Dietary proteins and atherosclerosis

Roger Darioli

More than 100 years ago the hypothesis «protein» of the pathogenesis of atherosclerosis and its association with cardiovascular disease was put forward on the basis of animal experiments; however, it has so far never been verified in humans. This theory was soon replaced by the «lipid hypothesis», which was confirmed in humans as of 1994. Epidemiological ecological studies in the 1960s showed significant associations between dietary animal protein and mortality from cardiovascular disease. However, animal protein intake was also significantly correlated with saturated fatty acid and cholesterol intake. In the last decades two prospective cohort studies demonstrated a decreased cardiovascular risk in women during high versus low protein intake when adjusting for other dietary factors (e.g. saturated fats) and other cardiovascular risk factors. A direct cholesterol lowering effect of proteins has not been shown. Despite earlier research indicating that soy protein has cardioprotective effects as compared to other proteins, these observations have not been confirmed by randomised placebo-controlled trials. However, experts recommend the consumption of foods rich in plant proteins as alternatives to meat and dairy products rich in saturated fat and containing cholesterol. There are no scientific arguments to increase the daily protein intake to more than 20% of total energy intake as recommended by the guidelines, in order to improve cardiovascular health.

Introduction

In 1909, the pathologist Ignatowski was the first to demonstrate the link between diet and atherosclerosis (1). He observed that rabbits fed eggs, meat and milk developed atherosclerosis of the aortic tree, which he attributed to the protein content of these foods. In 1913, Anitschkov Chalatov produced atherosclerosis in rabbits with a diet based on vegetable oil containing up to 1% cholesterol. They also show that if one removes cholesterol from the diet, there is a regression of initial lesions (2).

In subsequent years, some authors observed the onset of atherosclerosis in rabbits when they consumed a casein diet rich in lean beef, but not with a diet rich in soy protein (3, 4). In general, cholesterol levels rose in animals fed with animal protein, and vice versa they dropped under the influence of plant proteins. Moreover, in most animal studies, there was a direct correlation between the amount of animal protein consumed and degree of hypercholesterolemia, and conversely, between vegetable protein intake and hypocholesterolaemia. These findings have strengthened the theory of R. Virchow dating from 1856, for whom atherosclerosis was «a modified form of chronic inflammation induced by lipids». It should be noted that the injuries produced in these animals were not exactly the same as those observed in humans. Moreover, experimental data revealed that while a number of animal species (rabbits, chikkens, pigeons) were prone to atherosclerosis induced by the addition of dietary cholesterol to protein, other species were resistant, such as dog, guinea pig, rat or monkey (3). For these reasons animal testing is mainly focused on lipid disorders induced by diet as atherogenic factors, rather than the by proteins themselves.

In humans, the scientific interest on the relationship between nutrition and atherosclerosis started only in the 1960s, alongside with attempts to prevent ischemic heart disease as a major public health issue in industrialized countries. Early studies in humans were conducted by De Langen in the island of Java in 1916. They advanced the idea that the inhabitants of the island «have little atherosclerosis because their traditional diet contains little cholesterol and fat. But when they adop-

Abstract **Proteinzufuhr und Atherosklerose**

Vor über 100 Jahren wurde auf der Basis von Tierversuchen die Hypothese «Protein-induzierte Atherosklerose» und ihr Einfluss auf kardiovaskuläre Erkrankungen formuliert. Beim Menschen wurde diese Hypothese jedoch nie bestätigt. Bald wurde sie durch die «Lipidhypothese» abgelöst, die beim Menschen 1994 bestätigt wurde. Epidemiologische Studien aus den Sechzigerjahren zeigten einen signifikanten Zusammenhang zwischen tierischen Nahrungsproteinen und der Mortalität aufgrund kardiovaskulärer Erkrankungen. Allerdings war die Zufuhr von tierischen Nahrungsproteinen signifikant mit der Zufuhr gesättigter Fettsäuren und von Cholesterin verknüpft. Zwei in den letzten beiden Jahrzehnten durchgeführte prospektive Kohortenstudien konnten nach sorgfältiger statistischer Adjustierung für kardiovaskuläre Risikofaktoren und Ernährungsfaktoren (z.B. gesättigte Fettsäuren) ein vermindertes Risiko für koronare Herzkrankheit beim Vergleich einer hohen gegenüber einer geringen Proteinzufuhr bei Frauen belegen. Eine direkte cholesterinsenkende Wirkung von Proteinen konnte nicht nachgewiesen werden.

Trotz vielversprechender erster Ergebnisse zu kardioprotektiven Effekten von Sojaproteinen gegenüber anderen Proteinen konnten randomisierte, plazebokontrollierte Studien in den letzten Jahren diesen Vorteil pflanzlicher Proteine nicht bestätigen. Allerdings sind sich Experten einig, dass die Zufuhr von Lebensmitteln, die reich an pflanzlichen Proteinen sind, als Alternative zu Fleisch- und Milchprodukten, die reich an gesättigten Fettsäuren und Cholesterin sind, gefördert werden müsse.

Basierend auf dem heutigen Kenntnisstand gibt es keine wissenschaftlichen Argumente, dass für eine Verbesserung der Herzgesundheit eine höhere Proteinzufuhr als maximal 20 Prozent der gesamten Energiezufuhr empfohlen werden sollte. ***CR***

ted a European-style diet, their cholesterol rose» (5).

Mjassnikow in Leningrad in 1925 observed that subjects with aortic and coronary atherosclerosis often have high cholesterol levels which can be reduced with a diet rich in vegetables (6). It also appeared that man belongs to a species not susceptible to hypercholesterolemia induced by pure dietary proteins (3). This is probably why the protein hypothesis of atherosclerosis stated by Ignatowski was soon replaced by the lipid hypothesis.

This review therefore aims to summarize current knowledge on the role of dietary proteins in the development of atherosclerosis in humans.

Atherosclerotic diseases and their determinants

Atherosclerosis is defined as a chronic inflammatory disease of the arterial wall, characterized by the formation of atherosclerotic plaques that are focused and scattered throughout the arteries of medium and large calibre. Inflammation induces the formation, progression and rupture of plaques unpredictably. This results in instant formation of a thrombus at the site of rupture which may lead to arterial occlusion. This is the origin of major clinical complications such as acute coronary syndrome, angina pectoris, cerebral ischemic attack or peripheral arterial disease (7, 8).

The disease is silent for decades until the onset of the first clinical manifestations which are usually sudden. To date, it is well established that among the major risk factors for atherosclerosis are dyslipidaemia, hypertension, smoking, diabetes and obesity.

Apart from smoking, each of these risk factors is influenced by eating habits and can even be regarded as a marker, although imperfect, for certain eating habits. So far, we have no accurate epidemiological data on the early development of atherosclerosis; this gap is mainly due to the silent nature of the disease and the lack of imaging techniques applicable to large-scale, non-invasive investigations without radiation hazard and at acceptable costs. Thus, there are indirect criteria of atherosclerosis which are taken into account in studies, namely the cardiovascular morbidity and/or mortality.

Dietary protein and human atherosclerotic cardiovascular disease

Although few in number, some epidemiological studies performed since the 1950s in humans have examined the association between diet and cardiovascular disease. Overall, these studies showed a strong correlation between the consumption of animal proteins and cardiovascular mortality. Whereas animal protein consumption was clearly correlated with coronary heart disease (CAD [8]; r = 0.78), the reverse was true for the consumption of vegetable proteins (r = -0.40) (9).

However, these observations were flawed by various confounding factors such as socioeconomic status, lifestyle factors or lipid composition of the diet. In this regard, the consumption of animal proteins was also significantly associated with intake of saturated fat and cholesterol, factors known to be hypercholesterolaemic and atherogenic (10). Moreover, in countries with low protein intake, there was conversely a higher fibre intake.

Considering the cohort studies cited by F. Hu et al. (11) totalling 33 289 men followed for 5–20 years, only one of them showed a positive association between protein intake and risk of CAD, but it had not been adjusted for fat intake.

More recently, the «Nurses' Health Study» is of considerable interest because it used more refined methodology and had a large size. There were 80 082 healthy women included; they were aged 34–59 years, with no history of cardiovascular disease, cancer or hypercholesterolemia (11). The 14-year follow-up was conducted by sending a questionnaire relating to risk factors and the occurrence of diseases every two years, and by sending every four years a standardized food questionnaire. The results were adjusted for age, cardio-

Table 1: Relative risks (RR) of ischemic heart disease and 95% CIs according to quintiles of protein intake (11)

	Quintiles of total protein intake	
	1	5
Total protein intake:		
Median (% of energy)	14.7	24
Number of cases	211	169
Multivariate Relative Risk (RR) for CAD	1	0.72 (0.57, 0.91)
RR with additional adjustment for specific fats	1	0.74 (0.59, 0.95)
Animal protein intake:		
Median (% of energy)	11.6	20.6
Number of cases	195	172
Multivariate Relative Risk (RR) for CAD	1	0.86 (0.68, 1.09)
Further adjustment for vegetable protein	1	0.84 (0.65, 1.07)

vascular risk factors, total daily energy intake, and the specific type of fat consumed *(Table 1)*.

Unlike other studies mentioned above, this study showed an inverse association between protein intake and coronary risk. Comparing the first and fifth quintile of protein intake (14.7% vs. 24% of AETJ) shows a significant reduction in relative risk of CAD (multivariate adjusted RR = 0.72, 95% CI = 0.57–0.91). Interestingly, subgroup analysis revealed no significant further reduction of coronary risk in the high protein intake group when total fat intake was low compared to high (low fat intake RR of CAD: 0.76, 95% CI = 0.55–1.06) versus high fat intake RR of CAD: 0.72, 95% CI = 0.52–1.01). The same was true for subjects in the high protein in-take quintile regarding saturated fat in-take – high or low saturated fat intake had no additional effect on CAD.

The beneficial effect of higher protein intake was observed in both, animal and plant-derived proteins. In the opinion of the authors, this study has the same limitations as earlier ecological studies and it is possible that the observed inverse relation between protein intake and cardiovascular risk was due to unmeasured factors, such as the socio-economic status. Other limitations inherent to this type of study include possible errors of actual food intake based on self-assessment questionnaires. However, It should support the conclusion of authors claiming that their «data do not support the hypothesis of an increased coronary risk in case of high protein», contingent upon the fact that intake did not exceed 20% of total energy intake as recommended by experts (12).

In 2005, the «Iowa Women's Health Study» reported a decreased risk of CAD mortality among 29 017 women aged 55–69 years followed prospectively for 15 years during iso-energetic replacement, of carbohydrates with animal and vegetable proteins (13). By comparing the fifth and the first quintile of total protein intake (22.0% vs. 14.1% of total energy intake, respectively), and after adjusting for several factors (age, cardiovascular risk factors, hormonal status, socioeconomic status, dietary cholesterol), there was a nonsignificant reduction of coronary risk of RR of CAD mortality 16% (95% CI = 0.39–1.79). When more animal proteins were consumed 12% RR (95% CI= 0.39–1.86) was observed, in comparison to a significant RR of 51% (95% CI 0.49–0.99) with more plant protein intake.

In order to strengthen the conclusion of these two prospective studies, the «Cholesterol Lowering Atherosclerosis Study» should also be quoted (14). This randomized double-blind trial aimed to demonstrate the evolution of angiographic coronary atherosclerosis in 162 patients who were undergoing surgery for coronary revascularization surgery and who were treated with lipid lowering drugs. Dietary habits were assessed by a dietary recall questionnaire of 24 hours. Multivariate logistic regression analysis showed a protective effect defined by the lack of appearance of new coronary lesions when dietary proteins were increased. The combination of lean meats, and low fat dairy products was also protective (OR = 0.82, 95% CI = 0.69–0.96). Other protein sources were not associated with development of new lesions. These results are consistent and of great interest, but they deserve to be validated in other studies with expanded collectives, using imaging techniques of atherosclerosis more accurately than angiography and tools to assess dietary intake more suitable than the 24-h dietary recall. Also to be noted is the fact that the average protein intake in the protected group was 17.4% of total energy intake, and thus below the 20% upper limit currently recommended.

Therefore, on the basis of existing data, it is reasonable to conclude that the hypothesis of atherosclerosis induced by dietary protein has not been demonstrated. However, the evidence for the opposite is still insufficient to recommend a high protein diet for prevention of atherosclerosis.

Protein, atherosclerosis and stroke

A few ecological and cohort studies suggest that the rate of stroke mortality is higher in Asian regions such as Japan and China than in Europe or North America. This could result in eating habits characterized in Asia by a very low intake of fat and animal protein and high consumption of salt, a constellation that may be associated with higher rates of stroke, particularly hemorrhagic stroke (15). The gradual reduction of stroke observed in Japan since the early 60s has been attributed to improved treatment of hypertension and changes in eating habits. Increased consumption of animal products including meat, eggs, dairy products associated with elevated blood cholesterol has been suggested as potentially beneficial to the risk of hemorrhagic stroke, not only in Japan but also China (16–17). However, it is known that vegetarians who consume little protein and animal fat have an increased risk of stroke (18).

The U.S. «Nurses' Health Study» (19) involving the same cohort as that cited in (11) also shows an inverse association, but non-significant, between the risk of hemorrhagic stroke and animal protein con-

sumption (RR = 0.47, 95% CI = 0.2–1.11), vegetable protein intake (RR = 0.81, 95% CI = 0.4–1.63) or with the consumption of saturated fats.

In the prospective «Hiroshima/Nagasaki Life Span Study» 40 349 subjects followed between 1980 and 1996 using validated questionnaires, including 24-h dietary recalls, C. Sauvaget et al. (20) identified an inverse association between high vs. small consumption of animal products (beef, pork, chicken, dairy products, eggs, fish) and the risk of stroke mortality (RR = 0.88, 95% CI = 0.77–1.0) by hemorrhagic stroke (RR = 0.76, CI 95% = 0.58–0.99) and ischemic stroke, (RR = 0.89, 95% CI = 0.73–1.09), again suggesting a beneficial effect of dietary proteins. However, this analysis was adjusted for all confounding factors, but without the fat content of proteins. A significant positive correlation between total fat (coefficient β = regression -0.20, $p < 0.05$) and an inverse correlation between animal protein (coefficient β = regression -0.19, $p < 0.05$) and ischaemic stroke was also observed in the «Honolulu Heart Program» (21). These results are reversed in the recent publication of the Health Professionals Follow-up Study, another prospective cohort study totalling 43 960 men initially aged 40–75 years and followed from 1986 to 2004 using validated questionnaires (22). After 18 years of follow-up, no significant association was found between the risk of total stroke (RR = 1.14, 95% CI = 0.94–1.43) and consumption of proteins. Unlike other studies, this analysis includes a complete adjustment for confounding factors, including the type of fats.

The summary of the association between risk of stroke and levels of protein intake observed in these several cohort studies are illustrated in *Figure 1*.

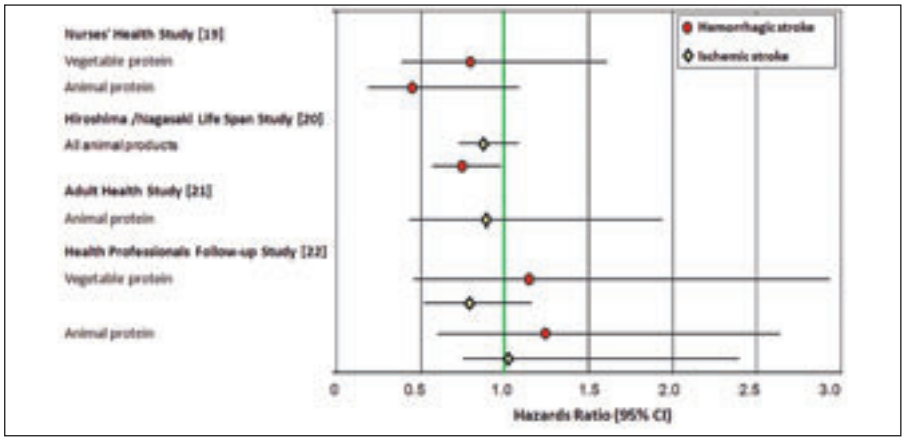

Figure 1: Relative hazards and 95% confidence intervals of stroke according to consumption level and types of proteins.

Table 2: **Risk of clinical events associated with the consumption of red meat, processed meat and meat products**

	Red meat	Processed meat products	Total meat products
Coronary heart disease (CAD)			
No. & type of studies	2 CS*+ 1 CCS	4 CS + 1 CCS	5
No. of subjects	56 312	614 063	658 696
No. of cases with CAD	766	21 308	24 437
RR (CI 95%)	1.00 (0.81–1.23)	1.42 (1.07–1.89)	1.27 (0.94–1.72)
Stroke			
No. & type of studies	2 CS	2 CS	2 CS
No. of subjects	108 898	108 898	115 500
No. of cases with stroke	1600	1434	601
RR (CI 95%)	1.17 (0.40–3.43)	1.14 (0.94–1.39)	1.24 (1.08–1.43)
Diabetes			
No. & type of studies	5 CS	7 CS	3 CS
No. of subjects	298 982	336 291	142 851
No. of cases with diabetes	7349	8888	5904
RR (CI 95%)	1.16 (0.92–1.46)	1.19 (1.07–1.27)	1.12 (1.05–1.19)

*CS = cohort study; CCS = case control study

*RR= Relative Risk for 100 g/d red meat, for 50 g/d of processed meat and for 10 g/d of meat products; statistical significance: $p < 0.05$ when the 95% CI does not cross the value 1.00

Meta-analysis of R. Micha et al. (25)

Protein foods of animal origin and cardiovascular diseases

In recent years, American and European recommendations for the prevention of cardiovascular disease advocated moderate consumption of red meat, sausages and processed meat products (PMP) (12, 23). These recommendations stem primarily from changes induced by these products on the blood lipid profile and atherogenic potential, as well as the consequences of excessive calories and fat intake.

Definition and classification of meat

According to Wikipedia Vulgaris-medical (24), meat is defined as the flesh, in terms of food, from mammals and birds. We distinguish:

a) red meat from beef, pork, veal, sheep and horse
b) white meat from poultry and rabbits.
c) dark meat from game

However, in their important review of the literature on the effects of red meat and PMPs, Micha et al. (25) used a different classification:

a) red meat = beef, pork and lamb,
b) processed meat products = ham, hot dogs, salami, sausages, meats.

Red meat and processed meat products

To this day, there are no randomized controlled trials to assess the impact of meat products on human health, given the dif-

ficulties of feasibility, methodology (e.g. double-blind, compliance, long duration and / or very large group to detect a number of events for statistical significance) or costs. In fact, despite their limitations already mentioned, prospective cohort studies, and to a lesser extent case-control studies provide today the best level of evidence. Rather than review the various epidemiological studies, only the results of the systematic review and meta-analysis by Micha et al. are presented here (25). Of the 1598 abstracts identified by computerized systematic research, only 17 prospective cohort studies and 3 case-control studies were selected because they contained the information necessary to judge the effect of red meat consumption on CAD risk, on stroke and diabetes. These 20 studies totalling 1 218 380 persons there were 23 389 subjects with CAD, 2280 with stroke and 10 797 with type 2 diabetes. The analysis of results took into account the necessary adjustments and assigned a quality score to each of the studies identified, the score of between 3 and 5/5 (mean = 3.8). As shown in *Table 2*, the consumption of PMP over 50 g/day was associated with a significantly increased risk of CAD (RR = 1.42, 95% CI = 1.07–1.89) and diabetes (RR = 1.19, 95% CI = 1.07–1.27). There was also a significantly increased risk of ischaemic stroke (RR = 1.24, 95% CI = 1.08–1.43) correlated to the total consumption of meat products, this increase was not significant for consumption of red meat or PMP. However, there was no evidence of an increased risk of CAD (RR = 1.0, 95% CI =

Table 3: **Comparison of nutrient composition between plant and animal proteins [26]**

Foodstuff	Energy Kcal	CHO g	Prot. g	Fat g	Fats sat. %	Fats, MUFA %	Fats, PUFA %	P/S ratio	Choles-terol mg	Fibre g
Red meat										
Beef: steak	138	0.0	22.3	5.4	46	7	48	1.0	63	0
Beef: filet	105	0.0	21.9	2.0	50	6	44	0.9	35	0
Pork chop	180	0.0	20.6	10.9	41	11	47	1.1	77	0
Pork tenderloin	128	0.0	22.3	4.4	38	10	51	1.3	60	0
Lamb chop	213	0.0	18.3	15.6	46	6	49	1.1	66	0
Lamb leg	173	0.0	19.6	10.5	49	9	42	0.9	84	0
Average	***156***	***0.0***	***20.8***	***8.1***	***45.1***	***8.0***	***46.9***	***1.1***	***64.2***	***0***
White meat										
Chicken thigh with skin	184	0.0	17.6	12.6	32	17	51	1.6	80	0
Veal: roast	124	0.0	20.2	20.2	42	15	42	1.0	81	0
Veal: cutlet	103	0.0	22.2	22.2	36	18	45	1.3	65	0
Average	137	0.0	20.0	18.3	36.9	16.9	46.3	1.3	75.3	0.0
Fish										
Cod, raw	79	0.0	18.1	0.7	20	20	60	3.0	43	0
Pike, raw	81	0.0	18.4	0.8	33	33	33	1.0	63	0
Salmon, smoked	171	0.3	22.5	8.9	21	35	44	2.1	70	0
Average	***110***	***0.0***	***19.7***	***3.5***	***24.9***	***29.3***	***45.8***	***2.0***	***58.7***	***0.0***
Sausage and processed meat products										
Saveloy	259	1.3	13.1	22.7	41	51	8	0.2	37	0.0
Pies	292	0.9	13.1	26.0	39	48	12	0.3	111	0.1
Roast pork sausage	253	0.4	15.7	21.0	38	50	12	0.3	53	0.1
Salami	424	0.3	25.2	35.2	39	50	11	0.3	61	0.0
Ham	248	0.4	29.4	14.3	26	66	8	0.3	70	0.0
Average	***295***	***0.7***	***19.3***	***23.8***	***36.8***	***52.9***	***10.3***	***0.3***	***66.4***	***0.0***
Plant proteins										
Soy milk	32	0.8	2.9	1.9	17	22	61	3.7	0	0.0
Tofu	78	0.7	8.1	4.8	3	28	69	27.0	0	1.2
Soybeans, dry beans	347	15.8	35.9	18.6	15	23	61	4.0	0	15.7
Soy flour, whole	453	23.5	36.8	23.5	15	24	61	3.9	0	13.3
Soy bruised	194	0.6	45.2	1.2	18	18	64	3.5	0	10.7
Chickpeas, dry	306	44.3	19.0	5.9	14	29	57	4.0	0	15.5
Dry bean, white	261	41.4	21.1	1.2	33	11	56	1.7	0	18.1
Lens, dry	308	50.4	24.0	1.2	25	25	50	2.0	0	11.2
Average	***247***	***22.2***	***29.0***	***5.0***	***17.6***	***22.6***	***59.8***	***6.2***	***0.0***	***10.7***

0.81–1.23), or reducing the risk of stroke (RR = 1.16, 95% CI = 0.92–1.46), linked to the consumption of red meat (> 100 g/d), which corresponds to 20% of total energy intake calculated for a diet of 2000 Kcal.
These data strongly suggest that a high consumption of meat products (> 100 g/d) or PMP (> 50 g/d) increases the risk of cardiovascular disease and of diabetes. Although not significant, it also appears that consumption of red meat (> 100 g/d) tends to adversely affect the risk of stroke and diabetes.

White meat

As it stands, the data are conflicting on lean meats whose characteristics are essential to their content and fat composition, illustrated in *Table 3* (15, 26).

Fish

In 1975, Bang and Dyerberg (27) showed a lower incidence of cardiovascular mortality in Eskimos living in Greenland compared to those living in Denmark, mortality rates being inversely correlated to the consumption of fish and marine mammals. Since then, most studies have demonstrated a cardioprotective effect of fish, specifically of its omega-3 polyunsaturated fatty acids. The latest meta-analysis of 13 cohort studies totalling 222 364 persons followed for an average of 11.8 years showed an inverse correlation between fish consumption and CAD (28). Compared to those consuming less than 1x/month, 5x/week consumption of fish reduced the risk by 38% (RR = 0.62, 95% CI = 0.46–0.82). For fish consumption 1x/wk vs. 1x/week the difference was less, but there was still a significant decrease in risk of 15% (RR = 0.85, 95% CI = 0.76–0.96). This study demonstrated that each 20 g/d of fish consumption was associated with a 7% reduction in coronary mortality. The same authors also conducted a meta-analysis of 8 cohort studies looking at stroke incidence; it demonstrated a reduced risk of ischaemic stroke only in people who consumed fish 1x/week compared to those eating less than 1x/week (RR = 0.68, CI 95% = 0.52–0.88). Consumption of 5x/week vs. less than 1x per week was associated with a further decrease of risk of ischaemic stroke (RR = 0.65, 95% CI = 0.46–0.93). The effect on hemorrhagic stroke was not significant (RR = 0.80, 95% CI = 0.44–1.47). Given these data, it appears that the minimum consumption of fish could resulting in reduced risk of cardiovascular mortality was at least 1x fish consumption per week. Current recommendations advocating 2x/week seem adequate, especially if one takes also into account ecological considerations, especially the fact that overfishing can cause important alterations in the structure and dynamics of a large marine ecosystem.
Plant proteins and cardiovascular disease
Many animal studies have shown a reduction of serum cholesterol during ingestion of plant proteins, especially for soybeans compared to animal proteins. In humans, epidemiological studies showed that in Asian countries soy consumption was much higher than in Western countries, associated with a lower incidence of ischemic cardiovascular diseases (30).
When animal and vegetable proteins are compared *(Table 3)*, plant proteins contain more carbohydrates, less total fat, more polyunsaturated fats, no cholesterol and more fibre.
Plant proteins with high quality because of their amino acid contents are found in legumes, whole grains and products imitating meat such as tofu and seitan. However, the main scientific interest during the past 30 years has focussed on soy protein and its influence on cardiovascular disease.

Soy proteins

Soy is a climbing plant of the Fabaceae family, close to the bean, widely cultivated for its seed oil which makes it the major edible oil consumed in the world. It contains a large amount of protein, carbohydrates, lipids, vitamins A and B, potassium, calcium, magnesium, zinc and iron. In addition, its proteins contain all essential amino acids. Furthermore, soy contains isoflavones or phytoestrogens with weak estrogenic activity.
Reports on anti-atherosclerotic effects of diets containing soy have been published repeatedly, but there is no clear evidence of such an effect in humans (31–33).
Nevertheless, in 1999 the U.S. Food and Drug Administration approved the labelling of foods containing soy protein as a cardiovascular protective. This was based on the fact that 25 g/d of soy would lower serum total and LDL cholesterol levels (32). In 2000, a scientific committee of the American Heart Association (AHA) concluded that «it is prudent to recommend the inclusion of foods containing soy protein in a diet low in saturated fat and cholesterol» (34). A new position of a scientific committee of the AHA published in 2006 on the basis of a rigorous assessment of new scientific knowledge on soy protein and isoflavone compound (35) based on a meta-analysis of 22 randomized controlled trials (RCTs) stated that ingestion of showed only a minor decrease of LDL-cholesterol (approx. 3%) obtained by the addition of extracts of soy protein plus isoflavones (25–135 g/d) compared to casein, milk protein or wheat, and a mixture of animal proteins.
These authors concluded: Previous studies demonstrating a clinically favorable effect of soy protein compared to other proteins has not been confirmed. Nevertheless, many soy products should be beneficial to cardiovascular and general health because of their high content of polyunsaturated fatty acids, fibre, vitamins, minerals and their low content in saturated fatty acids. In the recommendations of the AHA that followed, therefore, experts summarized their opinion as follows: A large amount of soy protein covering more than half the daily protein intake may lower blood levels of LDL-cholesterol by a few percent when they replace dairy protein or a mixture of animal proteins. Eating foods rich in soy protein may indirectly reduce cardiovascular risk if it replaces animal protein and dairy products containing saturated fats and cholesterol (25).
Recently, a new meta-analysis of 30 studies that included 2913 subjects RCT indicates that consumption of 25/d or more of soy protein is with a significant mean decrease of 6% of LDL-cholesterol ($p < 0.001$) and a nonsignificant increase in HDL-cholesterol. This meta-analysis demonstrated no dose response relations-

hip between soya protein intake in the range of 15–40 g and standard difference in blood LDL-cholesterol or HDL-cholesterol levels (36).

Conclusion

Initiated more than 100 years ago on the basis of animal experiments conducted in rabbits, the hypothesis «protein» of atherosclerosis and its association with cardiovascular disease has not been proven in humans. However, the studies conducted so far show that for the prevention of cardiovascular diseases, proteins have little beneficial effects per se, provided that their lipid content is taken into account.

Corresponding Author:
Prof. Roger Darioli
Centre Hospitalier Vaudois
Rue Dr César Roux 19
1005 Lausanne
E-Mail: roger.darioli@hospvd.ch

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