Dietetic Prevention of Arteriosclerosis

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ARTERIOSCLEROSIS AND ATHEROSCLEROSIS

Arteriosclerosis is the most common of the chronic pathologic alterations of arterial blood vessels. The term has been used since the time of Lobstein (1) to denote sclerosis of the arterial wall. Atherosclerosis is the circumscribed macroscopically visible deposit of lipoids together with the formation of fibrous tissue (atheroma), usually of the large vessels. The two terms, arteriosclerosis and atherosclerosis, cover overlapping aspects of a common pathological process of the arterial wall. They are often used interchangeably. This vascular pathology is associated with cardiovascular diseases. Available data support the view that this is a generalized process: calcified plaques in the thoracic aorta, as detected on chest X ray, are associated with a two-fold increase in risk of cardiovascular death in both men and women younger than age 65 years (2).

The pathogenesis of atherosclerosis can be divided into three stages (reviewed in ref. 3). In Stage 1, fatty streaks are visible in which lipid-filled macrophage-derived foam cells are a dominant feature. In Stage 2, the relatively reversible fatty streak is transformed into the less reversible fibrous plaque. Following the formation of an extracellular lipid core, migration and proliferation of smooth muscle cells in the thickening arterial intima, and finally continuous secretion of collagens, proteoglycans, and elastins consolidate the pathological transition. Stage 3 represents the mature fibrous plaque, with thinning of the media, and frequently a chronic inflammation in the tunica adventitia. Advanced lesions may additionally show macroscopic areas of surface ulceration, mural thrombosis, intramural or plaque hemorrhage, and calcification. The principal consequences are local stenosis and the initiation of thrombotic emboli.

The atherogenic process is thought to be triggered by several events (reviewed in ref. 3): microdomains of altered shear stress and blood flow, intimal influx and the accumulation of plasma proteins and lipoproteins including low density lipoproteins and lipoprotein-a, an augmented net intimal oxidative stress, and an autoimmune lymphocytic infiltration. In the presence of hyperlipidemia, hypertension accelerates the process of atherosclerosis. Diabetes is closely related to atherosclerosis (4). The relevance of hyperinsulinemia and insulin resistance as primary causes is reviewed next.
Arteriosclerosis and atherosclerosis are linked to the risk of stroke and coronary heart disease. In the Honolulu Heart Program, an association between atherosclerosis of the brain-supplying arteries and stroke was shown in a prospective study (5). A relation between hypertension, atherosclerosis, and stroke is well documented in humans (6). The progression of coronary atherosclerosis was shown to be linked to an increased number of cardiac deaths and hospital admissions for nonfatal myocardial infarction (7). Atherosclerosis also potentiates vasoconstrictor responses to serotonin (8,9), which explains the increased incidence of vasospasm during atherosclerosis.

Because thrombus formation plays a crucial role in acute ischemic events, hemostatic and hemorheologic factors have to be considered in atherothrombogenesis (10). Hyperinsulinemia, a key cardiovascular risk factor (see below), is related to a decreased activity of tissue and plasma plasminogen activator, and thus to reduced fibrinolysis (11,12). Fibrinogen has been identified as a cardiovascular risk factor (13,14). Hemostatic factors may be responsible for different risk patterns in coronary heart disease and stroke (15).

It is not arteriosclerosis itself but the ischemic sequelae that deserve our attention. In humans, the epidemiology of stroke and myocardial infarction and their risk factors are well studied. Arteriosclerosis is believed to be closely linked to these diseases. However, it was the epidemiology of the consequences of arteriosclerosis (cardiovascular disease) rather than an understanding of arteriosclerosis itself that first gave us a handle to change the risk. It was then only natural to pursue the question of how arteriosclerosis develops through investigating the risk factors for cardiovascular disease.

Valuable insight into cardiovascular risk factors has been gained from prospective studies like the Framingham Study. Diabetes was detected early as an independent risk for cardiovascular disease (16). Kannel and Larson (17) and Wilson and Evans (18) showed that age, gender, cigarette smoking, blood cholesterol, high-density lipoprotein (HDL) cholesterol, blood pressure, left ventricular hypertrophy, and diabetes mellitus all contribute to the development of coronary artery disease. Triglycerides have been shown to be an independent risk factor, at least in women (19). For stroke, the situation is similar. Wolf gathered age, systolic blood pressure, the need for antihypertensive treatment, diabetes mellitus, cigarette smoking, and previous cardiovascular disease into a risk profile (20). Using a similar procedure, age, cigarette smoking, low HDL, and high low-density lipoprotein cholesterol (LDL) were found to be risk factors for coronary artery disease (18). Hypertension, in particular, is a strong risk factor for cardiovascular disease and stroke. Although hypertension is linked to arteriosclerosis, this risk factor deserves separate consideration (21,22).

HYPERINSULINEMIA AND INSULIN RESISTANCE AS PROMOTERS OF ARTERIOSCLEROSIS

The relationship between hyperglycemia and cardiovascular disease was observed early on (23). Insulin plays a major role in the pathogenesis of atherosclerosis and
is now known to induce it (24–28). In the Framingham Study, diabetes doubled the risk of nonpalpable pedal pulse and bruits of the carotid and femoral artery (29). The strong correlation between raised serum insulin levels and essential hypertension was also shown early on (30,31). Noninsulin-dependent diabetes mellitus (NIDDM) predicts coronary heart disease (32) and stroke (33) in the elderly. In the 1988 Banting Lecture, Reaven reviewed all evidence for the strong association between hyperinsulinemia, insulin resistance, hypertriglyceridemia, decreased HDL cholesterol, hypertension, and risk of coronary artery disease. For this series of related variables, he proposed the term syndrome X (34). Six years later, Reaven added abnormalities of the fibrinolytic system and hyperuricemia to the list of associated symptoms (35). DeFronzo and Ferrannini argue that insulin resistance is the key factor within the disturbed metabolic system characteristic of NIDDM (36). This view is supported by observations of Lind and coworkers (37). Insulin resistance can be operatively defined as a less than expected biologic response to the hormone (38). There may be as many cellular insulin resistances as there are biologic effects of insulin. Feskens and Kromhout found in the Zutphen study that fasting insulin best characterized the insulin resistance or metabolic syndrome (39). DeFronzo and Ferrannini further argued that insulin resistance leads to different clusters of pathologic changes (NIDDM, hyperlipidemia, hypertension, and atherosclerosis) due to genetic polymorphism. Hyperinsulinemia, as a compensatory mechanism, is one consequence of insulin resistance. Reduced insulin binding correlates best with increase fasting plasma glucose (40), indicating that poor metabolic control causes deterioration of NIDDM. In the liver, insulin resistance results in the inability to suppress hepatic glucose production and, in muscle, impaired glucose uptake leads to hyperglycemia.

Obesity is another factor linked to diabetes, atherosclerosis, and gout. Hyperinsulinemia is a characteristic feature of obesity (38). In obesity, the turnover of free fatty acids (FFA) is increased and the circulating FFA may induce insulin resistance by their effect on gluconeogenesis (38). The lipolytic effect of catecholamines is markedly reduced in elderly men with the metabolic syndrome (41). The masculine type of obesity (42) or abdominal obesity (43) is frequently observed in individuals with insulin resistance. In the presence of androgens, hyperinsulinemia is related to upper body obesity (44), which is readily observed in affected patients. In the Helsinki Heart Study, dehydroepiandrosterone sulfate (DHEAS) was associated with a significantly increased risk for coronary heart disease (45). DHEAS showed a strong positive correlation with triglycerides and a negative correlation with HDL. As indicators of syndrome X, or insulin resistance, raised plasma triglycerides of more than 1.7 mmol/l, in combination with low concentrations of HDL, indicate a high cardiovascular risk (46). In syndrome X, the components blood pressure, serum lipids, and insulin levels have been identified as potential predictors of aortic stiffness (47).

Figure 1 gives a schematic representation of the indirect influence of diet and lifestyle on atherosclerosis and associated cardiovascular disease.
ALCOHOL INDUCES INSULIN RESISTANCE

 Alcohol can directly induce insulin resistance. Alcohol consumption is related to the metabolic variables associated with cardiovascular disease and NIDDM in population-based studies (48–50). Alcohol makes an important contribution to the prevalence of hypertension (51,52). In NIDDM (53,54) or the elderly (55), alcohol has been shown to impair the metabolic situation. Kromhout found in the Zutphen study (56) that the energy intake of obese men is less than that of lean men for all macronutrients investigated except alcohol. Alcohol induces hypertriglyceridemia, hypercholesterolemia, defective plasma cholesterol esterification, and decreased HDL cholesterol (57). In a prospective study in Paris, diabetic individuals had an increased risk of death from alcohol and cirrhosis similar to that from coronary heart disease (58). Ethanol impairs hepatocyte DNA synthesis and thus liver regeneration by directly acting on the insulin receptor substrate (IRS-1) protein that mediates
signal transduction (59). The result of the ethanol’s toxic effect is a reduced cell surface binding of insulin (60). In an acute experiment, Boden and coworkers demonstrated that alcohol suppresses the inhibitory actions of insulin on its own release and on lipolysis, thereby possibly producing a state of insulin resistance (61). Use of glucose by muscle tissue seems to be selectively inhibited by alcohol (62). Hypertriglyceridemia is a feature shared by diabetes mellitus and alcoholism (63,64), but alcohol has an effect on NIDDM independent of triglycerides (65). Alcohol consumption is related to an increased risk of stroke—though for reported moderate drinking a beneficial effect has been observed in white populations (66)—and in his detailed review, Camargo (66) cited relative risks increased up to four-fold depending on the reported dosage. The beneficial effect of moderate drinking was most pronounced in the Nurses Health Study (67), where age-adjusted relative risks for fatal heart disease of 0.2 were found for 1.5 to 25 g/day. This effect tended to be more pronounced among women age 50 years or older. In postmenopausal women, hyperinsulinemia is predicted by menopausal age and thus by the loss of ovarian function (68). The beneficial effect now can possibly be explained by a different pathogenic effect of alcohol: increased plasma estrogen has been found in postmenopausal women drinking alcohol (69). Estrogen use is consistently associated with a striking decrease in cardiovascular disease (70). Unfortunately, this bears the increased risk of breast cancer (71,72). There is also further indirect evidence: alcohol consumption is associated with increased bone mineral density in both men and women, which is probably due to altered estrogen levels (73). Past drinking is related to coronary heart disease mortality independent of other risk factors (21). Women have a greater susceptibility to the toxic effects of alcohol because of a lower activity of gastric alcohol dehydrogenase (74). The U-shaped risk curve may also have another explanation: it has been found that men with increased mortality who had reported abstention from alcohol had usually abstained because of chronic disease or even because of a history of alcoholism (75).

In diabetes, both hepatic glutathione and γ-glutamyl transferase (GGT) are affected (76,77). The efflux of glutathione in bile decreases whereas GGT activity increases considerably. Within the liver, glutathione is very important in the regulation of the redox state. GGT, which is commonly raised in cases with liver pathology such as alcoholic hepatitis, is believed to promote the transfer of glutathione from bile back to the liver (78). Raised GGT may be observed in diabetes alone (76,77) but, in NIDDM, the increase is also linked to diabetes-associated pathologies (79) like alcohol (80,81). GGT correlates strongly with the insulin response in a standard oral glucose tolerance test (OGTT) within the range that is considered normal (48). Serum GGT also allows the impact of dietary variables to be studied in a toxic situation: sugar and fruit intake reduce the ethanol-induced increase in the activity of the enzyme (82) as does NIDDM (83).

OVERNUTRITION AS A CAUSE OF NIDDM

During wars, the death rate from diabetes tends to fall due to food shortage (84). This is especially true for women over age 45 years. After World War II, it was
already noted that the change in mortality over time correlated best with fat consumption. Recent studies indicate that saturated fat intake, in particular, is related to body mass index, abdomen-to-hip ratio, and insulin level (85). The individual susceptibility to overnutrition has been studied in monozygotic twins (86). A daily consumption of 1000 kcal over the individual baseline energy intake over 100 days resulted in an increased insulin and glucose response to a standard OGTT. The correlation coefficient for concordance between twins was 0.71 for fasting insulin after overfeeding.

THE RELATION OF INSULIN RESISTANCE TO SERUM LIPIDS

Lipid synthesis is positively influenced by insulin (reviewed in ref. 87). Insulin resistance increases FFA concentrations because the release cannot be suppressed. Chronic hyperinsulinemia is strongly associated with an overproduction of very low density lipoproteins (VLDL). VLDL are the major vehicle for plasma triglyceride in the postabsorptive state (88). Most FFA are probably derived from lipolysis of adipose tissue triglycerides through the action of hormone-sensitive lipases (89). As reviewed by Sparks and Sparks (87), hypertriglyceridemia and increased fatty acids in plasma may be important for the development of insulin resistance. This raises the question of causality. At least, there is evidence that hypertriglyceridemia and low HDL are independent aspects of the insulin-resistance syndrome (90), different from central obesity, and the insulin/glucose factor. When large quantities of VLDL are produced by the liver, HDL decreases by transfer of its core cholesteryl ester into the large mass of circulating VLDL in exchange for triglyceride (88).

SERUM LIPIDS AND CARDIOVASCULAR RISK

In a combined view on the findings from long-term follow-up of Chicago cohort studies, Stamler and coworkers (21) reported that baseline serum cholesterol levels were positively associated with coronary heart disease and cardiovascular disease. Favorable serum cholesterol levels were in the range of 160–180 mg/dl. Pharmacological interventions in the U.S. Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT, cholestyramine) (91), in the Helsinki Heart Study (gemfibrozil) (92), and in the Scandinavian Simvastatin Survival Study (4S) (93) showed a reduced cumulative mortality in the treatment group. In a later analysis, it was discovered that the effect of gemfibrozil was predicted by serum triglycerides (94). Most of the treatment effect was confined to a subgroup with triglycerides > 2.3 mmol/l and LDL/HDL > 5. This, in fact, is the pattern of insulin resistance. In both studies, total and LDL cholesterol were lowered by the pharmacological agent, and in the Helsinki Heart Study, HDL was increased.

Within the substantially lower values of serum lipids in rural China (compared to Western values), no association between cholesterol and cardiovascular disease exists, whereas triglycerides are correlated with coronary heart disease and hypertension (95).
Mitchell argued in his review (96) that a reduction in cholesterol has only a modest effect on risk reduction compared to cessation of smoking. Hebert and coauthors recently concluded from their overview of randomized trials that there is no benefit of cholesterol lowering on the risk of stroke (97). This is in line with results from a meta-analysis by Atkins et al. (98). Many efforts have been made to demonstrate a critical role for cholesterol in the development of atherosclerosis, but with regard to triglycerides, Anne Nafziger concluded from her literature survey in a recent review that to date, no intervention trial has been conducted with the primary aim of reducing ischemic heart disease by lowering serum triglyceride concentrations (99).

**NUTRITION AND CARDIOVASCULAR RISK**

The habitual intake of carbohydrates and pastries is positively associated with the incidence of glucose intolerance (100). The odds ratio for pastries is approximately three-fold, but in relation to other food components like fat and protein, carbohydrates are negatively associated with hyperinsulinemia (83). *Trans* isomers of fatty acids, formed by the partial hydrogenation of vegetable oils to produce margarine and vegetable shortening (margarine, cookies, cake, and white bread), contribute to the risk of coronary heart disease (101). In the Zutphen Elderly study, the intake of saturated and monounsaturated fat was associated with indices of hyperinsulinemia (100). Polyunsaturated fat, carbohydrates, and dietary fiber were negatively correlated to hyperinsulinemia. From a population-based case-control study, Jamrozik reported that consumption of fish more than twice per month and the use of reduced-fat or skimmed milk reduced the risk of first time strokes, whereas consumption of meat more than four times weekly increased the risk (102).

Legumes significantly reduce the risk of glucose intolerance to about 0.4 (100). In the Framingham study, fruit and vegetable intake was found to be associated with a reduced rate of stroke events (103). This effect was independent of body mass index, cigarette smoking, glucose intolerance, physical activity, blood pressure, serum cholesterol, and intake of energy, ethanol, and fat. From the comparison of data from the National Food Survey with statistical reports by the Registrar General in Britain, Acheson and Williams (104) found strong negative correlations between mortality for all cerebrovascular diseases and fresh fruit and vegetable consumption, whereas for potatoes, the correlations were positive but nonsignificant. In a large survey carried out in rural China, Wenxun and coworkers found significant negative associations between the incidence of coronary heart disease, stroke, and hypertension, and the intake of rice, legumes, rapeseed oil, steamed bread, and green vegetables (95). Wheat flour and salt showed positive associations. Analysis of red blood cell fatty acids revealed favorable associations for oleate, gadoleate, and monounsaturated fatty acids. For arachidonate, total n-6, and polyunsaturated fatty acids, unfavorable (i.e., positive) associations were reported. The authors could not explain the unexpected finding regarding polyunsaturated fatty acids. In the Nurses Health Study, vegetable fat, potassium, calcium, and magnesium intakes were significantly
associated with a low risk for NIDDM after controlling for body mass index, previous weight change, and alcohol intake (105).

Drinking boiled unfiltered coffee may be associated with coronary heart disease (106). This effect is probably due to significant increases in serum cholesterol and triglycerides by the diterpenes kahweol and cafestol contained in coffee oil (107,108). Filtered coffee was not found to be hazardous (109). Green tea, on the other hand, was associated with a pronounced dose-dependent decline in observed stroke incidence after a 4-year follow-up in Japanese women over age 40 years (110).

**DIETARY INTERVENTION**

Dietary recommendations are indeed able to reduce not only laboratory measurements but cardiovascular morbidity and mortality. When Singh and coworkers (111) randomly assigned either a diet B (in which meat, eggs, hydrogenated oils, butter, and clarified butter were replaced with vegetarian meat substitutes and soy bean, sunflower, and ground nut oils) or a diet A (in which in addition to diet B patients were also advised to eat fruit, vegetables, pulses, nuts, and fish with a goal of at least 400 g/day of fruits and vegetables) to their patients after myocardial infarction, they observed a greater decline in cholesterol under diet B, but the incidence of cardiac events was significantly lower in group A than in group B (25% vs. 41%) after 1 year of follow-up. In the Lifestyle Heart trial, Ornish and collaborators found that a low fat vegetarian diet, stopping smoking, stress management training, and moderate exercise were able to bring about regression of even severe atherosclerosis after only 1 year (112). The multifactorial approach of the Stanford Coronary Risk Intervention Project (SCRIP; low fat, low cholesterol diet, exercise, weight loss, smoking cessation, and medication to alter lipoprotein profiles) reduced the risk of new coronary lesion formation over 4 years (113).

Fruits and vegetables contain numerous components which could explain the beneficial effect. High potassium alone markedly reduces the atherosclerotic cholesterol ester deposition (114). Increased daily potassium intake is associated with a significant reduction in the risk of stroke-associated mortality (115). For vitamins C and E, a clear and indisputable association has not yet been found (116,117). From the point of view of the “antioxidant hypothesis of arteriosclerosis,” it is argued that the overall antioxidant status rather than a single micronutrient should be optimized (118). Although the evidence remains slight (119,120), Hodis and coworkers recently presented encouraging data on vitamin E (121). The intake of dietary fiber is associated with improved indices of hyperinsulinemia (83). Dietary fiber and pectin reduce serum cholesterol (122,123). Citrus pectin was found to inhibit atherosclerosis independently of serum cholesterol levels in an animal model (124). Modest amounts of oat extracts in the diet improve glucose tolerance (125).

In hyperlipidemic subjects with NIDDM, fish oil supplementation instead of corn oil significantly lower plasma VLDL and triglycerides (126). A daily intake of 4 g fish oil concentrate (containing about 3.4 g eicosapentaenoic and docosahexaenoic
Acid) reduced serum triglyceride concentration by 19% on average (127). This is in line with cross-sectional data from the Tromsø study (128). The consumption of at least one to two fish meals per week is associated with a reduction in the risk of coronary heart disease (129,130). Overall, available data suggest that fish oil may have a role in attenuating the development of atherosclerosis (131).

A strict diet improves all parameters associated with NIDDM within a very short time. We regularly give dietary treatment to overweight patients with cardiovascular risk factors. The following example illustrates the effect of such a diet. Stroke patients received a 1000 kcal diet rich in salads and vegetables with enough protein but little animal fat (132). Alcoholic beverages were not permitted. Smoking is banned. Weight, blood pressure, fasting plasma glucose, total cholesterol, HDL, LDL, and triglycerides were recorded on admission (baseline) and the end of the period of hospital diet (discharge). The mean duration of treatment was 34 days. Every patient had a reduction in body weight. All risk factors improved, indicating that insulin resistance had also improved markedly (Table 1). For details, see Altmann et al. (132).

General knowledge about the origin of arteriosclerosis and the possibilities of intervention is not only important to the health professional: Näslund and coworkers (133) found that belief in treatment efficacy and perceived health threat rather than health knowledge predicted participation in a nonpharmacological intervention trial. Early intervention is necessary because hyperinsulinemia, with its relation with obesity, raised blood pressure, triglycerides, and hyperglycemia, can already be found in obese children and young adults (134–136).

## LIFESTYLE AND ATHEROSCLEROTIC RISK

Apart from diet, lifestyle has an important impact on the risk of arteriosclerosis (Table 2). In the Indian Diet Heart study, the effect of exercise on the decrease in

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Baseline Mean</th>
<th>Baseline SD</th>
<th>After Diet Mean</th>
<th>After Diet SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>75.1</td>
<td>10.9</td>
<td>69.4</td>
<td>10.1</td>
</tr>
<tr>
<td>Body mass index</td>
<td>26.7</td>
<td>3.0</td>
<td>24.7</td>
<td>2.8</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>167.5</td>
<td>22.7</td>
<td>127.8</td>
<td>12.2</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>88.3</td>
<td>10.7</td>
<td>74.8</td>
<td>9.1</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/l)</td>
<td>6.67</td>
<td>2.61</td>
<td>5.03</td>
<td>1.30</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.13</td>
<td>1.63</td>
<td>3.64</td>
<td>1.11</td>
</tr>
<tr>
<td>Fasting plasma triglycerides (mmol/l)</td>
<td>2.53</td>
<td>0.49</td>
<td>1.96</td>
<td>0.41</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>0.90</td>
<td>0.27</td>
<td>1.07</td>
<td>0.21</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>3.60</td>
<td>0.99</td>
<td>3.06</td>
<td>0.86</td>
</tr>
<tr>
<td>LDL/HDL ratio</td>
<td>4.27</td>
<td>1.49</td>
<td>2.96</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Body mass index = weight (kg)/height$^2$ (m$^2$).
TABLE 2. Adverse and beneficial influences of lifestyle and diet reported for risk of cardiovascular disease, atherosclerosis, NIDDM

<table>
<thead>
<tr>
<th>Adverse Lifestyle Effect</th>
<th>Beneficial Lifestyle Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol (21,48–67,79–81)</td>
<td>Increase of carbohydrates in relation to fat and protein (83)</td>
</tr>
<tr>
<td>Overnutrition (84,86)</td>
<td>Fish &gt;2 times/month, fish oil (102,111,126–131)</td>
</tr>
<tr>
<td>Saturated fat (85,100)</td>
<td>Legumes, fruit, vegetables (95,100,103,104,111,112,132)</td>
</tr>
<tr>
<td>Monounsaturated fat (100)</td>
<td>Rice, steamed bread (95)</td>
</tr>
<tr>
<td>Wheat flour (95)</td>
<td>Vegetable fat (105)</td>
</tr>
<tr>
<td>Habitant intake of carbohydrates and pastries (100)</td>
<td>Rapeseed oil (95)</td>
</tr>
<tr>
<td>Trans isomers of fatty acids (101)</td>
<td>Potassium (105,114,115)</td>
</tr>
<tr>
<td>Smoking (21,142–147)</td>
<td>Calcium, magnesium (105)</td>
</tr>
<tr>
<td>Boiled unfiltered coffee (106)</td>
<td>Green tea (110)</td>
</tr>
<tr>
<td></td>
<td>Vitamin E (121)</td>
</tr>
<tr>
<td></td>
<td>Physical exercise (137–141)</td>
</tr>
<tr>
<td></td>
<td>Dietary fiber and pectins (122–125)</td>
</tr>
</tbody>
</table>

Reference numbers in parentheses.

risk factors was additive (137). With regard to stroke, a protective effect at medium and high levels of exercise was found among men in the Framingham study (138). Exercise training further reduces fasting plasma insulin under a hypocaloric diet (139). Master athletes have enhanced insulin sensitivity compared to sedentary individuals of the same age and body fat (140). Strength training also improves insulin sensitivity (141). Smoking is an established risk factor (21,142–144). Chronic cigarette smokers were found to be insulin resistant, hyperinsulinemic, and dyslipidemic independent of other variables (145–147). The importance of regular physical exercise and avoidance of obesity to control hyperinsulinemia has also been stressed in a detailed review by Stout (148).

SUMMARY

Arteriosclerosis and atherosclerosis are strongly related to cardiovascular disease, coronary heart disease, and stroke. Hypertension, hypercholesterolemia, hypertriglyceridemia, raised LDL cholesterol, decreased HDL cholesterol, hyperinsulinemia, insulin resistance, abnormalities of the fibrinolytic system, and hyperuricemia are associated with cardiovascular disease. All available data point in one direction: the high risk of cardiovascular disease; most laboratory abnormalities are caused by insulin resistance or NIDDM. Overnutrition, alcohol, cigarette smoking, saturated fatty acids and animal fat, and consumption of meat more than four times a week contribute to the development of insulin resistance, and hence to arteriosclerosis and cardiovascular disease. Fruit and vegetables, polyunsaturated fatty acids, rice, legumes, vegetable fat, potassium, calcium, magnesium, fish and fish oil, dietary fiber, and pectins as part of
the diet both improve NIDDM and the risk of cardiovascular disease. Physical training in any form improves insulin resistance. This view has big advantages: we have a single common denominator to explain the otherwise complicated effects of diet and their various interactions. We now understand why we can alter the risk of cardiovascular disease dramatically by changing the diet, although atherosclerosis changes only modestly. All available knowledge about the relation between diet and NIDDM can be used for the prevention of arteriosclerosis. The impact of a particular diet now can easily be studied by simply performing a standard OGTT with insulin measurement and monitoring associated laboratory values like triglycerides and HDL. Patients at risk can be identified with sensitive and specific measurements. The effect of dietary efforts can be judged on an individual basis.

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DISCUSSION

Dr. Guesry: Did you try to modulate this very severe diet (1) according to the degree of obesity, to gender or to the degree of activity?

Dr. Kornhuber: The study was to see what happens on this particular diet. We could not control every individual all day, so we do not know what patients actually ate. This is the diet they got from the hospital canteen.

Dr. Wolf: I find that very interesting. Was there another group that was treated just with hospital admission, or with diet alone? When someone is admitted to hospital, their blood pressure comes down and various other things probably happen in the hospital that aren't necessarily related to alcohol.

Dr. Kornhuber: We did not have a control group and I have no data on the follow-up of these patients, which would have been interesting. The only thing I can say is that this type of diet is effective in reducing known risk factors for cardiovascular pathology. We don't really know how these variables measured within the study are interrelated—what the pathophysiology actually is—but there seems to be a common denominator, which is the improved insulin resistance situation. I can only show a correlation indicating this kind of pathophysiology.

Dr. Guesry: When we speak of alcohol, sometimes we speak of different things. When we speak of red wine, for example, as you mentioned earlier, we speak of flavonoids and maybe also salicylic acid and other things, but not only alcohol. I do not think the experiment to compare 20 g of pure alcohol and the equivalent given as wine or another type of beverage has been done.

Dr. Feller: I have a question about the elevated \( \gamma \)-glutamyl transpeptidase. It is known that \( \gamma \)-GTP is extremely sensitive and very nonspecific, and a number of factors can increase it such as alcohol, for instance, and a number of drugs. Practically the only use we have for \( \gamma \)-GTP is to monitor abstinence to alcohol. So when you talk of liver disease, do you have any indices besides \( \gamma \)-GTP to point toward liver disease?

Dr. Kornhuber: \( \gamma \)-Glutamyl transferase is known to be a very sensitive index of alcohol pathology and this is why it is recommended for the follow-up of alcoholics; there is no question about that. We do know that in most cases of moderately elevated values, alcohol is the major reason. So for pure statistics or epidemiology, it seems to be evident that in the majority of cases alcohol is the reason for an increase in this enzyme. I do not have data to prove that in our subjects the enzyme comes from the liver. It is known that you can measure raised levels of the enzyme in stroke (2), and this is why it would not have made any sense to include this in the stroke sample, but from the knowledge we have and from my general experience as a clinician, there is no doubt that alcohol is one of the major reasons for the increase of this enzyme.

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