

## **A Diet for Familial Transthyretin Amyloidosis: Strategies for Delaying the Onset and Progression of the Disease**

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The transthyretin type of familial amyloidosis, produced by mutations in the transthyretin (TTR) gene, is an autosomal dominant disease that first manifests itself in adults. The more than 90 so-called amyloidogenic mutations lead to destabilization of TTR that is formed in the liver and secreted into the bloodstream and eventually results in extracellular deposits of mostly insoluble amyloid on nerves and muscle fibers of the heart and blood vessels. The resulting familial amyloid polyneuropathy (FAP), which mostly affects the nervous system, is characterized by a slow loss of function of peripheral sensory and motor nerves that develops from the feet and hands and progresses towards the trunk. The autonomic nervous system is also compromised with effects seen in cardiovascular, digestive, and urogenital systems. Deposits in the arterial vessel wall and in the heart muscle are the primary characteristics of familial amyloid cardiomyopathy (FAC) and influence heart and circulatory functions. Hybrid forms of FAP and FAC as well as variations involving the eye (vitreous opacity) and the brain (leptomeningeal form) have also been reported. The heart is almost without exception involved with increasing age. In addition, the kidneys are often involved and kidney transplantation is occasionally required. Left untreated, the disease will result in death within 8 – 15 years after appearance of the first symptoms. In the TTR-type of senile systemic amyloidosis (SSA), it is primarily the heart and vasculature that are affected. There are no TTR mutations in this condition. In SSA, heart transplantation is the only treatment, but this is usually ruled out due to the advanced age of the patients.

The only therapy for FAP is liver transplantation at an early phase of the disease, which can stop its progression though seldom leads to improvement of the affected functions. In cases where the heart is considerably affected, additional heart transplantation prior to liver transplantation is often necessary. The survival rate after liver transplantation for older FAP patients and also for younger patients with mutations affecting the heart, is lower than for liver transplantation performed for other reasons because cardiovascular complications after transplantation often arise as an additional cause of death. Therefore, liver transplantation cannot be viewed as the optimal treatment of the disease. There are interesting laboratory data pertaining to a pharmacological treatment, but no definitive conclusions have yet been drawn. Results from a study of patients are not expected for several years at the earliest. Independent of surgical and pharmacological treatment, it is reasonable to consider whether onset or progression of the disease can be blocked or delayed through preventative measures.

Several phenomena have been observed for FAP that indicate that non-genetic factors have an important influence on the age of manifestation and progression of the illness:

- Interestingly, the disease is seen very rarely in children, and in patients of German ancestry it rarely begins before the age of 40. It is of note that FAP with the TTR-V30M mutation in Portugal begins between the ages of 25 and 35 and rarely later. In northern Sweden, the disease starts about 25 years later. In Germany, the TTR-V30M mutation occurs about as frequently as all other TTR mutations together. In some families, the disease begins early (age 30 – 40). In most cases, as in northern Sweden, there is a much later appearance of the illness (> 55 years of age). In northern Sweden, only 2 – 10 % of the adult carriers of the mutation TTR-V30M contract the illness. Also in Germany, there is frequently no evidence of the disease in the parents of affected individuals. In Portugal, the risk of contraction for carriers of this mutation is much higher. Taken together, it can be concluded that besides genetic predisposition, age plays a considerable role. We cannot help growing old, but by influencing our way of life we can influence the condition of the organs on whose functioning our quality of life and our lifespan depend. The indications are that the onset and progression of FAP can be influenced through lifestyle.

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- With illness beginning above the age of 40, there is almost without exception in Germany involvement of the heart and vascular systems. With some mutations, it is only the cardiovascular system that is affected.
- In northern Sweden, one member of a pair of identical twins at risk for FAP had liver transplantation approximately 16 years after his brother. The twin with later onset is convinced that in his case the disease has been induced by a coronary by-pass operation. Both twins live in the same region. The only difference that has been described is that the healthy twin has taken cod-liver oil daily for many years (Holmgren et al 1997, Ole Suhr 2006, personal communication).
- There are observations indicating that stress and chronic inflammation lead to an earlier onset of the disease and a more rapid progression
- The differences accounting for a different rate of illness between Portugal and northern Sweden/Germany have not yet been determined. The extremely high consumption of salt in Portugal might be a meaningful difference compared with the low consumption in northern Sweden. Elevated salt concentrations lead to low grade metabolic acidosis and a thickening of the interstitial space of cardiac muscle, vessel walls, and probably also other tissues and hamper the transfer of substances between cells and vessels. Results of laboratory studies suggest that an acidosis of the interstitial space favors the denaturing of TTR-V30M.

It must be pointed out that although no environmental factors that protect gene carriers from onset of the disease or slow its progression have ( Note: see line above: no environmental factors...) yet been clearly delineated, it can be assumed that such factors exist. From the observations mentioned above, it can be concluded that continual stress, chronic inflammatory processes, geographic factors, eating habits, and age-dependent changes in the interstitial space of nerves, heart, and vessels could all contribute. It is meaningful to speculate whether gene carriers or those who are already ill might benefit from measures that could not do any harm and might correct the factors already mentioned:

1. From middle age and beyond, people drink too little water. The disease process occurs in the interstitial space, which is very sensitive to a fluid deficit. The deposition of amyloid is partially a problem of solubility. Daily intake of 30 ml water/kg body weight (for athletic activity, even more) ensures a good flushing of the interstitial space. If tap water is not satisfactory or has a disagreeable taste, mineral water with a low sodium content and without added gas will do, or a water filter can be connected to the faucet (e. g. from MULTIPURE: [www.multipure.com](http://www.multipure.com)).
2. From animal and clinical studies, we know that increased consumption of salt results in an enlargement of the interstitial space of cardiac muscle, kidneys, and probably other tissues. Recently, it has been shown that – independent of dietary net acid load – increased consumption of salt is associated with low grade metabolic acidosis (Frassetto LA et al., 2006). Under these circumstances exchange of metabolites between cells and blood vessels can be reduced, and acidosis of the interstitial space can favor the denaturation of amyloidogenic TTR and its folding into amyloid. Reduction of daily salt intake and a diet designed to avoid acidosis would be good preventative measures. According to Eaton and Konner (1985), humans are genetically programmed for an intake of about 20 mmoles sodium per 2000 kcal energy consumption. In most of the population, this value is surpassed with an intake of 6-12 g salt, leading to an additional sodium excretion in 24-hour urine of 100 – 200 mmoles per day (in some regions of Portugal up to 400 mmoles). In northern Sweden, the norm (for 95 % of the population) for the daily excretion is lower (50 – 150 mmoles). No salt-dependent hypertension has been reported for a daily intake of 3 g (50 mmoles) or less, and existing hypertension is reduced under these conditions (Wardener and MacGregor (2002)). The Societies of Nutrition recommend a daily consumption of no more than 5 g (86 mmoles) of salt. If a causal relationship exists between the incidence of illness within the group of gene carriers and dietary salt intake, an attempt should be made to reduce salt intake to arrive at a lower sodium excretion, such as that for northern Sweden, in the lower norm area (50 – 100 mmoles/day). Measurement of sodium excretion in 24-hour urine is a simple way of determining salt intake. The salt content of various foods is shown in the following table:

<b>Protein and salt content of foods</b>			
(Approximate values for 100 g foodstuff according to GU Nutrition Table.)			
<b>Food</b>	<b>Protein in g</b>	<b>Sodium in mg (mmoles)</b>	<b>Salt in g</b>
Cottage cheese	8 – 14	30 – 40 (1.3 – 1.7)	0.08 – 0.10
Milk/Yogurt	3.3	49 (2.1)	0.1
Cream cheese/Feta/Mozzarella/Robeola	5 – 19	350 – 1300 (15– 57)	0.9 – 3.3
Processed cheese/Soft and hard cheeses/ Cheese food	12 –38	300 – 1520 (13 – 66)	0.8 – 3.8
Meats (unprocessed)	16 – 24	40 – 118 (1.7 – 5.1)	0.1 –0.3
Sausages/Hotdogs/Ham	10 – 29	400 – 2080 (17 – 90)	1 – 5.3
Fish (unprocessed)	8 – 22	< 120 (< 5.2)	< 0.3
Fish products	13 – 79	291 – 4070 (13 – 177)	0.7 – 10
Grains (unprocessed)	7 – 15	< 10 (< 0.4)	< 0.025
Bread	6.2 – 10	370 – 590 (16 – 26)	0.9 – 1.5

3. It is a safe assumption that an average person in Germany gets sufficient vitamins, antioxidants, trace elements, and plant products in his diet. However, the recommended daily allowances put out by National Societies of Nutrition can only be achieved if individual eating habits approach those recommendations. The significant digestive disturbances associated with FAP are enough to hinder an optimal dietary intake in accordance with these recommendations. In this case, basic nutrition for optimal metabolism can be maintained through the use of food additives in tablet form. It must be kept in mind, however, that the consumption of adequate quantities of fruit and vegetables is a better solution. The application of both measures together would not be detrimental and might actually be beneficial as a compensation for the dietary deficits accompanying the digestion problems associated with FAP.
4. Interviews with FAP patients about the time when their illness began have frequently revealed that it was a period of significant, chronic stress. There may be a causal relationship between the observation that with a statistically similar genetic ratio many more men than women have FAP, and the large amount of evidence that women can deal with stress better than men, which is possibly why they live longer. Stress is what disturbs our equilibrium. The individual ability to deal with stress in a constructive way can be significantly increased. Therefore, it would be beneficial for FAP patients and gene carriers who are still healthy to learn how to cope with stress and its consequences of anger, depression, agitation, immunodeficiency, etc., in order to return to psychological and physical harmony. David Servan-Schreiber (2004) has made some concrete suggestions and comments in this regard. A psychotherapeutic counselor should be considered if there are problems to deal with stress alone.
5. Inflammation including sunburn, infections, etc., leads to the production of free radicals and acidification of the interstitial space and results in the acceleration of the progression of FAP. These factors possibly also play an important role in the manifestation of FAP. Deleterious effects of free radicals can be handled by antioxidative protective mechanisms that arise from a combination of the body's own substances, vitamins, and plant products. Starting in middle age, the concentrations of the endogenous components of this protective system fall. Numerous studies support the assumption that reduced protection from free radicals accelerates the aging process and that this problem can be compensated through "healthy nutrition". It would thus appear to make sense to apply the suggestions described here in the battle against FAP and early aging. A recently published study of Alzheimer's disease (Zandi et al. (2004)) showed a lower incidence of the disease among the over-65 age group for persons consuming a daily dose of >400 IU vitamin E (400 – 1000 IU per day) together with >500 mg vitamin C (500 – 1000 mg per day) as food supplements. The number of new cases was also markedly lower for this dose regimen. Lower doses of both vitamins, intake of high doses of only one vitamin, or exclusive administration of a multivitamin preparation had no effect. According to the authors, it is apparently only the intake of higher doses of these two complimentary antioxidant

vitamins that is able to reduce damage to nerve cells by free radicals in older individuals. Although in Alzheimer's it is mostly the brain that is affected, whereas in FAP it is the peripheral nerves, it seems reasonable to assume that at an advanced age the peripheral nerves will also have the benefit of the protective effect of high doses of these two vitamins. Our Paleolithic ancestors had an average intake of 400 mg vitamin C and of 30 IU vitamin E per 2000 kcal per day (Eaton et al. (1997). It is apparent that the vitamin E dose used in the study is far above "normal". Recently, high doses of vitamin E have been suspected to increase mortality.

The following table gives the concentration of antioxidants in a variety of foods of plant origin. There is a very high value for rose hips (*Rosa canina*, available in powder/tablet form ( <http://www.hyben-vital.com> ) or for walnuts, which are also a good source of polyunsaturated fatty acids.

<b>Antioxidants in several types of fruits, berries, nuts and seeds</b>		
(acc. to Halvorsen et al. (2002), top 8 selected from a long list with permission)		
<b>Name</b>	<b>Botanical name</b>	<b>Antioxidants [mmoles/100 g]</b>
Rose hip	<i>Rosa canina</i>	39.5
Walnut	<i>Juglans regia</i>	21.0
Pomegranate	<i>Punica granatum</i>	11.3
Crowberry	<i>Empetrum hermaphroditum</i>	9.2
Blueberries, wild	<i>Vaccinium myrtillus</i>	8.2
Black currants	<i>Ribes nigrum</i>	7.4
Strawberries, wild	<i>Fragaria vesca</i>	6.9
Blackberries, wild	<i>Rubus nemoralis</i>	6.1

- Investigations from this laboratory (Altland et al. (2004)) show that numerous amyloidogenic mutations of TTR (especially the most common mutation TTR-V30M) are more easily denatured than normal TTR at pH values of 7 – 7.4. This pH can be reached during relatively light exercise in the interstitial space of the musculature (Street et al. (2001)). Inflammatory reactions and decreased perfusion over a more or less longer time course can also result in an acidosis of the interstitial space. With increasing age there is reduced ability of the kidneys to excrete the excess accumulating acids (protons). Our "normal" diet contains an oversupply of salt and acids. With too much salt and not enough basic foods in the diet, our body reacts with bone and muscle degradation to enable adequate excretion of excess acids through increased mobilization of calcium carbonate/phosphate from bone and nitrogen from muscle protein. Chronic pain can also be a result of excess acid (Vormann et al., 2001) and can be ameliorated by consumption of basic food additives. In case of a risk of FAP or when FAP is already present, acidosis of the interstitial volume should be avoided.

For the typical diet of our ancestors in the Stone Age and for that of tribal groups that have been left largely undisturbed by Western civilization, a marked excess in basic foodstuffs has been reported (Sebastian et al. (2002)). The average American has a net acid excretion of 50 mEq per day. The significant difference between these two types of diet is due to the fact that in the American diet more than 60% of energy needs are obtained from cereal products, isolated animal fats and vegetable oils, and refined sugars having a high energy density that were not available in the Stone Age and that supply no alkaline or basic foodstuffs. In spite of a high meat consumption, our ancestors had a basic nutrition, which, in comparison to our modern diet of high-energy fats and carbohydrates, contained a wide variety of "fruits and vegetables" (tubers, roots, fruits, and edible green leaves) with low energy density and had a surplus of basic foods. Fruits and vegetables contain less sulfuric acid-forming proteins and more potassium salts of organic acids, which are metabolized in the body to bicarbonate, the most important buffer against excess acidification.

Animal studies and observations with human subjects show that increased potassium intake can have many positive effects on health (e.g. lowering blood pressure, reducing damage to blood vessels, lowering the incidence of stroke, arrhythmias, kidney damage, osteoporosis, calcium loss,

glucose intolerance; see He and MacGregor, 2003). Our ancestors consumed more than 200 mmoles of potassium daily, mostly from fruits and vegetables, while today, the daily consumption in the Western industrialized nations is around 70 mmoles (25 – 125 mmoles).

A primarily basic diet can be taken from the table shown below describing the potential renal acid load of foods. The presence of kidney damage or organic acidosis can be medically diagnosed and treated. The measurement of urine pH can be done with paper strips available at a pharmacy and can serve as a crude control of net acid excretion. In the absence of renal impairment, the diet should be modified such that measurements during the day give a value of pH 7 – 8 or the 24-hour urine pH should be 6.9 – 7.5. According to Remer and Manz (1995), every 0.1 pH unit below pH 6.9 in 24-hour urine corresponds to about 10 mEq net acid excretion per day. Nutritional advice aimed at converting to a surplus base diet can be helpful.

The following table from Remer and Manz (1995) shows the renal acid load due to food intake. The PRAL value (Potential Renal Acid Load) of food was calculated from the content of protein, phosphate, chloride, sodium, potassium, calcium, and magnesium and respective intestinal absorption rates. A positive PRAL value corresponds to an acid overload, a negative PRAL value to a surplus of basic foods. Independent of the composition of dietary intake but dependent on body weight, there is a significant fraction of organic acids (OA), which cannot be metabolized to carbonic acid and contribute to the renal acid load.

<b>Mean Potential Renal Acid Load (PRAL) of several food groups based on 100-g portions</b>	
(acc. to Remer and Manz (1995), used with permission)	
<b>Food Group</b>	<b>PRAL (mEq)</b>
<b>Beverages</b>	
Alkali-rich	-1.7
Alkali-poor	0
<b>Fats and oils</b>	
	0
<b>Fish</b>	
	7.9
<b>Fruits and unprocessed fruit juices</b>	
	-3.1
<b>Cereal products</b>	
Bread	3.5
Flour	7.0
Pasta, Spaghetti	6.7
<b>Meats and meat products</b>	
	9.5
<b>Milk and milk products</b>	
Milk and non-cheese products	1.0
Low-protein cheeses (< 15 g)	8.0
High-protein cheeses (> 15 g)	23.6
<b>Vegetables</b>	
	-2.8

A complete version of this table can be found at [www.acid-base.de/tabelle.htm](http://www.acid-base.de/tabelle.htm). In general, it is difficult to establish a “basic” acid-base balance through a change in eating habits alone. The currently popular recommendation of five servings of fruits or vegetables daily does not go nearly far enough. Therefore, one should not hesitate to use basic food additives. An even acid-base balance may be achieved by the following recommendations:

- (1) Reduce salt in your diet.
- (2) According to Remer and Manz, a 70-kg person produces daily  $70 \times 0.66 = 46$  mEq of organic acids (OAs) independent of his diet. To neutralize this, 1.5 kg of fruits and vegetables must be consumed corresponding with a net intake of 470 kcal of energy and 70 mmoles of potassium. Under a doctor’s supervision (absolutely necessary), one can alternatively use 60 mmoles of potassium as citrate to attain an additional daily net intake (ca. 48 mEq) of base (as bicarbonate) and potassium (see: [www.drugs.com/pdr/potassium\\_citrate.html](http://www.drugs.com/pdr/potassium_citrate.html)).
- (3) With the help of the table from Remer and Manz ([www.acid-base.de/tabelle.htm](http://www.acid-base.de/tabelle.htm)), a dietary plan with an even acid-base balance can be produced (example: a 200-g steak (PRAL +17 mEq) and 120 g spinach (PRAL -17 mEq) or 200 g potatoes (PRAL -8 mEq) and 300 ml fruit juice (PRAL -9 mEq) yield an even acid-base balance) from food.

With this plan, the consumption of acids and bases is balanced. Every additional amount of fruit or vegetables results in a basic metabolic balance.

7. Cod-liver oil and oil from cold-water fishes contain vitamins A and D as well as the polyunsaturated n-3 (omega-3) fatty acids eicosapentaenoic acid (EPA, 8.6 %) and docosahexaenoic acid (DHA, 11 %). EPA and DHA can be produced in the body from essential n-3 linolenic acid or taken directly from a diet containing fish and game. EPA and DHA lower the risk of cardiovascular disease, reduce inflammatory reactions, and improve the function of the cell membrane of muscle fibers in heart and vessel walls as well as in nerve fibers. The essential n-6 fatty acids, which are also polyunsaturated and are the precursors to hormones, favor inflammatory reactions. A comparison of the foods of our Stone Age ancestors with today's diet shows that our ancestors were accustomed to a ratio of n-6/n-3 fatty acids of about 1:1, while the modern diet has a ratio varying from 15:1 to 20:1 (Eaton and Konner (1985), Simopoulos (2001)). For our ancestors, the daily intake of EPA+DHA was 0.66 g. Today the average daily consumption is about 0.13 g. Paleoanthropologists assume that humans changed the composition of their diet after the Stone Age and that we are not genetically suited to the make up of the modern diet. Numerous studies suggest that an abnormally high ratio of n-6/n-3 fatty acids may play an important role in the genesis of chronic diseases (including diabetes) and cancer (see Simopoulos, 1999, 2003).

The twin mentioned above who succumbed to FAP 16 years after his identical twin brother, may be able to thank the daily intake of cod-liver oil (about 1 tablespoon/day, equivalent to about 2.5 g EPA+DHA). Recommendations for stemming the onset of several cardiovascular conditions including arrhythmias vary between 1-4 g EPA+DHA per day (Nordoy et al. (2001)). EPA+DHA also have an immunosuppressive effect that can possibly be taken advantage of in the preparation for and post-operative treatment of liver transplantation as a result of FAP. The high concentrations of vitamins A and D found in cod-liver oil can be avoided through the use of specially prepared fish oil capsules (e.g. OMACOR, Solvay – Pharmaceuticals, 0.84 g ethyl ester of EPA (0.46 g) and DHA (0.38 g) per capsule).

A combination of rapeseed oil (22 % n-6, 9.5 % n-3) and fish oil capsules can be used to adjust the diet to a better ratio of n-6/n-3 fatty acids like that in the diet of our ancestors. Simopoulos (2001) recommends 4.4 g n-6 linoleic acid, 2.2 g n-3 linolenic acid, and 0.65 g EPA+DHA as a daily dose (adequate intake) per 2000 kcal energy consumption. These values would be achieved with 2 tablespoons of rapeseed oil and 1 capsule OMACOR. Addition of 3 capsules of OMACOR or a tablespoon of cod-liver oil would be equivalent to the intake of the "late onset FAP" twin or the medium recommendation for cardiovascular disease. Furthermore, a ratio of n-6/n-3 fatty acids like that of the diet of our Stone Age ancestors would be approximated with these additives. In this regard, it should be mentioned that consumption of safflower seed oil (74 % n-6, <1 % n-3), grape seed oil (69 % n-6, <1 % n-3), sunflower oil 61 % n-6, <1 % n-3), and other oils due to the relatively high content of n-6 linoleic acid compared to n-3 linolenic acid is not recommended. Walnut oil (57 % n-6, 10 % n-3), soybean oil (49 % n-6, 7 % n-3), and olive oil (10 % n-6, 1 % n-3) should be used only sparingly so that the average n-6/n-3 ratio does not rise above an upper limit of 4. If these oils are preferred, supplementation with linseed oil (13 % n-6, 54 % n-3, also available in capsule form) can correct the n-6/n-3 ratio. It should be noted that the visible and hidden fat in meats from grain-fed beef can have a very unfavorable n-6/n-3 ratio. In addition, one should bear in mind that the fatty acid composition of the diet over many months is reflected in the body's own fatty tissue. Therefore, a change in diet can only show effects after a longer period of time.

8. Numerous studies concerning the relationship between diet and cardiovascular disease (for review see Hu and Willett (2002); O'Keefe and Cordain (2004)) have arrived at the conclusion that at least three strategies can be used to help avoid heart disease: (1) replacement of saturated and *trans* fatty acids with unsaturated, non-hydrogenated fats and oils, (2) increased consumption of n-3 fatty acids (fish, fish oil, plant/vegetable sources, see above), and (3) use of whole-grain products as the main source of carbohydrates. Additionally, eating large amounts of fruits and vegetables, drinking of adequate quantities of water (see above) and tea (2-3 cups per day), avoiding smoking, undertaking regular physical activity, and keeping the weight in the normal range are all important factors.

Meat of commercially slaughtered beef contains about five times as much fat as game. The proportion of heart- and vessel-damaging saturated fatty acids (e.g. C14-myristic acid, C16-palmitic acid) in regular beef fat is about six times as high as in the fat of game animals. We consume up to thirty times more vessel-damaging fatty acids in 100 g of commercial beef as we would in the same amount of game meat (Eaton et al. (1997)). You can do your blood vessels a favor if you remove all visible fat and skin from commercially slaughtered meats, avoid sausage products, and eat only game meats or meats from animals kept under proper animal husbandry practice (nutrition).

*Trans* fatty acids are produced by industrial hardening (hydrogenation) of oils to margarines or “fry-able” vegetable oils, by the heating of oils, and in the stomach of ruminants. They can be found in fried or baked goods and in fat-containing dairy products. Our Stone Age ancestors had no access to *trans* fatty acids.

The whole-grain products mentioned above correspond to carbohydrates with a low Glycemic Index (GI), which means they release their sugar contents into the blood stream relatively slowly. Elevated blood sugar levels can damage the blood vessel wall (atherosclerosis, kidney failure, retinopathy), increase oxidative stress, and activate inflammatory processes. Besides inactivity, an improper composition of dietary fat, and obesity, a high intake of easily digestible carbohydrates is an important cause of diabetes, which is seen today even in the younger population. Recommendations for the prevention of diabetes can be found in numerous books available in bookstores. Carbohydrate sources that are mostly natural such as fresh (uncooked) fruit, vegetables, green lettuce, whole-grain products, and also beans, peas, and lentils made available by cooking release their sugar contents only slowly. In contrast, foods that contain refined sugars or cereal, rice, and corn products that are processed or practically pre-digested by grinding, cooking, or heating cause a very rapid elevation of blood sugar. As long as diabetes is not present, basic foods with easily digested carbohydrates like potatoes, dried fruits, and bananas, etc. do not need to be avoided. By eating such foods in small portions during the day, blood-sugar peaks associated with an overshooting of insulin release can be prevented.

9. In the region of northern Sweden with a low incidence of FAP among the gene carriers, there are probably many passionate sauna fans. Sauna stimulates the circulation, improves metabolite exchange in the interstitial space, and stimulates the vessels, which are commonly the cause of circulation problems. The circulation is best supported by exercise and movement. Our ancestors transferred much more of their energy intake into movement (Cordain et al. (1998)). One to two hours of additional exercise daily without overexertion is good for the circulation, reduces stress, and has an anti-depressant effect. By checking the pulse, one can make sure that overexertion does not occur and that a good circulatory training effect is achieved (see [www.brianmac.demon.co.uk/hrm1.htm](http://www.brianmac.demon.co.uk/hrm1.htm)). An exercise program should be discussed with a cardiologist or sports medicine physician after a thorough physical exam.

### Summary of important elements of the diet

- Increase daily water intake to 30 ml per kg body weight. Drink 2 - 3 cups of green or black tea daily.
- Reduce salt intake to 3 – 6 g per day. Check the salt content of prepared foods (see table).
- Increase consumption of fruits and vegetables and use basic food additives, if necessary, as discussed above until 24-h urine samples are within the pH range mentioned below.
- Check 24-h urine samples occasionally. For a bodyweight of 70 kg the volume should exceed 2 liters; sodium excretion should be 50 – 100 mmoles, potassium should be > 120 mmoles, the molar potassium/sodium ratio should have a value of >2, the pH should be 7 – 7.5.
- Add supplements to your diet to ensure an adequate intake of vitamins, minerals, trace elements, and antioxidants.
- A daily dose of about 2 tablespoons cold-pressed rapeseed oil should be taken along with 1 tablespoon of cod-liver oil or an equivalent in fish oil capsules. Eat fish twice a week (about 1 g EPA+DHA is contained in 60-70 g salmon, herring, or sardines, 80-110 g trout or tuna, or 140 g mackerel or halibut). Remove all visible fat and skin from meats and poultry. Choose meats from game or meat from animals kept under natural nutritional conditions. Reduce the consumption of milk fat (butter, cream, fatty cheeses) and processed baked goods. Avoid all sausage products and fried foods.
- Give preference to whole-grain carbohydrates and remove sugared products from your meal plan. Women should not consume more than 15 g of alcohol per day and men not more than 30 g. Red wine should be chosen above other wines.
- Reduce stress whenever possible. A psychotherapeutic counselor should be considered if you are unable to deal with stress alone.
- Undertake stress-free exercise as much as possible.
- Try to stimulate your circulation by visiting a sauna, or steam bath, or partaking in European hydrotherapy (acc. to the Kneipp method). If you are relatively insensitive to heat, be careful that you do not become overheated or burn yourself. If you already suffer from cardiovascular disease, the sauna temperature should not exceed 60 °C and 15 minutes in duration.
- If you are taking medication or have problems with a particular organ system (e.g. heart, kidney, liver) or if you have a metabolic illness (e.g. diabetes), be sure to consult your doctor about these recommendations. For drug interactions with sodium restriction see Bennett (1997).

This diet is for the most part based on the lifestyle of our ancestors in the Stone Age, to which humans of today are still genetically adapted, and takes into account what we know about possible non-genetic causative factors of the disease (see Cordain et al., 2005). For still healthy gene carriers, these diet and lifestyle recommendations could provide a chance that the onset of disease symptoms and the necessity for organ transplantation are significantly delayed. Furthermore, this diet could be suitable to reduce problems observed after organ transplantation.

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