

found that sTNF-R1 is independently associated with albuminuria in type 2 diabetic patients (4). To the best of our knowledge, however, it is not clear whether serum homocysteine is associated with TNF receptor in type 2 diabetic patients. The aim of the present study was therefore to investigate the relationships between serum homocysteine and TNF receptor in patients with type 2 diabetes.

Fifty nonobese Japanese type 2 diabetic patients were studied. Their BMI, HbA_{1c}, and serum creatinine were 22.6 ± 0.3 kg/m² (range 17.6–26.2), $7.8 \pm 0.2\%$ (5.5–12.3), and 0.70 ± 0.02 mg/dl (0.46–0.98), respectively. They had not been treated with insulin or any medications known to alter homocysteine level. In conjunction with homocysteine, systolic and diastolic blood pressure, HbA_{1c}, glucose, lipids, serum creatinine, TNF- α , sTNF-R1, and sTNF-R2 were measured after an overnight fast.

With univariate analysis, serum homocysteine was positively correlated with age ($r = 0.361$, $P = 0.012$), diabetes duration ($r = 0.292$, $P = 0.045$), serum creatinine ($r = 0.623$, $P < 0.001$), sTNF-R1 ($r = 0.415$, $P < 0.005$), and sTNF-R2 ($r = 0.371$, $P < 0.01$). Other variables including TNF- α , however, were not associated with homocysteine. Multiple regression analyses showed that serum homocysteine was independently associated with serum creatinine ($F = 20.1$) and sTNF-R1 ($F = 6.9$), which explained 49.3% of the variability of homocysteine. Thus, TNF system activity may be responsible for the evolution of atherosclerosis induced by homocysteine in nonobese Japanese type 2 diabetic patients.

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Phenformin-Induced Lactic Acidosis in an Older Diabetic Patient

A recurrent drama (phenformin and lactic acidosis)

Editor's note: The authors had the following statement in their letter to me, with which I agree, "Most physicians are aware of the risk of lactic acidosis in patients taking phenformin. However, this side effect is continuously observed because phenformin is still used in Italy, Brazil, and China. We believe that the publication of our observation in an important journal like Diabetes Care may help to prompt governments of these countries to ban phenformin, just like in the rest of the world. This is the only way to prevent further cases of this avoidable, unacceptable and life-threatening complication."

A 73-year-old man with diabetes presented with upper-abdominal pain and nausea. He also had a history of hypertension, a pace-maker implant, and peripheral arterial disease treated with amputation of his left leg. His therapy included ticlopidine, enalapril, omeprazole, and 2 mg glibenclamide/30 mg phenformin b.i.d. The patient was alert and cognitively intact. Blood pressure and heart rate were 120/70 mmHg and 70 bpm, respectively. Radiographs of the chest and abdomen and an abdominal ultrasound study were normal. Laboratory tests disclosed a severe lactic acidosis (pH 6.8, pCO₂ 14.1 mmHg, pO₂ 108 mmHg, HCO₃ 4.9 mmol/l, lactate 21 mmol/l, and anion gap 31 mmol/l). After phenformin discontinuation, the patient's conditions rapidly improved. He was treated with in-

travenous insulin and glucose (1) and discharged 7 days later in good condition.

This report confirms that phenformin-induced lactic acidosis (PLA) is still a public health problem (1,2). To our knowledge, phenformin is still used in Italy, China, and Brazil. In a Medline search, we found 12 cases that occurred in Italy between 1981 and 1998 (2). In two patients phenformin was even brought back into use soon after, thereby questioning the belief that PLA is adequately recognized (2). More importantly, according to data by Intercontinental Marketing Services (www.imshealth.com), 838,000 preparations of phenformin and a sulfonylurea have been sold in Italy between January and October 2005. Because PLA occurs in 1 of 4,000 patients (3) with a mortality rate of ~50%, these data raise worrying health care considerations. In fact, diabetic patients often have comorbid conditions known to favor PLA.

Phenformin was removed from the U.S. market in 1977, but, surprisingly, cases of patients who have been prescribed the drug abroad are continuously reported (1). Phenformin can also be illegally obtained online or through mail orders to replace metformin, which is more costly. Furthermore, herbal medicines containing phenformin are also consumed in developed countries. In February 2000, the Food and Drug Administration recalled five Chinese herbal medications containing phenformin (4), while Health Canada is currently warning consumers not to take "Shortclean," a phenformin-based Chinese "natural" medicine (5).

Phenformin can always be replaced by metformin, which should not be associated with a higher risk of lactic acidosis compared with nonbiguanide therapies (6). Despite most clinicians being aware of PLA, the only way for preventing further cases is to forbid phenformin in countries where it is still used.

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