Micronutrients and Diabetic Retinopathy
A Systematic Review

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Background: We have evaluated the evidence for the association between intake and blood levels of micronutrients and diabetic retinopathy. Treatment for diabetic retinopathy requires significant clinical input and specialist ophthalmologic care. Micronutrients, including vitamin C, vitamin E, and magnesium, may interfere with pathologic mechanisms of diabetic retinopathy and potentially alter its risk.

Methods: We conducted a search of epidemiologic literature in PubMed and Embase from 1988 to May 2008, using keywords for exposures, including magnesium, ascorbic acid, α-tocopherol and antioxidants, and outcomes, including diabetic retinopathy. Two authors independently extracted data and assessed the quality of the studies using the Newcastle-Ottawa Scale. The overall quality of evidence was graded as I (highest), II, or III (lowest).

Results: Of the 766 studies identified, we reviewed 15 studies, comprising 4094 individuals. For vitamin C, hospital-based studies reported an inverse association between plasma levels with retinopathy, whereas population-based studies showed no association between dietary intake and retinopathy. For vitamin E, there was no association with dietary intake or plasma levels and retinopathy. For magnesium, a single prospective analysis showed an association between low levels in plasma and progression of retinopathy, but cross-sectional studies reported inconsistent results. In the assessment of quality, population-based studies had higher ratings than hospital-based studies.

Conclusions: The evidence suggests that dietary intake or plasma levels of vitamins C and E and magnesium do not seem to be associated with diabetic retinopathy. Because of differences in study designs and measurement of micronutrients, incomplete ascertainment of retinopathy, and residual confounding, these findings require confirmation.

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Retinopathy is a serious microvascular complication of diabetes and a leading cause of visual impairment in persons with diabetes. The World Health Organization estimates that diabetic retinopathy accounts for approximately 5% of the global prevalence of blindness, with estimates of 15% to 17% in developed countries.1 Long-term glycemic control2,3 and optimal blood pressure levels4,5 delay or prevent retinopathy, and treating retinal vascular changes in patients with diabetes prevents visual loss.6 However, all require significant clinical input or specialist ophthalmologic care.

Micronutrients may potentially alter the risk of diabetic retinopathy by interfering with pathologic mechanisms. Among the micronutrients that have been studied are vitamin C, vitamin E, and magnesium. Vascular endothelial growth factors increase vascular permeability and stimulate retinal neovascularization.7 Vitamins C and E have been shown to suppress the production of vascular endothelial growth factor in animal models.8,9 Hyperglycemia causes an accumulation of advanced glycation endproducts,10 which can increase the adhesion of monocytes to retinal endothelial cells through expression of intercellular cell adhesion molecule-1.11 The overexpression of intercellular cell adhesion molecule-1 may be inhibited by vitamins C and E.12 Hyperglycemia increases endothelial dysfunction by protein kinase C–dependent endothelial dysfunction.13 Vitamin C may decrease activation of protein kinase C, restore production of endothelial nitric oxide, and improve dilation of vasculature.14 Magnesium acts as a physiological calcium antagonist.15 An increase in peripheral intracellular concentration of free calcium impairs insulin actions on glucose uptake and worsens hyperglycemia.16 This evidence suggests that nutrition factors may play a role in preventing or limiting the progression of retinopathy.

The observational evidence relating these micronutrients to diabetic retinopathy is limited, with conflicting results. A review of randomized, controlled trials evaluating the effects of vitamin C supplementation as treatment for diabetic retinopathy did not identify any relevant trials.17 One meta-analysis of observational studies showed that low levels of serum magnesium increased risk of retinopathy.18 We conducted a systematic review of the epidemiologic literature on the association between micronutrients, including vitamin C, vitamin E, and magnesium, and diabetic retinopathy.

Sources and Methods of Literature Review

Literature Search
We conducted a comprehensive literature search in 2 electronic databases: PubMed and Embase from 1988 to May 2008. We searched PubMed using standard medical subject
The search strategy is summarized in Table 1. We scanned the bibliographies of relevant articles and reviews. We included studies that measured these micronutrients using dietary methods or biomarkers. The outcome measure was diabetic retinopathy, including the presence or absence of nonproliferative and proliferative retinopathy. We considered proliferative retinopathy as growth of new retinal blood vessels (neovascularization), retinal or vitreous hemorrhages, and vitreoretinal traction. We included studies utilizing different diagnostic methods of ascertaining retinopathy, including fundus photography with or without mydriasis, fundoscopy, direct or indirect ophthalmoscopy, and fluorescein angiography, and studies using different criteria to grade the severity of retinopathy. We excluded visual acuity alone as an outcome measure.

We identified 17 articles from PubMed and 8 from Embase that met the inclusion criteria. We searched the lists of relevant articles and reviews. The search strategy is summarized in Table 1.

Selection of Studies

The database search identified 241 citations in PubMed and 531 citations in Embase. Two authors assessed the abstracts independently and selected potentially relevant studies according to predefined inclusion criteria. We included observational studies with cross-sectional, case-control, or prospective designs on human participants with diabetes published in English. We excluded reviews and interventional studies. The exposures were micronutrients, including dietary intake or serum/plasma levels of vitamin C, vitamin E, and magnesium. We included studies that measured these micronutrients using dietary methods or biomarkers. The outcome measure was diabetic retinopathy, including the presence or absence of nonproliferative and proliferative retinopathy. We considered proliferative retinopathy as growth of new retinal blood vessels (neovascularization), retinal or vitreous hemorrhages, venous abnormalities, cotton-wool spots, and hard exudates. We considered proliferative retinopathy as growth of new retinal blood vessels (neovascularization), retinal or vitreous hemorrhages, and vitreoretinal traction. We included studies utilizing different diagnostic methods of ascertaining retinopathy, including fundus photography with or without mydriasis, fundoscopy, direct or indirect ophthalmoscopy, and fluorescein angiography, and studies using different criteria to grade the severity of retinopathy. We excluded visual acuity alone as an outcome measure.

We identified 17 articles from PubMed and 8 from Embase that met the inclusion criteria. We searched the lists of references and identified an additional 2 articles. Excluding 6 duplicate studies, we retrieved 21 articles for review. Of these, we excluded 6 studies; reasons for exclusion were unrelated exposures/outcomes (n = 3), unable to locate (n = 1), combined micronutrient exposures (n = 1), and unrelated research question (n = 1). We included 15 studies in the systematic review on micronutrients and diabetic retinopathy (Fig 1).

Data Extraction

Two authors extracted information including study design, source of cases and controls, sample size, definition of micronutrient exposure and its measurement, and definition and measurement of diabetic retinopathy (Tables 2 and 3). We recorded variables on which investigators matched cases and controls as well as any confounders from regression models adjusted for factors in addition to vitamin C, vitamin E, or magnesium.

To assess the quality of the evidence, we used the Newcastle-Ottawa Scale which uses a 0- to 4-star rating for categories of selection and exposure/outcome measurement and 0- to 3-star rating for comparability. We modified the scale for this review. For cohort studies, we rated 1 star each if the exposed cohort represented the average micronutrient intake of the target population and if the nonexposed and exposed cohorts were selected from the same population. For cross-sectional studies, we rated 1 star each in the selection of the cases and controls if cases were defined with independent validation and if controls were selected from community sources. For all study designs, we assessed methods of measuring micronutrients, ascertainment of retinopathy, and comparability of cohorts by design and analysis. We rated 1 star for measurement of micronutrients if the study utilized validated or standardized methods, for example, validated food frequency questionnaires or standardized biochemical assays. We rated 1 star for ascertainment of retinopathy if assessments were blinded or from an independent source. We rated 1 star in each criteria of comparability if age, gender, and known risk factors for retinopathy (glycemic control or hypertension) were matched in design or adjusted in statistical analysis. According to the total number of stars, we summarized the overall quality of existing evidence into rat-

Table 1. Search Strategy to Identify Studies to Include in the Systematic Review

<table>
<thead>
<tr>
<th>Database</th>
<th>Term</th>
<th>Keywords Related to Micronutrients</th>
<th>Key Words Related to Diabetic Retinopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed</td>
<td>Medical subject heading</td>
<td>Magnesium, Ascorbic acid, α-Tocopherol, Antioxidants</td>
<td>Diabetic retinopathy, Diabetic complications</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For each keyword, explode using subheadings: administration and dosage, blood, metabolism, therapy</td>
<td>For each keyword, explode using subheadings: blood, complications, diet therapy, epidemiology, prevention and control, therapy, metabolism</td>
</tr>
<tr>
<td>Embase</td>
<td>Map term to subject heading</td>
<td>Magnesium, Ascorbic acid, α-Tocopherol, Antioxidants (explode, all subheadings)</td>
<td>Diabetic retinopathy, Diabetic complications, Diabetes mellitus (explode, all subheadings)</td>
</tr>
</tbody>
</table>
ings, with I as the highest quality and III the lowest. Two authors rated the quality of the evidence independently and resolved disagreements by discussion and consensus. Because of substantial differences between studies, we did not pool the effect estimates into a meta-analysis to quantify any associations.

Summary of Evidence

Of the 15 studies included in the systematic review on micronutrients and diabetic retinopathy (Fig 1), 12 studies contained cross-sectional analyses only,21,23,25–33,35 1 included cross-sectional and longitudinal analyses,22 and 2 were prospective cohort studies with longitudinal analyses only.24,34 Three out of 15 studies were population based22–24; the remaining were hospital based.21,25–35 Of the 15 studies, 4 studies examined the association with vitamin C and vitamin E,21–24 4 studies included vitamin C only,25–28 2 studies included vitamin E only,29–30 and 5 studies included magnesium only.31–35 The number of participants in the prospective cohort studies ranged from 61 to 1353. The number of participants with diabetic retinopathy in hospital-based, cross-sectional studies ranged from 20 to 83.
Exposure Measurement and Outcome Ascertainment

Thirteen studies measured vitamin C, vitamin E, or magnesium levels in serum or plasma samples. Two studies used dietary methods, including 24-hour recalls and food frequency questionnaires, to measure micronutrient intake. The diagnostic methods of diabetic retinopathy included retinal photographs, fundoscopy, ophthalmoscopy, and fluorescein angiography. Four studies performed the diagnostic tests after dilating pupils.

Quality of Evidence

In the assessment of quality, 3 out of 15 studies were rated 3 to 4 stars in the selection criteria; all 3 studies were population based. One study received a 3-star rating for comparability; the study was a population-based and controlled for age, gender, hypertension, and glycemic control. Fourteen studies received 2 stars in the exposure and outcome measurement criteria because they used structured dietary interview or standardized laboratory measurement, and used the same methods of measurement in cases and controls. In the overall quality of the evidence, 10 studies were graded II and 2 studies received a rating of I.

Associations between Micronutrients and Retinopathy

Vitamin C. For the association between plasma/serum vitamin C levels and diabetic retinopathy, all 5 hospital-based, cross-sectional studies consistently reported that diabetic patients with retinopathy had lower vitamin C levels than those without retinopathy. A cross-sectional analysis of National Health and Nutrition Examination Survey found no association between serum vitamin C level and prevalent diabetic retinopathy (odds ratio [OR], 1.3; 95% confidence interval [CI], 0.8–2.3, comparing the extreme quartiles of serum vitamin C level). A prospective analysis of the Atherosclerosis Risk in Communities Study did not find an association between dietary vitamin C intake and risk of diabetic retinopathy (OR, 1.1; 95% CI, 0.7–1.9, comparing the extreme quartiles of vitamin C intake), defined as the presence of diabetes-specific retinal lesions, including microaneurysms, retinal hemorrhages, hard or soft exudates, macular edema, intraretinal microvascular abnormalities, or venous beading. The San Luis Valley Diabetes Study did not find an association between dietary vitamin C intake and risk of proliferative diabetic retinopathy (odds ratio [OR], 1.2; 95% confidence interval [CI], 0.5–2.8, comparing the extreme quartiles of vitamin C intake).
not observe an inverse association when comparing extreme deciles of dietary vitamin C intake on prevalent diabetic retinopathy, as defined by the presence of background, preproliferative, or proliferative retinopathy.22

Vitamin E. With respect to vitamin E, there was no association between vitamin E and diabetic retinopathy in population-based studies (OR, 1.3; 95% CI, 0.8–2.2, comparing extreme quartiles of dietary vitamin E intake in the Atherosclerosis Risk in Communities Study; OR, 2.7; 95% CI, 1.6–4.6, comparing extreme quartiles of serum/plasma levels of vitamin E in the National Health and Nutrition Examination Survey study \(P \text{ for trend} = 0.14\)).22–24 Hospital-based, cross-sectional studies showed conflicting results. One study showed higher vitamin E levels in patients with retinopathy than in those without retinopathy,21 whereas 2 studies showed no difference in vitamin E levels between diabetic patients with or without retinopathy.29–30

Magnesium. Lastly, studies on the association between serum/plasma levels of magnesium and diabetic retinopathy were inconsistent. Cross-sectional studies reported that serum/plasma magnesium levels were either significantly higher or lower in diabetic patients with retinopathy, as compared with those without retinopathy.31–33,35 These studies used different methods to ascertain retinopathy, such as fundus photography,31 or ophthalmologic examination.32–33 One study did not describe the method of ascertainment of retinopathy.35 A single prospective cohort study demonstrated an inverse association of plasma magnesium with the progression of diabetic retinopathy. Retinopathy was measured by indirect fundoscopy in mydriasis and was defined as the development of background retinopathy with normal retina at baseline. The significant association remained after adjusting for potential confounders, including hemoglobin A1c levels and duration of diabetes.34

Discussion

This systematic review to assess the association between micronutrients and diabetic retinopathy suggested that vitamins C and E, and magnesium do not appear to be associated with diabetic retinopathy. Because few studies exist for micronutrient intake and diabetic retinopathy, little information is available on the true association. We considered possible sources of heterogeneity between the studies, including study designs, sample populations, exposure measurements, outcome ascertainment, and residual confounding, and we found marked differences.

Because there were few published studies, we included cross-sectional analyses. A cross-sectional design limits the ability to establish a temporal relationship, and does not preclude the possibility of reverse causation, namely, that the diagnosis of diabetic retinopathy leads an individual to increase his or her intake of micronutrients. The relatively small number of cases in cross-sectional studies and the number of participants in the prospective cohorts may not have provided sufficient power to detect an association. Two population-based studies acknowledged that the absence of an association was likely a result of insufficient statistical power.23–24

A large number of included studies considered the potential confounding effects of age and gender, but not of other risk factors for diabetic retinopathy, such as blood pressure and hyperglycemia. Studies have shown that plasma vitamin C, a biomarker of dietary vitamin C, is inversely associated with both hemoglobin A1c levels and blood pressure.36,37 Hospital-based, cross-sectional studies showed an inverse relationship between serum/plasma levels of vitamin C and diabetic retinopathy. A population-based study using dietary methods to measure vitamin C

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Table 3. Exposure and Outcome Definition of the Studies on the Association between Micronutrients and Diabetic Retinopathy

<table>
<thead>
<tr>
<th>First Author, Year of Publication</th>
<th>Exposure Definition*</th>
<th>Outcome Measurement*</th>
<th>Outcome Definition*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rema, 199521</td>
<td>Plasma vitamins C and E</td>
<td>No description</td>
<td>No description</td>
</tr>
<tr>
<td>Mayer-Davis, 199822</td>
<td>Dietary vitamins C and E (24-hr recall)</td>
<td>Mydriatic retinal photos (both eyes)</td>
<td>Airlie House Criteria</td>
</tr>
<tr>
<td>Millen, 200323</td>
<td>Serum vitamins C and E</td>
<td>Nonmydriatic fundus photos (1 eye)</td>
<td>Modified Airlie House Criteria</td>
</tr>
<tr>
<td>Millen, 200424</td>
<td>Dietary vitamins C and E (FFQ)</td>
<td>Nonmydriatic fundus photos (1 eye)</td>
<td>Modified Airlie House Criteria</td>
</tr>
<tr>
<td>Ali, 198925</td>
<td>Plasma vitamin C</td>
<td>Dilated eye fundoscopy</td>
<td>Presence/absence of DR</td>
</tr>
<tr>
<td>Sinclair, 199226</td>
<td>Serum vitamin C</td>
<td>Fundoscopy</td>
<td>Presence/absence of retinal lesions</td>
</tr>
<tr>
<td>Gurler, 200027</td>
<td>Serum vitamin C</td>
<td>Direct and indirect ophthalmoscopy with dilated pupils</td>
<td>Presence/absence of retinal lesions</td>
</tr>
<tr>
<td>Gupta, 200528</td>
<td>Plasma vitamin C</td>
<td>Direct ophthalmoscopy</td>
<td>Presence/absence of proliferative/ nonproliferative DR</td>
</tr>
<tr>
<td>Martinoli, 199329</td>
<td>Plasma vitamin E</td>
<td>Direct ophthalmoscopy/fluorescein angiograph</td>
<td>Presence/absence of DR</td>
</tr>
<tr>
<td>Willms, 199830</td>
<td>Blood vitamin E</td>
<td>Fluorescein angiograph</td>
<td>No description</td>
</tr>
<tr>
<td>Hatwal, 198931</td>
<td>Serum magnesium</td>
<td>Fundus photographs</td>
<td>Presence/absence of NPDR/PDR</td>
</tr>
<tr>
<td>Erasmus, 198932</td>
<td>Plasma magnesium</td>
<td>Ophthalmoscopy</td>
<td>Jackson classification</td>
</tr>
<tr>
<td>Walter, 199133</td>
<td>Plasma magnesium</td>
<td>Ophthalmoscopy</td>
<td>No description</td>
</tr>
<tr>
<td>deValk, 199934</td>
<td>Plasma magnesium</td>
<td>Indirect fundoscopy in mydriasis</td>
<td>Stable/progression of DR</td>
</tr>
<tr>
<td>Sharma, 200735</td>
<td>Serum magnesium</td>
<td>No description</td>
<td>Presence/absence of DR</td>
</tr>
</tbody>
</table>

DR = diabetic retinopathy; FFQ = food frequency questionnaire; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy.

*As described in studies.
intake reported no associations, but only after adjusting for a range of potential confounders, including glycemic control. With respect to magnesium, low serum magnesium levels predict incident diabetes, whereas high dietary magnesium intake is associated with lower levels of blood pressure and blood glucose. Oral magnesium supplementation may reduce fasting blood glucose in type 2 diabetes and improve blood pressure control. That a prospective analysis observed an association between low magnesium level and progression of retinopathy, adjusted for glycemic control and duration of diabetes, suggests a real association. However, because of the possibility of residual confounding, this finding requires confirmation. None of the included studies accounted for effects of blood pressure control.

Most of the studies provided little description on methods of selection of cases and controls. A limitation of studies that selected cases from hospitals’ wards or clinics is the possibility that cases may have been more likely to have retinal lesions detected than those selected from the general population, which would have overestimated the effect estimates. Patients from a single hospital may reflect the characteristics of population only in its catchment area. Ideally, the exposure of risk factors and confounding factors of the diabetic controls would be representative of the population at risk of being a case. Nondiabetic controls would resemble the demographic characteristics of the study population. In the studies reviewed, controls with diabetes were chosen from the same population from which cases were selected. Nondiabetic controls were chosen from a variety of sources, including patients’ spouses, hospital staff, and local communities. Controls who were selected from “convenience” sources, for example, hospital staff, may introduce selection bias as they might be more (or less) health conscious and their micronutrients intake may differ from diabetic patients with retinopathy.

Our quality assessment indicated that most studies used validated dietary methods or standardized laboratory measurements to measure micronutrient intake. Nonetheless, measurement error could lead to misclassification of exposure, that is, the individuals who had high intake of micronutrients may have been classified into the low intake group. To assess vitamin C and vitamin E intake, the San Luis Valley Diabetes Study used a single 24-hour recall, which may not reflect long-term dietary intake or account for day-to-day variation. By contrast, the Atherosclerosis Risk in Communities investigators used a validated food frequency questionnaire, evaluating the average dietary intake over the past year. The level of a nutrient in serum or plasma reflects dietary intake (usually short term) and absorption and metabolism of food or supplements. A single measurement, which occurred in most studies we reviewed, does not account for day-to-day variation of nutrient intake. Repeated measurements over time, not feasible in cross-sectional studies, could better capture daily variation and measure long-term intake.

Use of vitamin and mineral supplement is common in the United States. Recent consumption of vitamins and minerals directly affect the serum/plasma level of a nutrient. In a cross-sectional analysis of National Health and Nutrition Examination Survey, investigators found that excluding users of vitamin supplement from analyses changed the direction of association from increased to decreased risk for serum vitamin C, and attenuated the association for serum vitamin E and prevalent retinopathy, albeit not significantly. None of the hospital-based studies that measured the serum/plasma levels of micronutrients accounted for vitamin and mineral supplements in analyses.

Imprecise measurement of retinal lesions could lead to nondifferential misclassification of outcomes, that is, misclassification of retinopathy regardless of the level or intake of micronutrients, and underestimate the true association. The reference standard to detect diabetic retinal lesions is stereoscopic 7-field, 30° mydriatic fundus photographs as defined by the Early Treatment for Diabetic Retinopathy Study score. Various methods were used to ascertain retinopathy in the studies we reviewed including retinal photography, fundoscopy, ophthalmoscopy, and fluorescein angiography. In the Liverpool Diabetic Study, when grading against the simplified version of the Wisconsin protocol to detect sight-threatening diseases in persons with diabetes, retinal photography has a sensitivity and a specificity of 89% and 86%, whereas direct ophthalmoscopy has a sensitivity and a specificity of 65% and 97%. In another study, an ophthalmologist’s examination using direct ophthalmoscopy and indirect slit-lamp biomicroscopy compared favorably to 7-field stereophotography and 2-field digital photography to detect diabetic retinopathy. However, the lack of permanent retinal image, the limitation of the ophthalmoscope, and the potential for inconsistent results between ophthalmologists make the use of retinal photography preferable to an ophthalmologic examination. Mydriasis decreases the number of ungradable photographs and reduces measurement errors. Only 4 out of 15 studies reported dilation of pupils before taking retinal photographs or performing fundoscopy.

The classification of diabetic retinopathy, and therefore the reference group, varied. Some studies compared the presence or absence of any retinopathy, whereas others compared the presence or absence of proliferative retinopathy. The population-based studies used specific grading schemes, for example, the Modified Airlie House Classification and Early Treatment for Diabetic Retinopathy Study score. Comparing severe proliferative retinopathy with minimal background retinopathy could yield larger effect sizes. The results of the included studies may not be comparable because of the differences in grading criteria of retinopathy. The classification of International Clinical Diabetic Retinopathy Disease Severity Scale provides a means to categorize diabetic retinopathy consistently.

In conclusion, the observational evidence demonstrates that vitamins C and E and magnesium do not seem to be associated with diabetic retinopathy. However, because these studies are inconclusive and the prevention of retinopathy worthwhile, we advocate further prospective studies to characterize the nature of the associations between micronutrients and diabetic retinopathy. Ideally, these studies would repeatedly measure dietary and supplement intake and biomarkers. Two-field mydriatic retinal photography
and the International Clinical Diabetic Retinopathy Disease Severity Scale are sufficient for epidemiologic studies of diabetic retinopathy. If a protective effect is demonstrable, it would justify performing a randomized, controlled trial of micronutrient intake or supplementation to test this means to reduce the incidence of retinopathy.

Clinical Recommendations

This systematic review identified marked variation between the quality of studies. Differences in study designs and measurement of micronutrients, incomplete ascertainment of retinopathy, and residual confounding likely account for the inconsistent associations observed. We do not currently recommend supplementing the diet of diabetic individuals with vitamin C, vitamin E, or magnesium as a means to reduce the occurrence of retinopathy.

References


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