Associations Between Dietary Patterns and Skin Microcirculation in Healthy Subjects


Objective—Microvascular dysfunction is suggested to be a marker of common pathophysiological mechanisms in the development of insulin resistance, cardiovascular diseases, and type 2 diabetes mellitus. Given the established relationship of diet with the macrovascular disease, the aim of this study was to investigate for the first time the possible associations between dietary patterns and microcirculation.

Approach and Results—Two hundred ninety-one healthy men and women selected from the SU.VI.MAX2 cohort were assessed for anthropometric, nutritional, biochemical, and microcirculation parameters using finger skin capillaroscopy. Dietary intake was assessed cross-sectionally using a food frequency questionnaire, and principal component analysis was used to identify dietary patterns from 40 food groups. Six dietary patterns were identified. A dietary pattern characterized by increased consumption of vegetable oils, poultry, and fish and seafood was positively associated with both functional and anatomic capillary density after adjusting for confounders (β=0.13, P=0.05 and β=0.20, P=0.00, respectively). A second dietary pattern with increased consumption of sweets was inversely associated with functional and anatomic capillary density in all multivariate models (β=−0.14, P=0.03 and β=−0.17, P=0.01). There were no associations between any of the derived dietary patterns and capillary recruitment.

Conclusions—In healthy subjects, a dietary pattern characterized by an increased consumption of vegetable oils, poultry, and fish and seafood and low consumption of sweets was associated with better microvascular function. Further prospective studies are needed to confirm the present association. (Arterioscler Thromb Vasc Biol. 2014;34:00-00.)

Key Words: diet, microcirculation

Capillaries play a pivotal role in the microcirculation through the exchange of metabolic substrates and waste products between blood and tissues.1 This function is associated with the number of capillaries per volume unit of tissue (ie, the density of the capillary bed).2 The phenomenon of increased intercapillary distance, that is, of reduced capillary density, is called capillary rarefaction.3

On the basis of studies that investigated mostly the human cutaneous capillaries, capillary rarefaction has been described in hypertension,4–9 in subjects with metabolic syndrome,10 and in overweight individuals,11–13 even in the absence of insulin resistance or elevated blood pressure (BP). Of note, in healthy nonobese individuals, an inverse association between insulin resistance14 and BP levels,14,15 on one hand, with capillary recruitment, on the other hand, has been described, suggesting the presence of a possible pathophysiological continuum between them, even in normalcy.

The pathophysiological steps toward the development of capillary rarefaction are not elucidated yet.16–18 Capillary rarefaction may derive from (1) increased vasomotor tone in the precapillary arterioles as a result of increased pressure upstream,19 (2) a genetic predisposition as observed in young adults or even infants at high risk to develop hypertension,16–18 or (3) increased oxidative stress and inflammation in the microenvironment of the local microcirculation, resulting in endothelial dysfunction and vasoconstriction.18 The latter pathway might provide a pathophysiological link between the genesis of high BP and insulin resistance.9,11,14

*These authors contributed equally.

The online-only Data Supplement is available with this article at http://atvb.ahajournals.orglookup/suppl/doi:10.1161/ATVBHA.113.302411/-/DC1. Correspondence to Sébastien Czernichow, Unité de Nutrition, Hôpital Ambroise Paré, 9 Ave Charles-de-Gaulle, 92100 Boulogne-Billancourt, France. E-mail sebastien.czernichow@apr.aphp.fr

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There is indirect evidence to support the implication of nutrition in the pathophysiology of capillary rarefaction. First, several nutrients and vasoactive dietary compounds have been described to affect the microcirculation, as well as large artery function and structure. Second, the role of nutrition in the development of insulin resistance, diabetes mellitus, and hypertension is already well described, and it might be mediated by early alterations in the microcirculation. However, only 1 study has investigated to date the association between nutrition and capillary density.

Because foods are rarely eaten in isolation and because nutrient-based investigations underestimate the possible interactions between them, the evaluation of dietary patterns is an advanced method for dietary assessment because they represent the entire diet, not just a single nutrient. Recently, a study indicated that dietary patterns are well correlated with vascular function and affect endothelial function, arterial stiffness, and peripheral resistance in various groups of healthy individuals or patients with vascular diseases. To the best of our knowledge, there are no previous studies investigating the relationship between dietary patterns and capillary density. Therefore, the aim of the present study was to investigate the potential association between dietary patterns and capillary density in normotensive, relatively insulin-sensitive healthy subjects.

Materials and Methods

Materials and Methods are available in the online-only Supplement.

Results

In our study, men were older and had higher energy intake and BP than women; they tended to have lower functional and anatomic capillary density (Table 1).

Table 2 summarizes the loadings of the factors retained from the principal component analysis. The value of the Kaiser–Meyer–Olkin criterion indicates that the dietary variables entered in the analysis were strongly intercorrelated and that principal component analysis could be correctly used for assessing healthy or unhealthy dietary patterns. The principal component analysis indicated 6 dietary components explaining 54.4% of the total variance. These components were characterized as follows: higher consumption of spices, high-fat sauces, starch, and meat and processed meat (dietary pattern 1); higher consumption of legumes, vegetables, and fruits and fruit products and lower consumption of beverages (dietary pattern 2); higher consumption of oil, poultry, and fish and seafood (dietary pattern 3); higher consumption of nuts and salted snacks (dietary pattern 4); higher consumption of wine, beer, and cider and lower consumption of coffee and tea (dietary pattern 5); and higher consumption of high- and low-fat sweet products (dietary pattern 6). All the above dietary patterns were also confirmed through confirmatory factor analysis (data not shown). The relative contribution of each dietary variable according to factor analysis is as follows: spices 0.586, starch 0.569, sauces 0.530, meat and processed meats 0.660, legumes 0.542, vegetables 0.559, fruits and fruit products 0.527, beverages 0.413, oils 0.608, poultry 0.526, fish and seafood 0.612, nuts 0.688, snacks 0.547, wine 0.458, beer and cider 0.488, coffee and tea 0.401, low-fat sweet products 0.673, and high-fat sweet products 0.406.

Tables 3 and 4 present the associations derived from multiple linear regression analyses between functional and anatomic capillary density and dietary patterns. The results suggest that dietary patterns may have an impact on capillary density.
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Dietary Patterns and Microcirculation

anatomic capillary density (dependent variable), respectively, and the dietary patterns. Dietary pattern number 3 was positively associated with functional capillary density (β=0.15, P=0.03; model 1), and even after adjusting for several potential confounding factors in models 2 and 3, this association remained statistically significant (β=0.15 and β=0.13, respectively, all P<0.05; Table 3). The same significant association was revealed for dietary pattern 3 and anatomic capillary density (β=0.22, P=0.00 [models 1 and 2] and β=0.20, P=0.00 [model 3]; Table 4). Dietary pattern 6 was found to be inversely associated with functional capillary density in model 1 (β=−0.13, P=0.05), model 2 (β=−0.13, P=0.05), and model 3 (β=−0.14, P=0.03; Table 3). Dietary component 6 was also inversely associated with anatomic capillary density in all 3 models of multivariate analysis (β=−0.16, P=0.02 for models 1 and 2 and β=−0.17, P=0.01 for model 3, respectively; Table 4). There was no significant association between any of the derived dietary patterns and capillary recruitment (data not shown).

The logistic regression analysis summarized in Tables 5 and 6 showed that the third tertile of the dietary component 3 was significantly associated with the highest quartile of both functional and anatomic capillary density. Specifically, subjects who showed greater adherence to the dietary component 3 (highest tertile) were 2.24 ([1.12–4.47]; odds ratio [95% confidence interval]) times more likely of having elevated functional capillary density and 2.76 (1.35–5.64) times more likely of having elevated anatomic capillary density compared with subjects in the first tertile after controlling for several potential confounding factors. No similar association was found for dietary component 6.

Discussion

Few studies have investigated the relationships between foods or nutrients and microvascular function,22,31–33 but none has focused on the possible link of dietary patterns with capillary density and recruitment. In the present study, we investigated a healthy population free of hypertension and insulin

Table 2. Factor Loadings for the 6 Dietary Patterns Derived From Principal Component Analysis on Food Groups Consumed in the Study Population

<table>
<thead>
<tr>
<th>Predictors (Food Group)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spices*</td>
<td>0.741</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starch†</td>
<td>0.726</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sauces‡</td>
<td>0.672</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meat, processed meats</td>
<td>0.662</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Legumes</td>
<td></td>
<td>0.655</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vegetables</td>
<td></td>
<td>0.642</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruits and fruit products§</td>
<td></td>
<td>0.616</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beverages‖</td>
<td></td>
<td>0.428</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oils¶</td>
<td></td>
<td>0.428</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poultry</td>
<td></td>
<td>0.664</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish and seafood</td>
<td></td>
<td>0.597</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuts#</td>
<td></td>
<td></td>
<td>0.801</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snacks**</td>
<td></td>
<td></td>
<td>0.610</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wine</td>
<td></td>
<td></td>
<td></td>
<td>0.671</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beer and cider</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.630</td>
<td></td>
</tr>
<tr>
<td>Coffee and tea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.521</td>
</tr>
<tr>
<td>Low-fat sweet products†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.798</td>
</tr>
<tr>
<td>High-fat sweet products‡‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.456</td>
</tr>
<tr>
<td>Explained variance, %</td>
<td>12.73</td>
<td>9.11</td>
<td>8.96</td>
<td>8.7</td>
<td>7.95</td>
<td>6.96</td>
</tr>
</tbody>
</table>

Variable with the highest factor loading (>|0.4|) within the component.
*Added salt, pepper, ginger, and all spices in the recipes.
†Pasta, rice, and other cereals.
‡Mustard, ketchup, and high-fat sauces such as mayonnaise, carbonara, and béchamel.
§Fresh fruits, fruit juices, and dried fruits.
¶Olive oil, sunflower oil, peanut oil, rapeseed oil, and soya oil.
#Walnuts, almonds, peanuts, and hazelnuts.
**Salted snacks such as potato chips and popcorn.
††Marmelade, honey, nutella, added sugar in coffee and tea, chocolate, candies, and sorbets.
‡‡Biscuits, cookies, sweets (cakes, brownies, crepes, tarts), chocolate sweets and bars, and sweets with crème patisserie.

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A dietary pattern characterized by increased consumption of oil, poultry, and fish and seafood was positively related to both functional and anatomic capillary density after adjusting for several confounding factors. Another dietary pattern characterized by high intakes of high- and low-fat sweets was negatively associated with anatomic and functional capillary density in every multivariate model.

Dietary pattern 3 is characterized by foods containing high amounts of monounsaturated and polyunsaturated fatty acids such as olive or sunflower, rapeseed or soya oils, and fish and seafood and decreased amounts of saturated fatty acids. It is already known that long-term consumption of monounsaturated and polyunsaturated fatty acids may have beneficial effects on endothelial function and arterial compliance compared with diets high in saturated fat.24,34 Unsaturated fatty acids and especially fish oils may improve endothelial function and arterial stiffness through various mechanisms such as activation of nitric oxide synthase, protection of nitric oxide damage by decreasing oxidative stress, or prevention of the inflammatory process.35 In line with the mentioned findings in large vessel structure and function are few studies investigating the possible effects of fat in the microcirculation. In rodent experimental models, high-fat diets caused a decrease in capillary density.25,33 In human studies, 15 to 25 g of brazil nuts per day for 16 weeks improved functional microvascular parameters such as red blood cell velocity in female obese subjects,20 whereas 4 g of docosahexaenoic acid for 6 weeks improved forearm microcirculation in overweight, mildly hyperlipidemic men.21 Our findings suggest that a dietary pattern of increased consumption of vegetable oils, poultry, and fish and seafood characterized by increased consumption of monounsaturated and polyunsaturated fatty acids and reduced consumption of saturated fatty acids (in the absence of high BP and insulin resistance) might represent an association with higher capillary density, thus less functional and structural capillary rarefaction. We speculate that diet might be implicated in the development of insulin resistance and hypertension via this mechanism.

Another dietary pattern characterized by increased consumption of sweet products (both high and low in fat content) was found to be negatively associated with capillary density. Our data denote that increased consumption of refined sugar coming from sweets may have an adverse effect on microvascular function. It is already evident that high consumption of sweets is positively associated with insulin resistance36 because the short absorption time that follows the consumption of sugar

### Table 3. Associations of the Derived Dietary Patterns With Functional Capillary Density

<table>
<thead>
<tr>
<th>Components</th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
<th>Model 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>P Value</td>
<td>β</td>
<td>P Value</td>
<td>β</td>
<td>P Value</td>
</tr>
<tr>
<td>Dietary pattern 1</td>
<td>0.01</td>
<td>0.85</td>
<td>0.02</td>
<td>0.84</td>
<td>0.02</td>
<td>0.76</td>
</tr>
<tr>
<td>Dietary pattern 2</td>
<td>0.07</td>
<td>0.28</td>
<td>0.07</td>
<td>0.27</td>
<td>0.07</td>
<td>0.29</td>
</tr>
<tr>
<td>Dietary pattern 3</td>
<td>0.15</td>
<td>0.03</td>
<td>0.15</td>
<td>0.03</td>
<td>0.13</td>
<td>0.05</td>
</tr>
<tr>
<td>Dietary pattern 4</td>
<td>−0.09</td>
<td>0.17</td>
<td>−0.09</td>
<td>0.16</td>
<td>−0.08</td>
<td>0.20</td>
</tr>
<tr>
<td>Dietary pattern 5</td>
<td>0.02</td>
<td>0.78</td>
<td>0.02</td>
<td>0.78</td>
<td>0.03</td>
<td>0.72</td>
</tr>
<tr>
<td>Dietary pattern 6</td>
<td>−0.13</td>
<td>0.05</td>
<td>−0.13</td>
<td>0.05</td>
<td>−0.14</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Model 1: adjusted for age, sex, energy intake, and body mass index; model 2: model 1 + mean arterial pressure; model 3: model 2 + educational level, physical activity, smoking, and insulin resistance homeostasis model assessment; dietary pattern 1: higher consumption of spices, high-fat sauces, starch, and meat and processed meat; dietary pattern 2: higher consumption of legumes, vegetables, and fruits; dietary pattern 3: higher consumption of oil, poultry, and fish and seafood; dietary pattern 4: higher consumption of salted and unsalted nuts and salted snacks; dietary pattern 5: higher consumption of wine, beer, and cider and lower consumption of coffee and tea; dietary pattern 6: higher consumption of high- and low-fat sweets. β indicates standardized β coefficient.

### Table 4. Associations of the Derived Dietary Patterns With Anatomic Capillary Density

<table>
<thead>
<tr>
<th>Components</th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
<th>Model 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>P Value</td>
<td>β</td>
<td>P Value</td>
<td>β</td>
<td>P Value</td>
</tr>
<tr>
<td>Dietary pattern 1</td>
<td>−0.05</td>
<td>0.50</td>
<td>−0.05</td>
<td>0.50</td>
<td>−0.03</td>
<td>0.72</td>
</tr>
<tr>
<td>Dietary pattern 2</td>
<td>0.10</td>
<td>0.10</td>
<td>0.11</td>
<td>0.10</td>
<td>0.10</td>
<td>0.12</td>
</tr>
<tr>
<td>Dietary pattern 3</td>
<td>0.22</td>
<td>0.00</td>
<td>0.22</td>
<td>0.00</td>
<td>0.20</td>
<td>0.00</td>
</tr>
<tr>
<td>Dietary pattern 4</td>
<td>−0.08</td>
<td>0.22</td>
<td>−0.08</td>
<td>0.22</td>
<td>−0.07</td>
<td>0.26</td>
</tr>
<tr>
<td>Dietary pattern 5</td>
<td>0.00</td>
<td>0.97</td>
<td>0.00</td>
<td>0.97</td>
<td>−0.02</td>
<td>0.75</td>
</tr>
<tr>
<td>Dietary pattern 6</td>
<td>−0.16</td>
<td>0.02</td>
<td>−0.16</td>
<td>0.02</td>
<td>−0.17</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Model 1: adjusted for age, sex, energy intake, and body mass index; model 2: model 1 + mean arterial pressure; model 3: model 2 + educational level, physical activity, smoking, and insulin resistance homeostasis model assessment; dietary pattern 1: higher consumption of spices, high-fat sauces, starch, and meat and processed meat; dietary pattern 2: higher consumption of legumes, vegetables, and fruits; dietary pattern 3: higher consumption of oil, poultry, and fish and seafood; dietary pattern 4: higher consumption of salted and unsalted nuts and salted snacks; dietary pattern 5: higher consumption of wine, beer, and cider and lower consumption of coffee and tea; dietary pattern 6: higher consumption of high- and low-fat sweets. β indicates standardized β coefficient.
may impair blood glucose control, which may result in hyperinsulinemia and peripheral insulin resistance. In addition, a recent meta-analysis showed that there might be a significant role of microvascular function in insulin resistance and type 2 diabetes mellitus because microvascular dysfunction was associated with incidence of type 2 diabetes mellitus and impaired fasting glucose. In another relevant study, higher fasting plasma glucose was inversely associated with capillary density, indicating that abnormal alterations in microcirculation may occur in early elevations of blood glucose in healthy individuals. The outcome of the present study suggests that there might be a pathophysiological link between diet and insulin resistance mediated by early alterations in the microcirculation. However, because this is a cross-sectional study, the inverse hypothesis cannot be ruled out.

Our data showed no association between any of the derived dietary patterns and capillary recruitment. Previous studies have concluded that there is a positive association between capillary recruitment and insulin sensitivity in normotensive and normoglycemic subjects. In addition, this association between capillary recruitment and insulin sensitivity in healthy, lean individuals seems to be diminished in individuals with abnormal body weight. In our study, we included relatively insulin-sensitive volunteers. Therefore, the lack of insulin resistance in overweight/obese group in our study may explain the absence of an association between dietary patterns and capillary recruitment.

The current study has both strengths and limitations. The main strength is related to the large sample size regarding microcirculation function and inclusion of well-phenotyped men and women. In addition, exclusion of individuals with metabolic disease allowed us to examine microvascular structure and function in a straightforward way. Furthermore, the adjustment for specific confounders resulted in the extraction of more accurate results. One important limitation of the study is that our volunteers are health-conscious people, and they could be nonrepresentative of the general population. Furthermore, we cannot overlook the fact that perfusion of skin capillaries primarily serves the purpose of thermoregulation, whereas those in deeper tissues (eg, skeletal muscle) are much more closely linked to metabolic demand and oxygen supply to tissue parenchyma. There are well-described differences in pathways that control responses to ischemia/reactive hyperemia and heating. Nevertheless, the ability to perform minimally invasive in vivo mechanistic studies in human skin could have a profound influence on our understanding of how disease states adversely affect vascular function. It may be prudent to use cautious optimism when extrapolating findings from human skin to other vascular bed, and the present data should be tested in other experiments that will evaluate muscular microcirculation. In addition, we can speculate that the relationships between dietary patterns and microvascular function could be mediated by other factors that were not assessed in our study. Because

<table>
<thead>
<tr>
<th>Tertiles of dietary pattern 3 (higher consumption of oil, poultry, and fish and seafood)</th>
<th>First Tertile</th>
<th>Second Tertile OR (95% CI)</th>
<th>Third Tertile OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>1</td>
<td>2.13 (1.08–4.21)</td>
<td>2.46 (1.25–4.83)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1</td>
<td>2.16 (1.10–4.27)</td>
<td>2.44 (1.24–4.80)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1</td>
<td>2.03 (1.01–4.07)</td>
<td>2.24 (1.12–4.47)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tertiles of dietary pattern 6 (higher consumption of high- and low-fat sweets)</th>
<th>First Tertile</th>
<th>Second Tertile OR (95% CI)</th>
<th>Third Tertile OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>1</td>
<td>1.02 (0.53–1.94)</td>
<td>1.33 (0.69–2.56)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1</td>
<td>1.02 (0.54–1.94)</td>
<td>1.33 (0.69–2.56)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1</td>
<td>1.03 (0.53–2.00)</td>
<td>1.30 (0.66–2.55)</td>
</tr>
</tbody>
</table>

Model 1: adjusted for sex and body mass index; model 2: model 1+presence of hypertension; and model 3: model 2+educational level, physical activity, smoking, and homeostasis model assessment of insulin resistance. CI indicates confidence interval; and OR, odds ratio.
the study has a cross-sectional design, it is not suitable for interpreting causal relationships. Finally, although normality was not achieved for the majority of the food groups used in the principal component analysis, we think that the extracted components are robust because of the relative large sample size, the symmetrical distribution of the initial food variables, and the high level of intercorrelation between them (ie, Kaiser–Meyer–Olkin=0.7).

Conclusions

In a group of healthy men and women, adherence to a dietary pattern characterized by increased consumption of vegetable oils, poultry, and fish and seafood was positively associated with capillary density, whereas adherence to another dietary pattern characterized by increased consumption of sweets was inversely associated with both functional and anatomic capillary density. The effect of dietary behavior and food preferences in relation to several pathophysiological conditions is of great importance and should be included in future studies for identifying dietary patterns that might favorably affect early signs of a disease onset, such as microvascular structure and function.

Acknowledgments

We are indebted to the study participants.

Disclosures

None.

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acids on vascular function, endothelial progenitor cells and microparticles.


Significance

Several nutrients have been positively or negatively associated with macro- and microvascular function. Dietary patterns such as Mediterranean or Western diet have been associated with macrocirculation. To our knowledge, this is the first study investigating the possible association between dietary patterns and microcirculation. Given the established relationship of diet with the macrovascular disease and the fact that microvascular dysfunction may be a marker of insulin resistance, cardiovascular diseases, and type 2 diabetes mellitus, the aim of this study was to investigate for the first time the possible associations between dietary patterns and microcirculation. Two hundred ninety-one healthy subjects selected from the SU.VI.MAX2 cohort were assessed for anthropometric, nutritional, biochemical, and microcirculation parameters using finger skin capillaroscopy. Adherence to a dietary pattern characterized by increased consumption of vegetable oils, poultry, and fish and seafood and low consumption of sweets was associated with better microvascular function. Further prospective studies are needed to confirm the present finding.
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Materials and Methods

Materials and Methods are available in the online-only Data Supplement

Study population and protocol

The `SUpplementation en VitaminesetMinerauxAntioXydants" (SU.VI.MAX) study is a randomized double-blind, placebo-controlled, primary-prevention trial which started in 1994 in France. This epidemiologic study is designed to test the efficacy of a daily supplementation with antioxidant vitamins and minerals at nutritional doses, in reducing the main causes of premature death (cancers and cardiovascular diseases)\(^1\)-\(^2\). In 2006, about 7200 individuals have agreed to be followed-up in the SU.VI.MAX – 2 study, an additional follow up study, with the aim of exploring the associations between diet and aging in France. A specific sub-protocol was designed to assess microcirculation parameters in participants of the SU.VI.MAX – 2 cohort living in the Paris area. A total of 291 individuals without a history of type 2 diabetes (defined as fasting glucose>1.25 g/l and/or taking diabetes medication), hypertension (defined as BP<140/90mmHg and/or taking antihypertensive medication) and cancer or cardiovascular disease (CVD) events since 1994 was selected and included in the present study. Individuals were studied at the Department of Physiology and Noninvasive Investigations (Hospital Lariboisiere, Paris) between November 2006 and July 2007. The SU.VI.MAX and SU.VI.MAX – 2 studies were conducted according to the Declaration of Helsinki guidelines and were approved by the Ethics Committee for Studies with Human Subjects of Paris-Cochin Hospital (CCPPRB n° 706 and n° 2364, respectively) and the Comité National InformatiqueetLiberté (CNIL n° 334641 and n° 907094, respectively). Written informed consent was obtained from all participants.

Microvascular assessment

Capillaroscopy was carried out using a standardized validated technique elsewhere \(^3\)-\(^5\). Briefly, individuals were studied between 8:00 and 12:00 hr after an overnight fast. They were asked not to smoke from the previous evening. The capillaroscopy studies were performed in a temperature-controlled quiet room (21–24°C) after a10-min rest in the semisupine position. Patients were seated with the forearm and hand supported at heart level. The skin of the dorsum of the middle phalanx of then dominant hand was examined. Video microscopy was performed with an epi-illuminated optic fiber microscope containing a 100-W mercury vapor lamp light source and a M200 objective (Moritex, micro-ScopernanMS-500C, Tokyo, Japan); final x200 magnification was used. An approximately 3x3 mm skin area on the middle third of the phalanx was defined. Four microscopic fields (1mm\(^2\)each) were randomly chosen in this area for recording and measurements. Mean capillary density was defined as the number of capillaries per unit area of skin and was calculated as the mean of the four measurements performed in each individual. For each individual, images were acquired at baseline, to quantify the total number of continuously erythrocyte-perfused capillaries per dermal surface unit (resting or functional capillary density), and during venous congestion (by applying a cuff to the wrist and maintaining a 50-mmHg inflating pressure for 2 min), in order to obtain the maximal response of all existing capillaries and to assess structural (anatomical) capillary density. Indeed, it has been shown that this procedure maximizes visible capillary number more than reactive hyperemia\(^6\). A previous study \(^4\) has shown that intra-observer and inter-observer repeatability was 4.3 and 5.9%, respectively. Capillary recruitment (%) was defined as follows: [(capillary density during venous occlusion – resting capillary density)/resting capillary density] * 100.

Hemodynamic anthropometric and anthropometric measurements
Brachial blood pressure (BP) and heart rate (HR) were measured in the sitting position with a semi-automatic oscillometric device (Dinamap PRO 400V2; General Electric, Fairfield, Connecticut, USA) with appropriate cuff size. After 10 min of rest, two measurements in each arm were obtained at 5-min intervals. SBP and DBP were calculated as the mean of the left and right second measurements. Mean arterial pressure (MAP) was calculated as: (DBP) + (SBP-DBP)/3. Peripheral pulse pressure (PP) was defined as the difference between the values of brachial systolic and diastolic pressures. Body weight and body composition were measured using the Tanita DC-320 (Tanita Corp., Tokyo, Japan) bioelectrical impedance device based on four separate footpad electrodes mounted on the system’s base. All measurements were carried out at 50 kHz with a 0.8 mA, with individuals in indoor clothing and no shoes.

Biochemical measurements
Serum total cholesterol was measured using standard methods. Fasting plasma glucose was assayed enzymatically (hexokinase) using a multiparametric analyzer (C8000 Architect Abbott analyzer, Rungis, France). Fasting plasma insulin was measured by microparticle enzyme immunoassay (Axsym Abbott analyzer, Rungis, France). Insulin resistance was estimated by the calculation of the homeostasis model assessment-insulin resistance (HOMA-IR) index (fasting plasma insulin * fasting plasma glucose)/ 22.5.

Dietary data assessment
During the SU.VI.MAX 2 Study, subjects were invited to complete a validated food frequency questionnaire (FFQ) which assessed consumption of 250 food and beverage items during past year. Subjects were asked to report their consumption frequency the last 12 months, on the basis of how many times they ate the standard portion size proposed (photographs, typical household measurements such as spoon or standard unit such as a yogurt). Daily nutrient intakes were calculated using a composition table.

Information on smoking status (never smoked, former or current smoker), physical activity (irregular, equivalent to less than 1h of walk per day, equivalent to at least 1h of walk per day) and education (primary, secondary or university level) was collected using administered questionnaires.

Statistical analysis

Dietary pattern extraction
Data were analyzed using Statistical Package for Social Sciences software (version 13.0, 2004, SPSS Inc, Chicago, IL). Dietary patterns from 40 food groups were identified using principal components analysis (PCA). The Kaiser-Meyer-Olkin (KMO) criterion was applied and it was equal to 0.694. Derivation of optimal non-correlated components (dietary patterns) was performed using the orthogonal rotation (varimax option). Factor loadings represent the correlations of each food or food group with the dietary pattern score. Higher absolute values of factor loadings indicate that the food or food group predictor contributes most to the construction of this particular component. The dietary components (patterns) were named according to the factor loadings of those foods or food groups correlated most with the component (factor loadings > |0.4|). Dietary components derived from PCA were also confirmed using confirmatory factor analysis (CFA) with Stata statistical software release 12 (StataCorp LP 2011, TX, USA).

Descriptive and other Statistical Analyses
T-test or chi-square test was applied for the comparison of the population’s characteristics between men vs. women. Multiple linear regression analysis was used to evaluate the independent associations between functional capillary density, anatomical capillary density and capillary recruitment with dietary patterns derived from PCA which are treated as continuous variables. More specifically, 3 different models were applied: model 1: adjusted for age, gender, BMI and energy intake, model 2: model 1 plus MAP and model 3: model 2 plus smoking, educational level, physical activity, HOMA-IR. The results from the linear regression models are presented as standardized beta coefficients and the level of significance was defined as a P<0.05. Moreover, participants’ dietary pattern scores were categorized into tertiles so that for each dietary component, tertile 3 consisted of persons whose dietary intake was most adherent to that particular pattern. Based on the statistical significant associations provided by the linear regression models, logistic regression analysis was performed to evaluate the association between the tertiles of each dietary pattern and the highest quartile of microcirculation indices. The results of logistic regression models were presented as odds-ratios (OR) and 95% confidence intervals (CI).

References

I. Scatter plot of functional capillary density in both genders

II. Scatter plot of anatomical capillary density in both genders
III. Scatter plot of capillary recruitment in both genders

Error Bars show 95.0% CI of Mean