigations because it is not recommended by most as a first-line treatment. A recent study (2) addressed this issue to some extent by conducting a randomized controlled trial of risperidone and olanzapine in dogs. The dogs who received olanzapine developed hepatic insulin resistance, whereas those who received risperidone did not. Fur-

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Modeling Chronic Glycemic Exposure Variables as Correlates and Predictors of Microvascular Complications of Diabetes

Response to Dyck et al.

We read with interest the article by Dyck et al. (1), in which the authors described a chronic glycemic exposure variable (GE_i) in the Rochester Study. They examined GE_i and its individual components (A1C, duration, and age at onset) in terms of prediction/correlation with complications and concluded that GE_i is generally predicted better than its individual components (see Table 3 of ref. 1).

Dyck et al. compared their results with our previously published analyses (2) using a different chronic glycemic exposure variable, A_1 months, noting that (as also reported by the Diabetes Control and Complications Trial [3]) this combination variable did not predict better than its components (A_1 and duration). Our

analytic approach, however, was different; we compared the fit of models, including the components to a model, with the composite alone. The differences in fit were small but favored the separate components. It would thus be interesting to compare the total R^2 of alternate models, one with GE_i and another with its components, in the current study. We suspect that, as in our case, differences would be small.

Another interesting issue is the use of “age at onset” and “duration” (1) together effectively defining age itself. Could any enhanced prediction be related to age itself? Inclusion of the partial R^2 for age in Table 3 (see ref. 1) would be useful.

Dyck et al. further suggested that differences between these studies may be explained by the “choice of patients” and differences in outcome assessment. As the Epidemiology of Diabetes Complications study (4) is comprised of community-treated type 1 diabetic individuals from a childhood-onset cohort shown to be epidemiologically representative of type 1 diabetes, selection bias was unlikely. However, the inclusion of type 2 diabetic subjects in the Rochester Study may have influenced results. Nevertheless, we agree that a continuous neuropathy outcome measure may be preferable and that this difference also may have contributed to the differences reported. Consequently, a comparison of A_1 months and GE_i would be more informative if performed for the outcome common to both studies (Diabetes Control and Complications Trial protocol neuropathy).

Finally, one motivation behind developing the A_1 month measure was to address whether a glycemic threshold exists above which complications develop. Were the authors able to examine this issue using GE_i ? While unable to determine a clear threshold, we found that $\sim 1,000$ A_1 months were experienced before the advent of advanced complications. This translates to 42 years of A1C 2% above normal or 18 years at 5% above normal, which reflects another motivation for our chronic glycemic exposure variable—a clinically useful concept of risk.

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Modeling Chronic Glycemic Exposure Variables as Correlates and Predictors of Microvascular Complications of Diabetes

Response to Orchard et al.

We are pleased to respond to the letter by Orchard et al. (1), especially since they first raised the following question: Do composite measures of chronic glycemia correlate or predict complications better than individual components? Orchard et al. reported evidence against the hypothesis, while we (2) reported evidence for the hypothesis. Having considered their suggestions, we offer an explanation for why their conclusions differed from ours.

Orchard et al. (3) compared the fit

from two models, one consisting of only the composite and the other consisting of a regression model that included both components. The regression model is a linear combination of the two components in which the weights are chosen to obtain an optimal fit; thus, the regression model itself is a composite, though one in which the fit to the data should be better than A_1 months (which is exactly what they found).

Since comparing two composites was not the goal of our study (2), we approached the analyses differently. We developed one regression model including all variables that were significant in the multivariate modeling, including the composite as well as individual components, as candidates for the model. Each partial R^2 measures the explanatory value of the corresponding variable beyond the prediction already available from all the other variables in the model. Except for severity of retinopathy at baseline, we found that the composite was consistently the best predictor and that the individual components added little, if anything.

We agree that age at onset and duration added together equal the age of the patient at the time of study, although the appropriate weights for these two time periods in predicting the outcome may differ, and determining whether the weights significantly differ would be of interest. However, this was not a focus of our study.

We also agree that the patient population under study and the choice of outcomes to be analyzed can influence the results and that a continuous neuropathy measure is desirable. Although use of a common outcome measure would assist in comparing our results with those of Orchard et al. (3), such a comparison was not the focus of our study (2). Finally, determining the threshold of chronic glycemia, which induces complications, is a worthy goal, but before we do this we want to include studies of normal subjects and glucose-impaired individuals currently being studied.

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A Critical Appraisal of the Continuous Glucose-Error Grid Analysis

Response to Wentholt et al.

In a recent publication, Wentholt et al. (1) stated that their aim was to critically explore the continuous glucose-error grid analysis (CG-EGA) (2) and to compare it with traditional techniques using data previously reported from two sensors. As developers of the CG-EGA, we hoped that our method might stimulate a discussion on the important problem of the accuracy of continuous monitoring sensors (CGS); therefore, we read this critique with interest.

The methods used by Wentholt et al. (1) unfortunately failed to take into account the basic structure of CGS data, which represent time series (i.e., sequential readings that are ordered in time) (3). This structure leads to two fundamental requirements in their analysis. First, consecutive sensor readings taken from the same subject within a relatively short time are highly interdependent. Therefore, standard statistical analyses such as t tests, while appropriate for independent data points, will produce inaccurate results if applied to CGS data. Second, the order of the CGS data points is essential for clinical decision making. For example, the sequences 90 → 82 → 72 mg/dl and 72 → 82 → 90 mg/dl are clinically very different. Standard accuracy measures, such as the mean absolute deviation (MAD) used by Wentholt et al. (1), do not account for the data's temporal order; if reference-sensor data pairs are reshuffled, the MAD remains the same.

As a result, the primary statistical analysis used by Wentholt et al. is flawed, both to demonstrate significant differences between the sensors and to imply that CG-EGA is insensitive. The CGS data from 13 subjects were pooled to compare 2 MADs (15.0 ± 12.2 vs. $13.6 \pm 10.2\%$). The result was reported as significant ($P = 0.013$), but for these highly overlapping MADs to differ statistically required a large number ($>1,000$) of degrees of freedom, which was calculated by pooling the total number of CGS data points (735 and 1,156) across all subjects. Such an approach led to inaccurate conclusions because there were only 13 independent subjects, and the data points within each subject were highly dependent. If the correct number of degrees of freedom is used, the MADs of the two sensors are not different ($P > 0.5$), which confirms the CG-EGA results showing no differences.

Other conclusions by Wentholt et al. also deserve comment. First, they stated that CG-EGA is time consuming. Indeed, analyses of temporal data are intrinsically more sophisticated than standard time-independent statistics, but such analyses are essential for this type of data. CG-EGA software is available. Second, Wentholt et al. stated that "poor accuracy rate is barely noticeable in the final CG-EGA outcome," implying that this result of the CG-EGA is incorrect. However, this result is not incorrect because better combined (rate and point) accuracy during hypoglycemia is observed with the sensor, showing poorer rate accuracy in this critical region. It is

clinically apparent that when blood glucose is <3.9 mmol/l point accuracy should be given more emphasis than rate accuracy. A strength of CG-EGA is its ability to vary the input of either rate or point accuracy to overall clinical accuracy depending on blood glucose range. Third, the results of CG-EGA vary with time intervals. This is also an intuitive strength of CG-EGA, which is designed to account for increased noise associated with frequent sampling. We advocated (2) adopting a uniform sampling protocol with reference and/or sensor pairs taken every 10–15 min to standardize comparisons of rate accuracy, which is a sampling scheme based on physiological considerations of possible glucose change rates. Fourth, Wentholt et al. (1) questioned the appropriateness of the formulae to shift point EGA based on interstitial time lag. However, the authors reported an average time lag of ~7 min in one of their sensors, which is identical to that assumed for CG-EGA, thus confirming that ~7 min is a reasonable average for blood-to-interstitial diffusion delays. CG-EGA software allows setting this parameter to any value <7 min.

We are pleased that both the discussion regarding CG-EGA and the analysis of time series data have begun, and we look forward to continuing this important dialogue. However, we also recommend careful consideration of basic statistical assumptions when analyzing sensor-generated glucose data; their inherent temporal structure should be taken into account.

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A Critical Appraisal of the Continuous Glucose–Error Grid Analysis

Response to Clarke et al.

We thank Clarke et al. (1) for their thought-provoking response to our article (2). With their comments (1), they not only took on the important issue of how to optimally assess the accuracy of continuous glucose monitors (CGMs); they moved the discussion one step further.

In our study (2), we did indeed take the statistical liberty of deriving degrees of freedom from all pooled data points—in contrast to the proposal by Clarke et al. (1) who compared the accuracy of two sensors using one average mean absolute deviation (MAD) value per patient. The latter approach may be too rigid because not all readings are interdependent. For example, postprandial glucose sensor readings at lunch and at night depend little on each other, if at all. It is common practice to derive degrees of freedom from pooled data in the sensor field. In a previous study, Clarke et al. (3) compared the accuracy of two CGMs in 16 type 1 diabetic patients by using the continuous glucose–error grid analysis (CG-EGA). The difference in pooled readings in the hypoglycemic area that ended up in zones A and B was reported to be highly significant between both sensors (88 vs. 62.8%, respectively) ($P < 0.0005$). This level of significance implies that degrees of freedom were derived from all data pairs in the hypoglycemic range (250 mg/dl) rather than from the actual amount of participants ($n = 16$). Even with a strict statistical policy, the better MAD for the microdialysis sensor in the hypoglycemic area in our study (2) (12.0% for the 7-min corrected microdialysis sensor vs. 25.2% for the needle-type sensor, calculated per patient [$df = 12$], $P = 0.036$ by Wilcox-

on's signed-rank test) and the larger sensitivity for hypoglycemia associated with this sensor (75.0 [75 data pairs] vs. 55.9% [56 data pairs], $P = 0.018$ by Pearson's χ^2 , with 16 of 16 and 12 of 15 hypoglycemic episodes detected by the microdialysis and needle-type sensor, respectively, $P = 0.06$ by Pearson's χ^2) contrasted with the CG-EGA that noted no difference (51.5 vs. 60.0% accurate readings and benign errors in the hypoglycemic range [$df = 42$], $P = 0.841$ by Pearson's χ^2 for the microdialysis and the needle-type sensor, respectively). Therefore, even with a mild statistical approach (i.e., deriving degrees of freedom from 43 data pairs rather than 13), CG-EGA could not confirm the different accuracy of the sensors in the hypoglycemic range.

As to the order of CGS data points, the sensor's ability to follow the rate and direction of glucose changes is nicely reflected by the MAD: A sequence of glucose values that has been incorrectly reported by a given sensor (e.g., 90 → 82 → 72 mg/dl instead of 72 → 82 → 90 mg/dl) will result in a worsened MAD.

In reaction to the comment by Clark et al. (1) in regards to time consumption, we were happy to learn that the software for CG-EGA has become available. Nevertheless, the laborious collection of frequent blood samples on fixed intervals (in addition to the construction of a rate, a point accuracy plot, and, finally, a combining matrix) will remain inevitable drawbacks of CG-EGA.

With the attempt to standardize the length of the time intervals, Clark et al. clearly tried to improve the CG-EGA methodology. Nevertheless, a time interval that can vary by 5 min (10–15 min) still leaves the door open for interobserver variability.

As to our finding in a previous study (4) of a 7-min delay that was inherent to the microdialysis instrument itself and not seen in the needle-type sensor, Clarke et al. (1) alluded to a (much-disputed) constant 7-min physiological delay resulting from the relationship between interstitial and blood glucose. This physiological delay has been reported to be anywhere between 0 and 30 min, so the 7-min assumption made for the CG-EGA is questionable. Fortunately, Clarke et al. have now implemented into the software the possibility of setting the delay <7 min.

Currently, the optimal way to assess a CGM seems to be the combination of MAD calculated per glucose range, com-

fects on glucose tolerance resulting from increased relative weight, as also observed in our study (2).

We strictly support the statement of Mayer-Davis et al. (1) that breast-feeding should be recommended for all women. However, against the background of the rather exemplary arguments provided here, this story is far from being finished. Much more research is urgently needed, especially to ensure safety of our general recommendation also in the case of early neonatal breast-feeding by diabetic/overweight mothers.

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Breast-Feeding and Risk for Childhood Obesity

Response to Plagemann et al.

We appreciate the interest and comments of Plagemann et al. (1) regarding our study (2) on maternal status as a potential modifier of association of breast-feeding on childhood obesity. As noted, for the contrast of breast milk only versus formula only, the 95% CI excluded the null value, thus necessarily including values >1.0. From a statistical perspective, however, the best estimate for this contrast is an odds ratio (OR) of 0.79, not a value >1.0. Furthermore, the test for dose response suggested a statistically significant trend in the direction of protection by breast-feeding for both groups. Finally, there is no indication of a differential effect of breast-feeding according to maternal status. Specifically, for both exclusivity and duration of breast-feeding, the interaction term from fully adjusted models was $P = 0.50$ and $P = 0.66$, respectively. Thus, our interpretation of the data is that there is no evidence of a deleterious effect of breast-feeding according to maternal obesity or diabetes status.

With regard to the second point raised by Plagemann et al. (1), the OR of 1.11 for overweight among children of diabetic mothers who were breast-fed <1 month compared with those who were formula fed was in the same direction (i.e., potentially deleterious) as observed in the previous work by Plagemann et al. (3). We note that for this specific contrast, the 95% CI was quite wide (0.22–5.60), making interpretation difficult. Interestingly, the OR for the same contrast for nondiabetic mothers with BMI >25 kg/m² was also >1.0 (OR 1.46 [95% CI 1.01–2.13]). We noted in our original article (2) that to interpret this finding, one must consider potential circumstances related to the decision to stop breast-feeding at such a young age, as well as the infant-feeding behaviors in response to those circumstances. Here, while we agree with Plagemann et al. (1) that there

is a need for further work in this regard, we note that the context of breast-feeding duration during the neonatal period (i.e., choosing to stop or to continue breast-feeding) is extremely important to consider, rather than simply focusing on this time period in isolation.

Finally, our work was, in fact, very specifically motivated by that of Plagemann et al., and thus we certainly agree that this topic is of considerable importance. Our comments in our study (2) regarding potential explanations for differences in our findings were speculative; thus, we have no further comments in this regard.

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