OBSERVATIONS

The Effect of Vitamin E Supplementation on Cardiovascular Risk in Diabetic Individuals With Different Haptoglobin Phenotypes

Several clinical trials (1) have demonstrated that vitamin E does not reduce future major cardiovascular (CV) events. However, these trials could not rule out the potential benefit for high-risk subgroups. Diabetic individuals who are homozygous for the haptoglobin 2 allele (Hp 2-2) are at high risk for CV events (2–4); moreover, the Hp 2-2 protein product is an inferior antioxidant compared with the Hp 1 allele (5). We therefore hypothesized that vitamin E may reduce CV events in Hp 2-2 diabetic individuals.

Hp type was measured in 3,167 participants (1,078 with diabetes) of the Heart Outcomes Prevention Evaluation (HOPE) trial, which evaluated the 4.5-year effects of 400 IU vitamin E daily on the primary composite of CV death, myocardial infarction, and stroke (1). No significant benefit of vitamin E supplementation was detected in either the entire group or in the diabetic subset, consistent with what was previously reported for the entire HOPE cohort (1). In Hp 2-2 diabetic participants, there was a trend toward a reduced primary composite outcome (relative risk 0.70 [95% CI 0.45–1.10]) and a statistically significant reduction in the risk of CV death (0.45 [0.23–0.90]) and nonfatal myocardial infarction (0.57 [0.33–0.97]). However, this trend was not observed for strokes (1.15 [0.47–2.82]), and there was no statistical interaction between vitamin E use and haptoglobin type for either the composite outcome or any of its components.

In conclusion, the absence of any statistical interaction indicates that these data do not support the hypothesis that the effects of vitamin E differed by Hp phenotype. Therefore, the results noted above in Hp 2-2 diabetic individuals demonstrating a significant reduction in CV death and myocardial infarction could be spurious and clearly require prospective testing in future trials.

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A.P.L is the author of a patent that claims to predict diabetic vascular disease on the basis of haptoglobin phenotyping.

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Effect of Controlling Hyperglycemia With Diet on QT Abnormalities in Newly Diagnosed Patients With Type 2 Diabetes

Diabetic patients have an excess risk of dying from cardiovascular diseases. Recently, several studies have reported a high prevalence of QT prolongation and increased QT dispersion (QTd) in patients with diabetes. These abnormalities have been shown to be associated with sudden death and poor survival in both type 1 (1) and type 2 (2) diabetes. QTd, i.e., the difference between the maximum and minimum QT intervals on the 12-lead electrocardiogram (ECG) (QTd = QT max − QT min), is claimed to reflect the degree of inhomogeneity of myocardial repolarization. The role of hyperglycemia in causing QT abnormalities in people with diabetes is not clear. The present study was therefore undertaken to assess the effect of controlling hyperglycemia on QT intervals and dispersion.

A total of 26 newly diagnosed type 2 diabetic patients with no coronary artery disease or autonomic dysfunction were recruited. Each was examined and had three ECGs recorded before and after 8 weeks of dietary intervention. All ECGs were analyzed automatically by the previously validated Glasgow program (3). The Hodges formula [corrected QT (QTc) = QT + 1.75 (rate − 60)] was used to correct QT interval. The mean of the three estimates of QTc and QTd before and after intervention was used to improve accuracy. QTc >440 ms and QTd >50 ms were considered as abnormally prolonged (4).

The mean age of 10 men and 16 women was 55.6 ± 12.0 years. Four patients (15.4%) had QTc >440 ms but none had increased QTd at baseline. After

dietary intervention, even though glycemic control improved (HbA_{1c} 8.1 ± 1.9% to 7.2 ± 1.3%, $P < 0.01$), no significant change was noticed in QTc (415.7 ± 19 to 415.1 ± 16.3 ms, P = NS) or QTd (25 ± 7.5 to 23.5 ± 6.7 ms, P = NS). Individual changes in QTc and QTd were not significantly correlated with corresponding initial levels or change in HbA_{1c}. The subset of patients who had prolonged QTc or microalbuminuria at baseline did not show statistically significant differences postintervention. There was no correlation between HbA_{1c} or fasting blood glucose and QTc or QTd before or after intervention. However, a significant correlation was observed between QTc and QTd before ($r = 0.590$, $P < 0.05$) and after ($r = 0.405$, $P < 0.05$) intervention.

It is surprising that despite the conservative criterion for the diagnosis of increased QTd (many previous studies have considered QTd >80 ms as abnormally prolonged), no patient was found to have prolonged QTd. This contrasts with other studies that have reported a high prevalence of QT abnormalities in diabetes (5).

In conclusion, this is the first prospective interventional study in a well-defined cohort of newly diagnosed type 2 diabetic patients to demonstrate that dietary treatment does not influence QT abnormalities in the short term. This study also shows that the prevalence of abnormal QTc and QTd in type 2 diabetes may not be as high as previously thought.

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Impact of Metformin on Glucose Metabolism in Nondiabetic, Obese African Americans

A placebo-controlled, 24-month randomized study

Pharmacological therapy using antidiabetic drugs can delay the onset of type 2 diabetes in individuals with impaired glucose tolerance (IGT) (1–3). These drugs lower blood glucose, but each drug class impacts glucose dysregulation by a different mechanism (4). It is unclear whether simply lowering mean blood glucose can reduce the risk of type 2 diabetes or whether it is the drug effect on particular targets of glucose dysregulation or other unknown drug effects that allow for the decreased incidence of type 2 diabetes in IGT.

Metformin decreases the incidence of type 2 diabetes in IGT (3). But whether metformin treatment earlier in the disease process might further delay progression to IGT/type 2 diabetes is unknown. We performed a double-blind placebo-controlled study of metformin in first-degree relatives of African Americans with type 2 diabetes for 24 months. The aim of the present study is to examine the effect of metformin on glucose metabolism in normal glucose tolerant (NGT) African Americans at risk for type 2 diabetes.

The study included 126 NGT African Americans. The MET group ($n = 45$) received 500 mg/day metformin and the PLA group ($n = 81$) received placebo for 24 months. Yearly oral glucose tolerance tests and frequently sampled intravenous glucose tolerance tests were performed.

Baseline clinical characteristics were similar between groups. There were no sex differences. The MET group demonstrated a reduction in weight (−1.4 ± 1 kg) and BMI (−0.53 ± 0.4 kg/m^2). Weight (1.4 ± 0.8 kg, $P < 0.02$) and BMI (0.5 ± 0.34 kg/m^2, $P < 0.01$) increased in PLA. Following metformin therapy, acute first- and second-phase glucose, insulin, and C-peptide area under the curve did not change. However, hepatic insulin extraction (HIE) was increased 21% in the MET group vs. 5% in the PLA group.

As increased hepatic glucose production and decreased HIE is commonly seen as a component of glucose dysregulation in type 2 diabetes and other high-risk populations (5–7), improvement in HIE could potentially lead to overall improvement in glucose metabolism. In this study, the MET group was associated with modest weight reduction and enhanced HIE. The reason for the improved HIE is unclear but may reflect a mechanistic change at the level of the liver in response to metformin. Our findings of increased HIE could partly be responsible for the hepatic effect on glucose regulation previously reported (4). This finding is of great interest, demonstrating a "resetting" of the hepatic response to insulin resistance and a return to a more physiologic glucoregulation with even small doses of metformin in nondiabetic at-risk individuals.

Although other glucose-lowering drugs have been found to both improve (8) and worsen (9) HIE, to the best of our knowledge, the current findings repre-

sent a unique response not previously reported with metformin usage in an NGT population. Whether this restoration of HIE translates to a reduced occurrence of IGT/type 2 diabetes in our at-risk African-American population is not known. The drug was well tolerated for the 2-year duration without significant adverse events. Further studies are needed to determine the optimal dose of metformin for maximum benefit on early abnormalities in glucose dysregulation while minimizing side effects. Based on our current data, the treatment of at-risk African Americans with metformin is safe and may be beneficial in preventing conversion to IGT/type 2 diabetes.

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Elevated C-Reactive Protein Levels Do Not Correspond to Autoimmunity in Type 1 Diabetes

A large body of data now supports that high normal or elevated C-reactive protein (CRP) levels are a marker of ongoing low-grade chronic inflammatory process and may predict a higher risk for cardiovascular disease. Type 1 diabetes is a T-cell–mediated disease (1), and autoantibodies (2) are considered to be the surrogate markers for the autoimmune process and have been used for disease prediction (3). However, little is known about the relationship between diabetes autoimmunity and the acute-phase response. We studied the relationship of islet cell autoimmunity in type 1 diabetes as reflected by the presence of GAD65 and ICA512 autoantibodies and CRP titers. We analyzed the following five groups of individuals: pre-diabetic (n = 10) , new-onset (n = 29), long-term type 1 diabetic (n = 16), and long-term type 2 diabetic (n = 55) patients and healthy subjects (n = 50). CRP levels were significantly higher in long-term type 1 diabetic patients (0.11 mg/dl [range 0.014–1.39]) than in either new-onset type 1 diabetic patients (0.061 mg/dl [0.012–1.12], P = 0.04) or healthy control subjects (0.06 mg/dl [0.007–1.33], P = 0.02). Long-term type 2 diabetic patients have higher CRP levels (0.24 mg/dl [0.03–4.41]) than healthy control subjects (P = 0.04). We could not find any correlation between CRP levels and any combination or titer of autoantibodies in pre-diabetic, new-onset, and long-term type 1 diabetic patients.

The lack of elevated CRP in the pre-diabetic and recently diagnosed patients with type 1 diabetes is consistent with the notion that chronic localized autoimmune inflammation does not result in appreciable changes in the CRP levels, thus making it unsuitable as a marker of type 1 diabetic autoimmunity. The difference in CRP levels in long-term and new-onset type 1 diabetic patients may be related in part to the vanish of the intrinsic physiologically secreted insulin once extending the honeymoon period in type 1 diabetes. Insulin has been shown to have anti-inflammatory properties, including downregulation of acute-phase protein production of the liver (4); thus, it may lead to lower CRP levels.

The underlying mechanisms behind elevated CRP levels in long-term type 1 and type 2 diabetic patients might be different, as elevated glucose levels as well as insulin resistance are contributing factors to the inflammatory process. Prolonged elevated blood glucose levels are implicated in chronic inflammatory changes in the tissues in both type 1 and type 2 diabetic patients and reflected by the elevated CRP values. However, in type 2 diabetes, insulin resistance is also likely to be a major factor (5), as elevated CRP values have been found in near-normoglycemic pre-diabetic type 2 diabetic and metabolic syndrome patients.

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COMMENTS AND RESPONSES

Orlistat Augments Postprandial Increases in Glucagon-Like Peptide-1 in Obese Type 2 Diabetic Patients

Response to Damci et al.

Damci et al. (1) suggest that the lipase inhibitor, orlistat, stimulates the postprandial secretion of glucagon-like peptide-1 (GLP-1) after meals containing fat and speculate that this may lead to reductions in both postprandial glycemia and energy intake. The authors observed (in a cohort of 29 type 2 diabetic patients) that after ingestion of a 600 kcal breakfast (comprising 38% fat, 50% carbohydrate, and 12% protein), the increases from baseline in plasma GLP-1 and serum C-peptide were slightly greater and that of serum glucose slightly less, as measured in a single blood sample taken 60 min after commencement of the meal. The authors have apparently failed to appreciate the following: *1*) While fat is a potent stimulant of GLP-1 secretion, the latter appears to be dependent on the digestion of fat to fatty acids (2,3), e.g., in healthy subjects, the stimulation of GLP-1 by intraduodenal triglyceride is abolished by concomitant administration of orlistat (2). *2*) As the regulation of gastric emptying of fat is also dependent on lipolysis (4,5), orlistat may accelerate gastric emptying of meals containing fat (4). If the meal also contains carbohydrate, orlistat has the capacity to exacerbate overall postprandial glycemic excursions in type 2 diabetic patients by this mechanism (3). Even relatively minor variations in gastric emptying of carbohydrate are now known to potentially have a major effect on postprandial glycemia and insulin responses in both healthy subjects and type 2 diabetic patients (6,7). 3) In healthy subjects, acute lipase inhibition with orlistat attenuates rather than increases the inhibitory effects of fat on subsequent energy intake (2,8).

The effects of orlistat on glycemic, insulin, and incretin responses to a meal, including the time course of these effects, are likely to be critically dependent on both the macronutrient composition and energy content of a meal, perhaps particularly the ratio of fat to carbohydrate. It should also be recognized that in patients with type 2 diabetes, gastric emptying is frequently abnormal and may influence these responses (7). In relation to the study by Damci et al. (1), we would offer an alternative interpretation, i.e., after administration of orlistat, the carbohydrate, fat, and protein components of their meal (the type of meal is not described) initially emptied from the stomach more rapidly, and this was reflected in a relative increase in C-peptide and GLP-1 at 60 min and a slight reduction in plasma glucose at that time. The stimulation of GLP-1 would reflect the greater small intestinal carbohydrate load during this time as well as the presence of fatty acids that escaped lipase inhibition. We would anticipate that the overall GLP-1 response to the meal would be less and initial postprandial glycemia worse. It would require more frequent blood sampling over a longer period of time to fully interpret the action of orlistat on incretin and insulin secretion and to draw conclusions about GLP-1 as a mediator of the effects of orlistat on body weight in obesity.

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Orlistat Augments Postprandial Increases In Glucagon-Like Peptide-1 in Obese Type 2 Diabetic Patients

Response to Horowitz et al.

We thank Horowitz et al. (1) for their comments on our article (2) on the effect of orlistat on postprandial glucose, insulin, and incretin levels. They raise criticisms regarding the increase in postprandial GLP-1 levels, asserting that it is a result of fat digestion rather than the fat content of the meal. They also state that to draw more definitive conclusions, more frequent blood sampling over a longer period of time is required rather than a single sample at 60 min after the mixed meal. Ours was an observatory pilot study that tested the effect of this drug on postprandial incretin levels. Putative mechanisms of action will be addressed in further studies in which we will take these criticisms into account. Horowitz et al. also state that orlistat would be expected to worsen postprandial hyperglycemia since this drug accelerates gastric emptying. Apart from our study, orlistat was previously shown to ameliorate postprandial blood glucose levels in long-term studies (3).

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