Constituents of areca nut and *Piper betle* flower may exert sympathomimetic effects (4), which might elevate blood pressure leading to increased UAER. However, because the effect was independent of blood pressure, other mechanisms should have been in play. Reactive oxygen species and *N*-nitroso compounds can be formed in the oral cavity during betel nut chewing, and in vitro studies also demonstrated that betel nut components increased the release of inflammatory mediators including prostanoids, interleukin-6, and tumor necrosis factor-α (1). Increased oxidative stress and inflammation are also associated with glomerular damage and increased UAER (2). Therefore, the inflammatory mediators produced with betel nut chewing could be responsible.

In conclusions, betel nut chewing is independently associated with increased UAER and albuminuria in Taiwanese type 2 diabetic male patients in this cross-sectional observation. However, future prospective longitudinal studies are warranted for confirmation.

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Effect of Multifactorial Intervention on Diabetic Macular Edema

Clinical trials (1,2) have shown that intensive control of blood glucose and hypertension reduce development of clinically significant macular edema (CSME). Elevated HbA$_{1c}$ (A1C) is a risk for persistent CSME (3). Gross proteinuria is associated with a 95% increase in the incidence of macular edema (4). However, the effect of control of systemic factors before focal laser photocoagulation is not known. We aimed to determine whether multifactorial intervention over 4–6 weeks before focal laser photocoagulation would reduce macular thickness.

In a prospective nonrandomized pilot study, 14 consecutive patients (10 men and 4 women, aged 44–65 years) with type 2 diabetes presenting with nonproliferative diabetic retinopathy and CSME underwent multifactorial interventions including single or multiple modifications in oral hypoglycemic agents ($n = 10$), atorvastatin ($n = 11$), antihypertensive drugs ($n = 12$), and losartan ($n = 4$) to control A1C, fasting and postprandial blood glucose, systolic and diastolic blood pressure, lipid profile, and 24-h urinary proteins. Detailed ocular examination at recruitment and 6 weeks after interventions included fundus fluorescein angiography and measurement of macular thickness using stratus optical coherence tomography done between 12:00 P.M. and 3:00 P.M. Quantitative data are shown as means ± SD. Intergroup comparison was performed by unpaired *t* test.

At 6 weeks postintervention, we found a statistically significant decrease in mean A1C (8.3 to 7.62%, $P < 0.01$), LDL (125.14 to 99.5 mg/dl, $P < 0.001$), fasting blood glucose (142.07 to 117.5 mg %, $P < 0.01$), systolic blood pressure (141.43 to 126.43 mmHg, $P < 0.002$), and diastolic blood pressure (87.14 to 81.54 mmHg, $P < 0.001$). There was significant decrease in mean retinal thickness in both central 1 mm (244.20 ± 64.30 to 220.30 ± 59.68 μm, $P < 0.001$) and 6 mm (282.87 ± 51.09 to 261.65 ± 40.08 μm, $P < 0.001$) of the macula that resulted in a trend toward improvement in visual acuity (logarithm of minimal angle of resolution 0.53 ± 0.29 to 0.52 ± 0.27).

Decreasing macular edema on optical coherence tomography with multifactorial control before laser photocoagulation is encouraging in the management of CSME. Reducing macular thickness facilitates application of a low-energy laser beam. Previously, we found that atorvastatin 6 weeks before focal laser photocoagulation reduced subfoveal migration of lipids in patients with macular edema and dyslipidemia (5). We propose larger studies to determine the role of optimizing systemic factors before laser in CSME.

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The −8503 G/A Polymorphism of the Adiponectin Receptor 1 Gene Is Associated With Insulin Sensitivity Dependent on Adiposity

Adiponectin has beneficial effects on insulin sensitivity. Unexpectedly, adiponectin knockout mice exhibit no or only mild insulin resistance. Nevertheless, under a high-fat/high-carbohydrate diet, severe insulin resistance was induced in those animals (1). Consistent with this, recent evidence (2) suggests that the relationship of adiponectin with insulin sensitivity is stronger with increasing adiposity. In addition, a haplotype in the adiponectin gene was associated with type 2 diabetes only in obese and morbidly obese subjects but not in lean subjects (3).

Single nucleotide polymorphisms (SNPs) of the genes encoding adiponectin receptor (ADIPOR) 1 and 2 were associated with type 2 diabetes (4) or prediabetes phenotypes (5) in some but not in all (6) studies. We found that the −8503 *G/A* SNP of the *ADIPOR1* gene was associated with insulin sensitivity (7). In a very recent study (6) in rather lean subjects with a mean BMI of 21 kg/m^2, no associations with insulin sensitivity were found. In our study (7), subjects were more obese (BMI 26 kg/m^2). This new information lead us to investigate whether the association of the −8503 *G/A* SNP of *ADIPOR1* with insulin sensitivity is modulated by adiposity. If this was the case, then this may partly explain the inconsistent results regarding SNPs of *ADIPOR1* and 2.

Recently reported data (7) from 502 nondiabetic Caucasians were analyzed. Insulin sensitivity was estimated from an oral glucose tolerance test and determined during a euglycemic-hyperinsulinemic clamp (*n* = 299). Subjects were divided into two groups by the median percentage of body fat (PFAT). In the more obese group (*n* = 250, PFAT 27–55%), carriers of the −8503 *A* allele had lower insulin sensitivity estimated from

the oral glucose tolerance test using the formula proposed by Matsuda and De-Fronzo (8) (*G/G*, *G/A*, and *A/A*: 14.4 ± 0.8, 11.9 ± 0.9, and 9.2 ± 1.7 arbitrary units, respectively, *P* = 0.003, ANOVA) and determined during the clamp (0.07 ± 0.005, 0.06 ± 0.005, and 0.04 ± 0.01 μmol · kg^{-1} · min^{-1} · pmol/l^{-1}, respectively, *P* = 0.007) compared with homozygous carriers of the G allele, independent of age, sex, and PFAT. In contrast, in the lean group (*n* = 252, PFAT 7–26%), no significant relationships were found (oral glucose tolerance test: 24.6 ± 1.0, 27.2 ± 1.1, and 23.0 ± 2.4, respectively, *P* = 0.60; clamp: 0.13 ± 0.006, 0.13 ± 0.007, and 0.12 ± 0.016, respectively, *P* = 0.84).

In summary, we show that the A allele of the −8503 *G/A* SNP of the *ADIPOR1* gene is associated with less insulin sensitivity only in more obese but not in lean individuals. This finding may be important for further studies on the relationships of genetic variants of *ADIPOR1* and possibly of *ADIPOR2* with metabolism.

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Evaluation of a Diagnostic Algorithm for Hereditary Hemochromatosis in 3,500 Patients With Diabetes

Hereditary hemochromatosis may lead to hepatic cirrhosis, cardiomyopathy, diabetes, arthritis, and impotence (1,2). In the Caucasian population, *HFE* gene mutations (*C282Y* and *H63D*) are present in the majority of patients demonstrating phenotypic expression (3–6). Conversely, the clinical penetrance in mutation carriers is low (7).

In the precirrhotic stage, ~20% of hemochromatosic patients demonstrate hyperglycemia, with the prevalence increasing to >70% in the presence of liver cirrhosis (8). Two mechanisms contribute to the development of hyperglycemia and diabetes. Liver iron overload leads to insulin resistance, and the pancreatic β-cell iron accumulation results in cell damage and diminished insulin secretion (1). The