Genes, diet and public health

Udo Seedorf · Helmut Schulte · Gerd Assmann

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Abstract Common chronic diseases such as coronary heart disease (CHD), diabetes, cancer, hypertension and obesity are significantly influenced by dietary and other behavioural habits. There is increasing scientific evidence that genetic factors (SNPs), conferring either protection or risk, also contribute importantly to the incidence of these diseases. SNPs are of particular interest because they influence disease in a complex but largely unknown manner by interacting with environmental and lifestyle factors. Because genetic factors also affect a person's response to dietary habits, SNPs likely will be useful in helping to determine and understand why individuals differ in their response to diets. Therefore, the discovery of SNPs will likely revolutionize not only the diagnosis of disease but also the practice of preventative medicine. Other developments, like new biomarkers and noninvasive imaging techniques, might turn out to be highly sensitive and specific in order to identify patients at risk, especially in cases with asymptomatic coronary heart disease. Thus, further knowledge of such new risk factors and their interaction with nutrition, has the potential to provide a more precise and personalized approach to prevent and treat chronic diseases like coronary artery disease, myocardial infarction and stroke.

Keywords Myocardial infarction · Epidemiology · Genetics · Disease prevention · Biomarkers · Dietary recommendations

Diet and risk factors for coronary heart disease

In the European Union, roughly every 5th man and every 5th woman is affected by cardiovascular disease (CVD) resulting in a mean death toll of almost 4,500 per day. Despite considerable progress with respect to primary, secondary and tertiary prevention of coronary heart disease (CHD), stroke and related end points over the past 10 years, CVD prevention will remain the major public health challenge of the future. The clear benefits which came with the wide-spread introduction of effective cholesterol lowering drugs (i.e. statins) and an increasing awareness concerning a healthy lifestyle are counteracted by the steeply rising incidence rate of overweight and obesity currently observed in the US and Europe. If we are not successful in turning back this development, the consequences will soon be observed as rising incidence rates of Diabetes, hypertension, hyperlipidemia and consequently CVD. Thus, improved means of disease prevention by introducing better individualized risk algorithms, new drugs and diet recommendations and improved patient compliance will be crucial for public health in the future.

The ranking of independent risk factors for myocardial infarction (MI) in men according to the PROCAM study, a large-scale prospective epidemiological study performed in our laboratory in Munster, Germany, is shown in Table 1. The study was initiated in 1979 and involves almost 50,000 participants. With the exception of smoking, age and family history, all other risk factors depend considerably on dietary habits. Especially relevant in this respect are

U. Seedorf (✉) · H. Schulte · G. Assmann
Leibniz Institute for Arteriosclerosis Research,
University of Munster, 49149 Munster, Germany
e-mail: u.seedorf@uke.uni-hamburg.de

G. Assmann
Institute of Clinical Chemistry and Laboratory Medicine,
Central Laboratory, University of Munster,
49149 Munster, Germany

Table 1 Ranking of risk factors for MI in men according to the PROCAM risk algorithm

Rank	Factor	R
1	Age	0.2418
2	LDL cholesterol	0.1935
3	Smoking	0.1552
4	HDL cholesterol	-0.1003
5	Systolic blood pressure	0.0975
6	Diabetes	0.0781
7	Family history	0.0477
8	Tryglicerides	0.0426

overweight and obesity caused primarily by over-ingestion of high caloric nutrients with a high content of saturated fat. The study showed that total cholesterol and LDL cholesterol is significantly lower in lean than in overweight or obese men, particularly at younger ages, whereas this relationship is less prominent in pre-menopausal women. Conversely, HDL cholesterol levels are considerably higher in lean than in overweight or obese men and women, particularly in middle aged and older probands (Fig. 1). Blood pressure is strongly correlated with BMI in

both sexes (Fig. 2) which is also true for triglycerides (Fig. 3). The relative hazard to develop Diabetes is 4 to 15 times higher for overweight and obese men and women than for lean individuals. Thus, overweight and obesity as measured by BMI affect multiple risk factors in an adverse manner. In summary, the study data show that despite the fact that BMI is not an independent risk factor, it nevertheless is a very prominent risk factor for CHD in men (see Fig. 4) and also in women [1].

Many dietary intervention studies support the concept that restricting saturated fat and cholesterol and increasing the intake of essential fatty acids, especially n-3 fatty acids, can reduce CHD risk. However, the variability in dietary effects on LDL cholesterol is large and relates in part to APOE and APOA4 genotypes (for review see [2]).

What is the optimal diet?

Based on various dietary consensus recommendations, we know fairly well how an optimal diet should look like (see for example <http://www.chd-taskforce.de>), but compliance with dietary recommendations remains a major problem. Most experts agree that positive health effects result from a

Fig. 1 Shown are HDL cholesterol levels of men according to age and BMI. Lean men tended to have higher HDL cholesterol levels than overweight men in the same age group. The relationship is particularly evident for men aged 46–65. The evaluation is based on 16,288 men. Similar data are available for women

Fig. 2 Shown are diastolic blood pressures of men according to age and BMI. Lean men tended to have lower values than overweight men in the same age group. The evaluation is based on 16,288 men. Similar data are available for systolic blood pressure and women

Fig. 3 Shown are triglyceride levels of men according to age and BMI. Lean men tended to have lower triglyceride levels than overweight men in the same age group. The evaluation is based on 16,288 men. Similar data are available for women

Fig. 4 Shown is the relationship between BMI and CHD risk among middle-aged men in PROCAM. Lean men tended to be at low CHD risk, while overweight men tended to be at high risk. However, this distinction is not very clear-cut. For example, 7.8% of overweight men were in the lowest quintile of risk while 14% of lean men were in the highest quintile of risk. The evaluation is based on 325 incidences in 4,818 men aged 35–65 years

diet which is high in fruit, vegetables, legumes, and whole grains, and which includes fish, nuts and low-fat dairy products. Such a diet need not be restricted in total fat as long as there is not an excess of calories, and should emphasize predominantly vegetable oils that are low in saturated fats and partially-hydrogenated oils. The traditional Mediterranean diet, whose principal source of fat is olive oil, encompasses these dietary characteristics. The Mediterranean diet contains significant amounts of antioxidants, like vitamins E, C, and carotenoids as well as various polyphenols. These compounds are present in vegetables, fruit, nuts, whole grains, legumes, virgin olive oil, and wine and are absorbed to some extent, which could play an important role in the prevention of cardiovascular disease, cancer, and premature aging.

Dietary recommendations aimed at preventing atherosclerosis include substantial reduction of saturated fat and substitution of saturated fats by unsaturated fats, preferably monounsaturated fats and oils. In addition, high consumption of fish, vegetables, fruit and whole grains is

recommended. Possible mechanisms by which dietary factors decrease the risk of coronary heart disease include improvement of the plasma lipid profile (lowering LDL cholesterol and triglycerides while increasing or maintaining HDL cholesterol), anti-oxidative and anti-inflammatory effects, anticoagulation, improved endothelial function and insulin sensitivity, reduction in plasma homocysteine concentrations and decreased ventricular irritability. With respect to Diabetes, the principal message should be: “control weight, increase physical activity, and reduce sedentary behaviour”. Moreover, carbohydrate diets that are based on minimally processed cereal grains, vegetables, and fruit that are also high in fibre can be used to improve blood glucose levels and the lipid profile. The same beneficial effects are usually obtained with diets emphasizing vegetable oils that are predominantly mono-unsaturated, along with the food listed above. Almost identical recommendations are valid in order to prevent obesity: “balancing energy intake and energy expenditure through a healthy diet and regular physical activity” should be taken as the primary advice. Obesity clearly is a common and increasing health problem in almost all developed and developing countries. Since obesity affects multiple risk factors in an adverse manner (see above), its prevention is emerging to be the main public health challenge to further reduce the incidence of coronary heart disease, stroke and vascular dementia.

There is also substantial and consistent evidence that diets rich in vegetables, fruit, and whole grains reduce the risk of cancer, especially of the colon. Whereas total fat intake does not seem to be related, saturated fat may increase risk. Conversely, dietary olive oil, marine oils, antioxidants and phytosterols are likely associated with reduced risk.

Gene environment interaction

Results obtained from twin studies support that MI and death from CHD is influenced considerably by genetic

factors in women and men, particularly at younger ages. According to the Swedish Twin Registry study, the relative hazard of death from CHD when one's twin died of CHD before the age of 55 years, as compared with the hazard when one's twin did not die before 55, was 8.1 for monozygotic twins and 3.8 for dizygotic twins. Similarly among women, the relative hazard was 15.0 for monozygotic twins and 2.6 for dizygotic twins (cutoff: death from CHD before the age of 65 years) [3]. These relative hazards were little influenced by other risk factors for CHD. With completion of the human genome sequence, it is expected that a comprehensive catalogue will soon be available of all important genetic susceptibility variants for CHD and related atherosclerotic cardiovascular disease (CVD) [4]. Although a positive family history of CHD is present in the majority of cases of premature CHD, currently, the family history of CHD has not played a central role in risk prediction and disease prevention by clinicians and public health professionals [5]. In cases of familial hypercholesterolemia and other rare forms of premature CVD, CHD often segregates in a mendelian fashion. However, for most cases of premature CHD, the mode of genetic transmission in families is more complex. According to current views, both CVD and CHD are caused genetically by complex interactions among multiple genes as well as environmental and lifestyle factors which are not fully understood at present. Thus, the family history of CHD has not been incorporated along with other established risk factors such as hyperlipidemia, hypertension, and cigarette smoking in some of the widely applied multivariable risk algorithms [6], whereas the PROCAM risk algorithms does incorporate family history information [7]. Besides twin studies, considerable efforts have been taken to localise and subsequently identify genes affecting lipid levels, CVD, CHD or MI by means of genetic linkage studies and by combined linkage/association analysis. Meanwhile, genome-scans are available for diverse populations and endpoints. For example, the PROCARDIS study provided a broad linkage peak on chromosome 17 for the MI phenotype and tentative loci at chromosomes 3 and 11 with the CAD phenotype (Farrall et al. submitted). Conversely, Samani et al. [8] observed suggestive linkage, for both CAD and MI, in a region on chromosome 2. Other genomewide linkage scans, mainly of affected sib pairs, have mapped CAD and/or MI loci to chromosomes 1, 2, 3, 12, 13, 14, 16, and X. [9–15]. However, only in one case (chromosome 13) has the putative underlying gene been identified [14]. In a recent meta-analysis, suggestive linkage was reported for HDL-C levels on 8p23.1 and 12q21.2 and for ApoAI on 1q21.3. For LDL-C and ApoB, linkage regions frequently coincided (2p24.1, 2q32.1, 19p13.2 and 19q13.31). Six of the putative QTLs replicated previous findings and fine mapping provided three maximum LOD

scores mapped within 1 cM of major candidate genes, namely APOB, LDLR and APOE. APOB haplotypes explained 27% of the QTL effect observed for LDL-C on 2p24.1 [16]. Taken together, the linkage data point to multiple candidate genes at diverse and partly overlapping chromosomal locations involved in CVD, CHD, MI, and/or related QTLs. Given the genetic complexity implied by these results, the positional cloning of underlying genes will represent a particular challenge. Thus, new strategies are warranted to further pinpoint genes that are involved in the genetic predisposition of CVD and the related endpoints and QTLs. Promising approaches currently taken by our group and others are genomewide case-control association studies employing marker sets of high density (i.e. the 500 K MendelArray marker sets developed by Affymetrix). In the early phase of our study, more than 20,000 SNPs located in more than 1,000 genes were found to be significantly associated with the MI phenotype. The challenge of the future will be to evaluate the enormous amount of data in a meaningful manner and to validate the results of early phase studies in replication studies. With respect to the impact of nutrition, it seems likely that individuals with a high genetic risk may be treated first line by lifestyle modification, including adjusting their dietary habits.

Biomarkers

Biomarkers are compounds that may serve as markers for certain biological conditions an organism is exposed to (i.e. disease or disease risk). They may be proteins, peptides, hormones or low molecular weight compounds that differ in concentration or other properties depending on the conditions an organism is exposed to. Biomarkers may be particularly important in current and future epidemiology because they often have the potential to integrate the information of a person's genes with the environment. Examples for biomarkers that function as emerging risk factors for CVD are Lp(a), C-reactive protein (CRP) and asymmetric dimethylarginine (ADMA). Our laboratory has recently studied the role of certain plant sterols (i.e. sitosterol) for CHD risk. High dietary intake of sitosterol reduces LDL cholesterol and thus a diet rich in sitosterol may be considered beneficial. On the other hand, individuals who are carriers for mutations in two genes called ABCG5 and ABCG8 (encoding ABC transporters which are involved in intestinal absorption of plant sterols) develop sitosterolemia, a rare inborn error of metabolism associated with elevated sitosterol concentrations and very high risk for CHD and MI. In order to investigate whether plasma sitosterol is associated with risk or protection for CHD in the general population, we performed a nested

Fig. 5 Shown are univariate hazard ratios for major coronary events (defined as fatal or nonfatal MI or sudden cardiac death) according to sitosterol plasma levels in comparison with well-established risk factors. Study participants who had sitosterol levels higher than 5.25 µmol/l had a hazard ratio of 1.82-fold relative to participants with sitosterol levels below 5.25 µmol/l. Further details of the study design are described in the text

prospective case-control study based on PROCAM. A cohort of 160 men and 17 women who suffered a major coronary event (fatal or non-fatal MI or sudden coronary death) was matched with 354 controls. Cases also matched for sex, age, date of investigation and smoking status. Sitosterol concentrations were measured in stored serum samples using gas chromatography mass spectrometry. As shown in Fig. 5, univariate hazard analysis showed that sitosterol plasma level is a risk factor associated with a similar relative hazard ratio as other well established risk factors for the development of major coronary events, like hypertension, Diabetes, the metabolic syndrome and family history. Since sitosterol plasma concentrations correlate with plasma cholesterol levels, we also evaluated the data according to sitosterol/cholesterol ratios. As shown in Fig. 6, high sitosterol/cholesterol ratios were associated with a much higher hazard ratio for the development of a major coronary event (15.96 vs. 4.28) than low ratios in patients with a global risk of >20% in 10 years follow-up according to the PROCAM risk algorithm. Conversely, no difference was observed in patients with low or intermediate global risk. Thus, sitosterol fulfils the criteria that must be met for a useful biomarker for CHD risk assessment in patients with very high global risk for CHD. On the other hand, it must be emphasized that these data do not allow concluding that dietary intake of food that is supplemented with sitosterol or related plant sterols (as is the case for certain margarine brands and dairy products which are available on the food market today) are associated with increased risk for CHD.

Fig. 6 Shown are hazard ratios for major coronary events according to sitosterol/cholesterol ratios and global risk according to the PROCAM risk algorithm. Study participants with a very high global risk (>20% within 10 years follow-up) and sitosterol/cholesterol ratios >0.00097 had a significantly higher hazard ratio than those with ratios <0.00097. Note that this difference was not present in the probands with lower global risk. Further details of the study design are described in the text

Outlook

It may be expected that new risk factors emerging from research on biomarkers and SNPs will provide more precise and personalized approaches to prevent and treat chronic diseases like coronary artery disease, myocardial infarction and stroke. Also very promising are new non-invasive imaging techniques, like MRI and MS-CT, which do allow already today a very detailed description of the vascular system in situ. Nutrigenomics has the promising potential to provide new insights into the interaction of emerging risk factors with nutrition and thus may provide important contributions to better understand the causal relationships existing between diet and disease.

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