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REVIEW

Acute and ''chronic'' phase reaction—a mother of disease

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Summary The world is increasingly threatened by a global epidemy of chronic diseases. Almost half of the global morbidity and almost two thirds of global mortality is due to these diseases—approximately 35 million die each year from chronic diseases. And they continue to increase. Increasing evidence suggest that these diseases are associated with lifestyle, stress, lack of physical exercise, over-consumption of calorie-condensed foods rich in saturated fat, sugar and starch, but also under-consumption of antioxidant-rich fruits and vegetables. As a result the function of the innate immune system is severe impaired. This review discusses the changes induced in response to mental and physical stress and their association with the subsequent development of metabolic syndrome, and its association with various chronic diseases. The endothelial cells and their function appears to be of great importance, and the function of their cellular membranes of special importance to the function of the underlying cells; their ability to obtain nutrients and antioxidants and to eliminate waste products. The abdominal adipocytes seen to play a key role, as they have the ability to in stressful situations release much of proinflammatory cytokines, PAI-1 and free fatty acids compared to elsewhere in the body. The load on the liver of these various substances in often of greater magnitude than the liver can handle. Some of the most common chronic diseases and their potential association with acute and ''chronic'' phase response, and with metabolic syndrome are discussed separately. The need for studies with lifestyle modifications is especially emphasized.

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Chronic locomotor disease;
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Inflammatory bowel disease;
Irritable bowel syndrome;
Polycystic ovary syndrome.

Contents

Defence in acute diseases

A series of complex reactions occur in the body when an individual is threatened by stress, mental or physical; infection, trauma, surgical operation, advanced medical treatment or child delivery—all aimed to provide optimal protection against progress of disease. These changes are usually summarized under the name of acute phase reaction (APR). These changes involve the whole body, but especially the central nervous system (CNS), the hypothalamus and the hypophysis, which via the so called neuro-endocrine axis activates all the organs in the body, particularly the adrenals, the thyroid, the gonads, the liver, the gut and its mucosa and lymphatic system, but also, as more recently recognized, the intestinal flora. It is of special importance to remember that there are more nerve endings in the gut than anywhere else in the body. The intimate connection between the CNS and the intestine makes the gut early and deeply involved in the APR. The increased secretion of norepinephrine in stress is shown to activate potentially pathogenic microorganisms (PPMs) in the gut, which will lead to a dramatic increase in their virulence. These, under normal circumstances indolent colonizers will under stress change their phenotype and become life-threatening pathogens.[1] Central to the APR is release of various pro- and anti-inflammatory cells and to a large extent from cells which usually not are labelled as immune cells such as mucosal, endothelial and fat cells, but also by the flora. Important is also the release of fibrinolysis-regulating substances such as

plasminogen activator inhibitor type 1 (PAI-1). The dominating part of the immune defence, even if flora is excluded, is localized in the gut—no less than 75% of the immune cells of the body are suggested to be found in the G-I tract.[2]

Defence against chronic diseases

Similar, but not identical, defensive mechanisms are activated when an individual is affected by a long-lasting, continuous but discretely wearing mental and/or physical stress. The observed mechanisms have similarities with APR but also important differences. There are good reasons to keep them apart by defining the later as chronic phase response (CFR).[3] Characteristic to APR is increase in temperature, chills, somnolence, anorexia and profound changes in blood levels of plasma proteins, lipids, minerals, hormones, cytokines as well as in cellular elements. CFR manifests itself mainly in chronic fatigue, asthenia, reduced appetite, reduced physical activity, reduced mood, sometimes also mental depression and in reduced muscle mass. The changes in chemical and cellular parameters in CRP, although obvious, are more discrete. Individuals, who later in life develop clinical manifest chronic disease will often during months and years before show discrete but significant, plasma elevations in acute phase proteins, in PAI-1 and in pro-inflammatory cytokines. About 5% of the body's total protein synthesis in CPR is acute phase proteins, in contrast to as much as 30% in APR.[4]

Common to both APR and CPR is hypermetabolism, increased hepatic glycogenesis, increased glucose turnover, reduced muscle uptake of glucose, hyperlipemia and increased lipolysis of adipose tissues, especially visceral fats, increased production of non-esterified fatty acids (NEFAs), increased protein synthesis in the liver and increased protein turnover in the body, increased blood glucose levels, increased insulin secretion and insulin resistance. Fibrinogen and PAI-1 are significantly elevated in CPR, and significantly impaired fibrinolysis. Typical for CPR is increased levels of pro-oxidants such as homocystein, and low levels of antioxidants such as folic acid and glutathione.[5,6]

The homeostasis hypothesis

It has always been difficult to define health and wellbeing. One interesting suggestion is that health is a dynamic balance, homeostasis, in the control of body functions,[7] e.g. processes such as supply/use of calories and nutrients, growth/apoptosis, cellular/humoral immunity, Th1/Th2 immune defence, pro-/anti-inflammatory cytokines, saturated/unsaturated fatty acids, omega-3/omega-6 fatty acids, glucagon/insulin and numerous other systems, functions which together involve the more than two million different molecules, in which the body is said to consist. Several of these functions are seemingly out of balance in individuals who suffer CPR, and who sooner or later will show manifest signs of the so-called metabolic syndrome (MS) and subsequent chronic diseases. MS is a syndrome said to today affect about 25% of Americans and at least 15% of Europeans, and increasing in incidence all around the globe. It is strongly associated with global epidemy of chronic diseases, all from Alzheimer and prostatic hyperplasia, to cancer and diabetes. Other rapidly increasing conditions associated with MS are chronic liver diseases, such as hepatic steatosis and cryptogenic cirrhosis. The global incidences in most of these conditions are forecasted to double within two or three decades, if no radical preventive measures are instituted.

Recent statistics from the World Health Organization (WHO) suggests that chronic diseases now constitute 46% of the global disease burden and 59% of global deaths; each year about 35 million people will die from chronic diseases. The incidence of critical illness, especially severe infections, is also fast increasing, and to a large extent in parallel with the increase in chronic illnesses and it is the chronically ill who often are affected by critical illnesses. Only in the US does severe sepsis annually affect 751,000 persons, leading to death in 29% of the patients, which makes critical illness the eight cause of death in the country. Furthermore, its incidence increases by 15% per decade.

Reduced function of the cellular membranes?

There are many data supporting the notion that diet-associated structural changes in the cellular membranes are central to CPR and the development of various chronic diseases. The most obvious changes seem to consist in increased deposition in the cellular membranes of saturated fatty acids and cholesterol at the expense of the polyunsaturated fatty acids (PUFA) and phospholipids, which are the normal ingredients of these membranes. These structural changes induce membrane dysfunction, further accentuated by oxidative injuries of the

remaining NEFAs and also of membrane proteins. A increased quotient of saturated fat and cholesterol relative to polyunsaturated and cholesterol leads to reduced fluidity in the membranes, explaining the drastically reduced membrane function; its ability to take up nutrients and to eliminate waste products. Such changes affect also the function of various immune cells. For example the capacity of the macrophage to absorb foreign material and micro-organisms is greatly inhibited by larger consumption of saturated fats.[8] The reduced cellular fluidity affecting both supply of nutrients and elimination of waste products results in cellular starvation, intoxication and under severe circumstances to cell death—changes commonly observed in chronic conditions.

An exaggerated CFR occurs in patients with prestage of chronic disease observed during months, sometimes years, and sometimes long before obvious signs of manifest disease. Cytokines such as IL-6 and TNF-α are early significantly elevated, so are also acute phase proteins such as C-reactive protein (CRP), fibrinogen and PAI-1,[9] changes, which signal a state of increased inflammation and increased coagulation in the body, and associated with increased deposits of fibrin on endothelial (blood vessels) and mesothelial (body cavities), and also with increased incidence of thrombosis. High levels of insulin, blood glucose, and NEFA are commonly observed.

The adipose tissues in focus

The adipocytes are of particular importance to health. They serve as metabolic ''shock absorbers'' with the important task to adjust the metabolic activities in the body to the availability of calories. Absence of adipocytes, lipodystrophy, is a condition seen in some diseases, particularly in HIV, with manifestations such as insulin resistance, glucose intolerance, and dyslipidemia, which makes this condition to resemble MS.[10] The fat cells are far from, what we might have believed in the past, a passive storage place for fats. Instead these cells are among the most active endocrine and metabolic cells in the body. These adipocytes release in stress-full situation significant amounts of cytokines such as IL-6 and TNF-α. IL-6 released from the visceral fat, is largely responsible for the release of CRP from the liver. The turnover of fat varies to a great extent between different cells and tissues in the body, among the most active are blood-born cells and visceral cells, and the least active cells are those in the CNS. It is somewhat simplified said that ''the fats that we eat today will remain in the blood for days, in the visceral adipocytes for weeks, in subcutaneous tissue for months and in the CNS for years''.

Visceral fat has a special role

Characteristic to abdominal fat is that it in stress situations is more readily mobilized than fats from other sources. It is important to recognise that the abdominal adipocytes per gram tissue produce three times as much of proinflammatory cytokines such as IL-6 and TNF-α than fat from extravisceral sources, and also large amounts of PAI-1.[11,12] The amount of fat tissue in the abdomen can according to MRS studies vary between a few millilitre and 6 l.[13] It is easy to imagine the huge amounts of FFAs, proinflammatory cytokines and PAI-1, which in obese persons in stress will hit the liver, and when released through the lymphatics, also the lungs. Increased amounts in the blood of NEFA, IL-6, TNF-α and PAI-1 is responsible for the fatty infiltration of the liver and subsequent reduction in liver function.[14,15] Parallel with the increased release of PAI-1 will also occur increased blood levels of fibrinogen, reduced fibrinolysis and increased coagulability/thrombogenicity.[16,17]

Increased blood levels of molecules such as IL-6 and CRP are among the most sensitive predictors of endemic diseases such as type 2 diabetes mellitus.[18] These changes are always accompanied by increased leukocyte activity, complement binding and thrombocyte activation, but also by reduced leukocyte activation.[19,20] Observations which has lead to the suggestion that chronic diseases such as type 2 diabetes are a result of malfunctioning innate immune defense.[21,22]

The endothelial cells—the key to metabolic syndrome?

The majority of *cis*-fatty acids in blood is normally bound to albumin and the content of unbound NEFAs is normally quite low (<10 nmol/l). Increased amounts of NEFAs in the circulation is strongly associated with significant reductions in the innate immune defence of the body.[17,18] Elevated levels of NEFAs are reported in several conditions of chronic diseases such as Alzheimer,[23] diabetes,[24,25] cancer,[26,27] heart ischemia,[28] congestive heart failure,[29] chronic infections such as HIV,[30,31] chronic arthritis such as gout,[32,33] chronic liver disease,[34] chronic renal disease,[35] and in

postoperative as well as in critically ill patients.[36] Elevated levels of *trans*-fatty acids, due to consumption of partially hydrogenated oils, meat and dairy products are strongly associated with conditions such as coronary heart disease,[37,38] and with sudden cardiac arrest.[39,40]

The condition of the endothelial cells and their ability to promote transfer to underlying cells of glucose, fatty acids and other nutrients is of extreme importance for the function of all cells and tissues, adipose cells as well as various immune cells. The endothelial cells do exhibit strong endocrine activities, and have documented ability to produce and release larger amounts of cytokines such as IL-6 and TNF-α. Some evidence suggests that the transport of NEFA over the endothelial cells is a passive process and not mediated by endothelial receptors.[41] This important transport function is severely impaired by circulating drugs, toxins and microbes.[42] Increased levels in the blood of circulating NEFA has also been shown to be deleterious to the endothelium and its function, induce changes in the physical properties of the cell membranes and impair the transport of and uptake of both glucose and FFA in underlying cells.[43] The impaired transport out of the cells of FFA is, in combination with a reduced lipolysis, regarded as the main factor behind accumulation of triglycerides in muscles and liver, but also in cells such as immune cells and neurons.

Metabolic syndrome, chronic diseases, aging

In a recent study 208 healthy individuals, who at the beginning of the study all showed normal glucose tolerance and no obvious obesity, were followed during app. six years.[44] Thirty-seven of these individuals (18%) developed during the study period signs of chronic disease. As much as every third person in the group with the lowest insulin sensitivity (blood glucose >7.8 mmol/l) developed during the study period symptoms of chronic disease, compared with none in the group with the highest insulin sensitivity (blood glucose <4.4 mmol/l). As a matter of fact, as much as seventy per cent (25/37) of the individuals with the lowest glucose sensitivity/highest glucose resistance were during the study period diagnosed with chronic diseases such as hypertension (15), cancer (9); prostate 3, stomach 2, breast 1, colon 1, urinary bladder 1 and, kidney 1], coronary/vascular insults (7), stroke (4), and type 2 diabetes (4).

Aging is associated with a series of modest but obvious increases in blood levels of cytokines such as TNF-α and IL-6.[45,46] Genetic factors play an important role in aging but also life style; stress, reduced physical activity, smoking, alcohol consumption, and the food we eat – seem all to accelerate the unavoidable process of aging and contribute both to a state of premature aging and development of age-related chronic diseases. A modest but significant increase in activity of the chronic phase response and increased proinflammatory activities in the body is associated with/instrumental to development of MS seen in and preceding various chronic diseases. Chronically elevated levels of cytokines such as TNF-α and IL-6 are strongly associated with increased levels in blood of glucose and NEFA, insulin resistance, reduced endothelial function and increased coagulability. Individuals, who reach high age without obvious signs of physical and mental deterioration, have better than others succeeded in maintaining normal activity of the sympathetic nerve system, glucose tolerance and maintain intact immune functions.[47] Common to these individuals are well preserved cellular membranes,[48] as mainly observed in studies of erythrocytes, but most likely valid for most if not all cells in the body.

From Alzheimer's disease to prostatic hyperplasia

Alzheimer's disease and Parkinson's disease: The incidence of both Alzheimer's disease (AD), Parkinson's disease (PD) is increasing. In the Western world, about 10% of the individuals at the age of 65, and half of the individuals at the age of 85 show signs of AD. The eventual association of these two neurodegenerative diseases with MS is in recent years receiving an increasing scientific interest, but the association of other neurodegenerative diseases with MS remains still unexplored. Insulin and intact insulin receptors are of outmost importance for good cerebral function, and the regions of the brain most involved with memory-related functions are known to have the greatest density of insulin receptors, and are especially rich in insulin-regulating so called glucose transporters.[49] Insulin is of the greatest importance for regulation of the protein amyloid and its derivate beta-amyloid (Abeta) and is indirectly associated with the development of senile plaques, typical to AD.[50] The development of senile plaques is known to be accelerated by elevated serum levels of NEFA.[51] Both AD and PD, although in different regions of the

brain, exhibit similar cellular and functional changes with signs of increased oxidative stress, reduced mitochondrial function, reduced glucose uptake and increased peroxidation of cellular membranes,[52] and in both diseases combined with significant alterations in the phospholipid and cholesterol structure of the cellular membranes and their synaptic functions.[53] Common to these diseases are also high levels of pro-oxidants such as homocystein,[54] and low serum levels of antioxidants, such as glutathione, folic acid, carotenoids, and of the vitamins C and E.[55,56]

Arteriosclerosis and coronary-vascular diseases: Arteriosclerosis and coronary-vascular diseases (CVD) are also associated with MS. In 400 BC, Hippocrates already pointed out that ''Individuals who have a full habitus die earlier than slim persons.'' Experimental studies performed in rabbits almost 100 years ago (1908) showed that larger consumption of milk, meat and egg results in advanced arteriosclerosis, and large epidemiological studies in the 1930s, showed that this is also valid for humans. Milk-based diet was till the middle of the 20th century a common treatment of peptic ulcer, but was discontinued when it was observed in the treated patients to lead to a drastic increase in mortality in coronary heart disease. It is an interesting observation is that the incidence of CVD is much higher in the Northern ''milk-drinking'' France than in the Southern ''wine-drinking'' part of the country. It is also observed that the incidence of CVD in European countries seem to decrease much in parallel with a decreasing milk consumption.[56] Only in one European country is milk-consumption increasing, that is Portugal, and this country is the only European country with an increasing incidence of CVD.[56] It is also of special interest that individuals, who suffer other MS-related disease such as type-2 diabetes, more often than others develop CVD. Common to these conditions are chronically elevated NEFAs and serious changes in the endothelial cell structure and function,[57] increased levels of pro-inflammatory cytokines, inhibited fibrinolysis and increased coagulability. It might well be that one single episode of high levels of FFA in blood is enough to induce a coronary infarction in individuals, who suffer MS, and who are both anatomically and metabolically predisposed. It is well known that a single meal rich in saturated FFA is enough to produce endothelial dysfunction.[58] Intake of 2 g of vitamin C in association with such a meal has proven effective to prevent this disaster from happening.[59] Not only insulin resistance but also metabolic abnormalities induced by long-term consumption of drugs such β-blockers and diuretics, especially in middle-aged men, will significantly increase the risk of coronary infarct.[60] That consumption of drugs can contribute to metabolic syndrome and to increased risk of coronary heart disease is also known from studies in other groups of sick individuals; after transplantation, in patients with chronic renal disease who undergo dialysis, in patients with diseases such as HIV or cystic fibrosis, and in patients on steroids, immuno-suppressives, anti-retroviral and other drugs, especially when consumed during longer periods of time.[61]

Cancer: An association between MS and cancer has been demonstrated for an increasing number of cancers such as breast, prostatic, colorectal and endometrial cancers, forms of cancer which are several times more common in Western countries than, for example, in China, and especially in its rural districts. Obesity in childhood, early menarche and large body are known risk factors for development of cancer later in life, especially breast cancer.[62] It is known since long that consumption of fat food (saturated *cis*- and *trans*-fatty acids) is an important risk factor for development of cancer; for each percent of fat in the food the risk of developing breast cancer will increase by 10%,[63] and the risk of treatment failure, when on treatment for breast cancer, with 8%.[64] Furthermore, persons, who eat fat food show a higher histological degree of malignancy, and increased tendency to produce metastases.[65]

High blood levels of insulin-like growth factor-1 (IGF-1) are strongly associated with visceral obesity and several forms of cancer.[66,67] While the anti-apoptotic and mutagenic effects of insulin are short-lasting so are the effects induced by IGF-1 both stronger and more long-lasting. IGF-1 is to a large extent produced by the body, but also supplied through food. Especially dairy products, but not if fermented such as yoghurt and cheese, are shown to contain large quantities of IGF-1, and consumption of milk and butter suggested to be associated with an increased incidence of breast, prostatic and colonic cancers.[68,69] The content in cow's milk of IGF-1 is further increased when the animals are supplied synthetic growth hormones.

Diabetes: The manifest type 2 diabetes is usually preceded by a period with signs of chronic inflammation exhibiting all the known ingredients of chronic phase response (CPR). Discretely elevated levels, especially of Il-6 and acute phase proteins are well documented predicting factors of diabetes, as of several other of the diseases discussed in this review.[70] This might explain the observation that patients with diabetes have a much higher risk to also acquire other chronic diseases. Type-2 diabetes increases in the Western

world in an almost un-controllable manner and is one important factor behind the fast increasing health expenditure in Western countries. Eighteen million are estimated to suffer the condition only in the US, of whom an estimated 6 millions are unaware of the condition, and another 18 million known to be in pre-stage of type-2 diabetes. With the present pace of increase at least ten per cent of Americans are calculated to suffer diabetes by the year 2050.[71] The annual cost of diabetes care in the US have according to American Diabetes Association doubled in recent five years, from 44 billion dollars in 1997 to 92 billion dollars in 2002, and if costs for lost work is included with as much as 132 billion dollars. It is especially worrying that the fastest increase in seen in children under the age of ten, especially as this disease could be prevented by significant changes in life style.

Chronic liver disease and gallbladder disease: Gallstone disease (GD) belongs to the most common diseases, especially among women in Western countries. Every fourth woman in the US above the age of fifty is estimated to have GD and as many as 700,000 cholecystectomies are annually performed only in the US. CD is the disease, which was the first to be associated with Western lifestyle and insulin resistance.[72,73] Another common and fast increasing entity is non-alcoholic steatosis hepatis (NASH) and its late consequence, cryptogenic liver cirrhosis. Some countries report a higher mortality in chronic liver disease than in coronary-vascular disease.[74] Some evidence suggests that food abuse is a more common cause of chronic liver disease than abuse of alcohol. We observed more than 30 years ago that presence of steatosis is a strong risk factors for poor outcome in liver resections,[75] today this is also the experience in liver transplantation,[76] as in several other acute diseases. An over-stimulated innate immune system and an increased CPR is associated with high incidence of MS as well as with development of NASH, chronic liver disease, and GD.[76,77] Increased NEFAs are frequently observed in NASH,[78] which most likely will significantly influence the development of liver cirrhosis.

Chronic renal disease: It is an old observation that patients, who suffer chronic renal disease (CRD) are at risk of developing other chronic diseases such as diabetes and CVD. Increased blood levels of IL-6, CRP and other inflammatory markers are observed early in the disease process, as are dyslipidemia and insulin resistance.[79,80] Signs of malnutrition, inflammation and arteriosclerosis, a triad suggested to be called the MIA-syndrome, is observed early in the disease process, and often some time before dialysis treatments are considered.[81] Patients with CRD show frequently increased serum levels of NEFA. Advanced inflammation as manifested in increased CRP is strongly associated with poor outcome, especially in men.[82] Control of malnutrition and inflammation is generally regarded as powerful tools to prevent further development of arteriosclerosis and to contribute to improved prognosis for patients with CRD.

Chronic locomotor system diseases: An eventual association between various locomotor system diseases and MS has this far not been studied. A recent study provides, however, strong evidence that elderly women and men (69–93 years of age) who eat larger amounts of sweets and/or consume alcohol have significantly reduced mineral density in contrast to those who consume larger amounts of fruits and vegetables, who show a significantly increased mineral density.[83] The association between locomotor system disease and increased CPR is best documented for gout. Increased production of uric acid is strongly associated with visceral obesity, coronary-vascular disease, reduced glucose tolerance, dyslipidemia, reduced HDL cholesterol, increased fibrinogen/s in patients with gout.[84] Patients with rheumatoid arthritis (RA) are known to have a reduced hypothalamo-pituitary-adrenal response to stress, with reduced release of cortisol, ACTH and growth hormone,[85] but its association with increased CPR and MS is largely unknown, with the exception of an isolated study, which reports frequent insulin resistance in RA patients.[86] It has also been observed that RA patients, like diabetic patients, suffer a significantly increased risk of developing coronary heart disease. However, as only about one third of the patients with RA have signs of insulin resistance other not fully understood underlying mechanisms are probably more important.[87]

Chronic intestinal diseases: The situation in chronic intestinal diseases, such as inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS), resembles in many aspects that of RA. Clearly, chronically elevated levels of pro-inflammatory cytokines and of an increased coagulability is seen in IBD,[88,89] as are signs of epithelial and endothelial dysfunction, changes demonstrated to significantly relate to disease activity, especially in ulcerative colitis (UC). Changes in IGF-1 and in its binding protein (IGFBP) have also been observed and shown to relate to the disease activity.[90] mRNA of both IGF-1 and IGFBP, and of TGFβ express high activity in the intestinal wall of patients with active Crohn's disease (CD), changes which have been suggested responsible for the increased collagen synthesis and increased connective tissue in the

intestinal wall, characteristic of CD.[91] Such changes are in CD observed in all layers of the intestinal wall but in UC only in lamina propria and the submucosa.[92] A few studies report insulin resistance in IBD patients,[93] but these might be secondary manifestations, as they disappear when the disease goes into remission. As is the case in RA, more and extensive studies are highly desirable in order to clarify an eventual association with MS.

Polycystic ovary syndrome: Polycystic ovary syndrome (PCOS) is one of the diseases most clearly associated withy MS. Consequently, the incidence of PCOS is dramatically increasing in the Western world. Some studies suggest that as much as 10% of fertile women in Western countries suffer from the condition. Women with signs of PCOS suffer a several times increased risk of developing hypertension, diabetes, and coronary heart disease, but also cancer, particularly breast cancer. The patients with PCOS do almost invariably show signs of an increased CPR; increased plasma homocystein levels[94] increased coagulability and reduced fibrinolysis,[95] increased activity of pro-inflammatory cytokines,[96] abdominal obesity,[97] dyslipidemia, reduced glucose tolerance and insulin resistance.[98] Other manifestations are menstrual disturbances, reduced reproductivity, increased risk of preeclampsia, hirsutism and acne.[99,100] It has been observed that women in Western countries have menarche about three years earlier than in rural areas of Asian countries, their menstruation periods are in average three days shorter and their menopause occur significantly later in life. It has been calculated that Western women produce twice as many menstruations in life compared to women in developing countries, which is interesting as some female cancers are strongly related to the numbers of menstruations produced in life time. Obesity before menarche, insulin resistance in 5–10 year old girl, and early menarche are predictors of PCOS and of endemic disease later in life.[101]

Prostatic hyperplasia: Prostatic hyperplasia (PH) affects about 8% of the males in Western countries, beginning already at an age of 30 and successively increasing in incidence to be $>80\%$ in the age groups above 70. An association between PH and type-2 diabetes, hypertension, and various chronic diseases has been observed. In recent years have also significant documentation been provided of a causal association between PH and metabolic syndrome; obesity, dyslipidemia and hyperinsulinemia.[102,103]The increased consciousness of the association of PH and lifestyle has lead to attempts to, instead of radically changing life style, try unconventional drugs of various kinds.[104] It is estimated that only in the US about one billion dollars are paid annually for consumption of products based on bark, roots, seeds, fruits and other parts of plants, suggested to inhibit prostatic enlargements, a market, which is fast increasing.[61]

Other MS-associated conditions: A long row of diseases have been suggested to contain an ingredient of chronic inflammation as in CRP and MS. Among these are conditions such as late-onset-autism and cystic fibrosis. It can well be that the observed changes are secondary and the result of an over-ambitious nutrition of the children with these conditions, but the association might also be of pathogenetic importance. An association is also observed between the incidence of allergy and consumption of saturated fat. Of special interest is the observation that children of breast-feeding mothers, who consume large amounts of saturated fat and less plant fibres, have a significantly increased tendency to develop allergy.[105]

Conclusions and final remarks

More than 80 years have passed since the Swede Eskil Kylin in an article, published in the German language, suggested the existence of what he called a hypertension-hyperglycemia-hyperuricemia syndrome,[106] and ten years later followed by an article in the Lancet by Englishman Himsworth, suggesting that human diseases are associated with insufficient insulin function.[107] Thirty years did the Frenchman JP Camus in an article in the French language suggest the existence of what he called metabolic trisyndrome; gout, diabetes, hyperlipidemia.[108] It should, however, take another twenty years before the medical world would become aware of the obvious associations between MS and various conditions of chronic unhealth. The credit goes to the American Gerald M Reaven, who with his Banting-lecture, published in 1988 managed to get the whole medical world interested in metabolic associations between various chronic conditions, and especially between diabetes and CHD.[109] Since then the number of publications about metabolic syndrome are steadily and almost exponentially increasing; 1990: 4, 1995: 34, 2000: 148, 2003: 1274 publications. Despite that, a lot of questions remain unanswered. Of special importance for the future is to investigate how modifications in lifestyle: control of stress, increased physical exercise and most important radical modifications in diet can normalize the phase reactions and stop the flood of chronic diseases.

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