its use (1). Metformin has been associated with lactic acidosis. Although metformin-associated lactic acidosis (MALA) is rare, it is fatal in approximately half of all cases. MALA is precipitated by clinical conditions that cause substantial tissue hypoperfusion and hypoxia and thus are identified as precautions and contraindications to its use in package labeling (1,2). Four studies have previously found that metformin is commonly prescribed, despite risk factors, with a range of 24.5–54% in outpatients and 64–73% in inpatients (3,5–7). The purpose of our study was to determine the frequency of inappropriate prescribing of metformin to patients with precautions or contraindications at an academic health center and secondarily to compare the findings with previously published studies.

This retrospective study was approved by the institutional review board of the University of Michigan. We performed a chart review where 100 inpatients and 103 outpatients were randomly selected from 300 patients who received metformin between January and June of 2003. Patients' medical records were used to collect demographic data, clinical characteristics, laboratory parameters, and information about contraindications and precautionary conditions. Risk factors for MALA were identified through ICD-9 codes in the clinical data repository, laboratory tests, and medical notes.

A power analysis estimated that a sample size of 78 patients in each group was sufficient to detect a 20% difference in the frequency of inappropriate prescribing compared with the frequency (73%) reported by Holstein et al. (α = 0.05, β = 0.8) (3). A sample size of 100 patients per group was selected for simplicity. Frequencies of inappropriate prescribing were compared with literature-reported rates using Fisher's exact test (4). Inpatient results were compared with those of Calabrese et al. (5). Outpatient results were compared with those of Emslie-Smith et al. (6).

Of 103 outpatients, 3 (2.9%) had contraindications to metformin use. This is significantly lower than the 24.5% incidence of contraindications reported by Emslie-Smith et al. (P = 0.0001) (6). The contraindication present in all three of these patients was congestive heart failure requiring drug therapy.

Of 100 inpatients, 68 (68%) had contraindications or precautionary conditions to metformin use. This incidence of inappropriate prescribing is not significantly different (P = 0.2524) from the results of Calabrese et al., who found a similar incidence of 62% of inpatients receiving metformin. In our inpatient sample, the most commonly seen precautions were concomitant cationic drug use and failure to measure serum creatinine before restarting metformin after a surgical procedure. No cases of metabolic acidosis were documented. Approximately 25% of inpatients had more than one precautionary or contraindicating condition; however, there were no patients with more than three risk factors.

We have demonstrated that in our health system, prescribing patterns do not conform to the guidelines established by the manufacturer and the Food and Drug Administration. While the incidence of inappropriate prescribing for outpatients is lower than that reported in the literature, inappropriate use of metformin among inpatients is frequent and occurs at a rate similar to that reported in the literature. Frequent metformin use in patients with risk factors was not accompanied by lactic acidosis in our population. Reexamination of these precautionary and contraindicating conditions in light of extensive worldwide experience with metformin could be helpful in more precisely identifying patients who are likely to develop MALA. This would minimize unnecessary avoidance of the drug in patients with type 2 diabetes who could benefit from treatment.

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The Peroxisome Proliferator–Activated Receptor-γ2 P12A Polymorphism and Type 2 Diabetes in an Arab Population

The association of type 2 diabetes with the P12A polymorphism of the peroxisome proliferator–activated receptor gene (*PPAR-γ2*) has been established in several populations (1). However, no studies have thus far been reported for Arab populations. While many variants have been identified in this gene, the most prevalent and best studied is the P12A polymorphism. There is considerable interpopulation variance in the incidence of the risk allele (P12). This ranges in frequency from a high of 0.96–0.98 in populations including the Japanese, Chinese, and African Americans to 0.91 in Pima Indians and a low of 0.81 in the Finnish population (2).

We utilized a case-control study to test association of the *PPAR-γ* P12A variant with type 2 diabetes in an Arab (Saudi) population for the first time. Genotyping was performed using a molecular beacon–based real-time PCR assay developed in our laboratory and validated in >100 samples by direct sequencing. The study population consisted of 1,137 individuals of Saudi ancestry with type 2 diabetes as defined by World Health Organization criteria and ranging in age from 20 to 85 years. The control group consisted of 219 individuals of Saudi ancestry >60 years old (range 60–92 years) having a fasting blood glucose <7 mmol/l. The control

group was restricted to normoglycemic individuals >60 years of age to minimize inclusion of those likely to develop type 2 diabetes later in life. In addition, P12A genotyping was also performed on a random sample of 727 Saudi neonatal bloodspots to ascertain P12A allele frequencies in an unbiased sample.

Data analysis was first performed for an age- and sex-matched cohort in which the type 2 diabetic cases (n = 118) and control subjects (n = 219) were >60 years old. The male-to-female ratios of these case and control subjects were 1.40 and 1.43, respectively. The *P*, or risk allele, frequency was 0.974 and 0.968 in type 2 diabetic and control subjects, respectively, and was not statistically significant (P = 0.633). However, given the very high incidence of the *P* allele in this population, the study size was extremely underpowered. No age-related differences in P12A allele frequencies were observed. Demonstration of statistical significance or lack thereof in the Saudi population, at a 95% CI or better, is impractical, as this would require case and control populations where n is >175,000. The high incidence of the *P* allele in the Saudi population was confirmed by the neonatal sample set in which frequency of this allele was found to be 0.957. Clearly the risk allele frequency of the Saudi population is comparable to the Japanese, Chinese, and African Americans and is among the highest observed to date.

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The Application of Synthetic hANP in Diabetic Nephropathy With Nephrotic Syndrome

Although the optimal time to initiate hemodialysis is not well defined, it is necessary to start extracorporeal ultrafiltration methods (ECUM) earlier in uremic diabetic patients to avoid life-threatening events, such as anasarca, heart failure, and lung congestion. These patients frequently manifest the poor response to the administration of high dosage of loop diuretics. To investigate the effectiveness of concomitant usage of synthetic human atrial natriuretic peptide (hANP) with loop diuretics, we administered carperitide (hANP) in a case with diabetic nephropathy and nephrotic syndrome.

A 44-year-old woman with 10-year history of type 2 diabetes was referred to our hospital because of oliguria, generalized edema, repeated vomiting, and severe diarrhea. She developed overt proteinuria 3 years ago and has been treated with glimepiride. She presented severe anasarca and gained >15 kg body wt during the past 2 months. Blood pressure was 147/87 mmHg, and Achilles tendon reflex and vibrating sense of lower extremities disappeared. She had diabetic retinopathy and received photocoagulation 3 years before. Serum albumin was 1.9 g/dl, serum creatinine 1.92 mg/dl, total cholesterol 419 mg/dl, daily urinary protein secretion 12.4 g, and creatinine clearance 18.4 ml/min. Cardio-thoracic ratio was 51% in chest X-ray, and pleural effusion and ascites were seen in computed tomography. We started oral and intravenous administration of furosemide (200 mg/day) and infusion of albumin. However, she became anuric at the 7th hospital day, 250–300 ml/day. Before we performed ECUM, we started continuous infusion of carperitide from a dose of 0.025 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and maintained at 0.08 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The concomitant use of furosemide brought prominent diuresis reaching 2,000 ml/day, and we gradually tapered the dosage and continued for 25 days. Finally, she maintained the daily urine volume of 1,000–1,500 ml/day with the oral administration of furosemide (120 mg/day) without deterioration of renal functions. Edema, ascites, vomiting, and diarrhea disappeared, and her body weight returned to 56 kg (Fig. 1).

Although the remission and regression of nephrotic syndrome due to diabetic nephropathy was reported (1), the massive proteinuria is usually intractable, and most patients finally manifested end-stage renal disease. The use of a high dosage of diuretics also accelerates intravascular dehydration, elevation of creatinine and uric acid levels, and impaired renal function. Synthetic hANP elevates glomerular filtration rate by increasing renal blood flow and relaxation of the mesangial cells. It also increases the medullary blood flow and inhibits reabsorption of sodium and water of collecting duct cells. The concomitant use of synthetic hANP and loop diuretics enhances the diuretic action and may suppress furosemide-induced aldosterone activation (2). Instead of ECUM, the administration of synthetic hANP in nephrotic patients with diabetic nephropathy is useful to avoid life-threatening anasarca and may prevent the progressive deterioration of renal function.

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