Nutrition-related diseases such as obesity, hyperlipidaemia, liver cirrhosis, hypertension, cardiovascular diseases or atherosclerosis and malnutrition resulting from different diseases contribute significantly to the mortality and morbidity in the population. Understanding the cellular background of nutrition-related diseases and disease-related malnutrition may enable their prevention and therapy. This paper focuses on several cellular aspects of nutrition whose pathophysiological mechanisms and potential clinical relevance have all been characterized. The list, therefore, is certainly incomplete.

**Obesity**

Obesity is a familial disorder associated with genetic predisposition, excessive food intake, and low rate of energy expenditure [1].

Reduced sympathetic nervous system activity plays a causative role in obesity of rodents [2]. The study of Peterson et al. [3] suggests that decreased sympathetic activity may also be a cause of obesity in humans. Decreased sympathetic activity may lead to excessive energy storage in adipose tissue by means of decreased lipolysis and increased lipogenesis. Increased parasympathetic activity may lead to excessive energy intake (hyperphagia). Muscle sympathetic nerve activity was significantly related to percent body fat and correlated with energy expenditure adjusted for fat-free mass, and age in Caucasians, but not in Pima Indians, a population with a high prevalence of obesity [4]. Clonidine, a central sympathetic inhibitory agent, causes a 6% reduction in resting metabolic rate and 33% reduction in the thermic effect of a meal [5]. Beta-adrenoceptor blockade with nadolol decreases resting metabolic rate by 7% without changes in thyroid hormone levels [6]. Taken together, individuals with reduced sympathetic nervous system activity may be at risk for body weight gain resulting from a lower metabolic rate. Obesity is associated with the development of coronary heart disease, stroke, hypertension and diabetes mellitus.

**Diabetes mellitus**

Hyperglycemia of patients with non-insulin-dependent diabetes mellitus (NIDDM) is the result of glucose overproduction by the liver, impaired insulin secretion and peripheral insulin resistance [7]. Magnusson et al. [8] have shown that after 22 h of fasting hepatic glucose output was 25% higher in patients with NIDDM than in normal subjects. Despite being fed identical diets, patients with NIDDM had half the amount of hepatic glycogen compared to normal subjects. Furthermore, the rate of hepatic glycogenolysis in NIDDM patients was less than half the normal value. However, the rate of gluconeogenesis was 50% higher in NIDDM patients than in normal subjects and responsible for 90% of hepatic glucose output in NIDDM patients [8]. It was further demonstrated that the mechanism for impaired muscle glycogen synthesis in NIDDM patients is a defect in glucose transport and phosphorylation [9].

**Role and benefits of carbohydrate in the diet**

For non-diabetics, meals commonly supply 50–150 g carbohydrate. To avoid hyperglycaemia and spillage of glucose into the urine, glucose transferred into the circulation has to be rapidly transferred into cells. Glucose oxidation in the postprandial state consumes only 10 g/h. Therefore, most of the glucose taken up must be stored by conversion to glycogen. Glucose uptake and glycogen synthesis are stimulated by insulin. Two moles ATP are expended to incorporate 1 mol glucose into glycogen, whereas 36 moles ATP are gained during the complete oxidation of one molecule of glucose. After a typical meal, one-quarter to one-third of the carbohydrates is converted to glycogen in the liver and one-third to one-half to glycogen in muscle, whereas the remainder is oxidized during the postprandial hours [10].

Gold [11] demonstrated that systemic glucose injections ameliorate the effects of many drugs, including reversing impairments in learning and memory produced by opiate and gamma-aminobutyric acid receptor agonists, and cholinergic and glutamatergic antagonists. Relatively modest increases in circulating glucose concentrations enhanced learning and memory processes in rodents and humans, and enhances several other cognitive functions in subjects with severe cognitive pathologies [11]. A careful examination of the benefits of 'high'-carbohydrate diet has to consider the effect of carbohydrates on energy metabolism and whether a large carbohydrate intake leads to increased lipogenesis in humans [12].

**Role of glutamine supplementation**

Total parenteral nutrition is associated with gastrointestinal complications, mainly mucosal atrophy,
increased intestinal permeability, bacterial translocation, and impaired host gut-immune function. Data of Li et al. [13] suggest that glutamine, when added to the total parenteral nutrition solutions, reduces atrophy of the jejunum and jejunal permeability. Glutamine is an important metabolic fuel of the enterocyte. The addition of glutamine to total parenteral nutrition solutions maintains small intestinal mass, nitrogen content, villous height, and mucosal function even during prolonged periods of bowel rest [14]. Possibilities for glutamine supplementation in the frame of enteral/parenteral nutrition include glutamine-rich proteins, free glutamine and glutamine-containing dipeptides. Several authors recommend early enteral nutrition to avoid atrophy of the intestinal tract ("use it or lose it").

Surgical trauma induces a decline of protein synthesis in skeletal muscle associated with a decrease in free glutamine. Total parenteral nutrition supplemented with glutamine maintains the free glutamine levels in skeletal muscle after surgery [15]. After fasting, glutamine is preferentially used by the liver and not by skeletal muscle or by gut tissues [16].

Tumour progression is associated with a depletion in host glutamine stores, which leads to net proteolysis and the development of cancer cachexia, and also with depression of natural killer cell activity. It has been shown that glutamine-enriched diets repleted the depleted host [17]. Data of Fahr et al. [18] also indicate that oral glutamine supplementation, through support of host glutamine stores and glutathione production, may decrease tumor growth by enhancing natural killer cell activity.

Hyperhomocysteinaemia

Hyperhomocysteinaemia is an independent risk factor for vascular disease. With increasing plasma homocysteine, a graded increase in the prevalence of stenosis [19] or thickening of the intimal-medial wall [20] of the carotid artery, and increase in myocardial infarction [21] are observed. Homocysteine is toxic to the vascular endothelium. It causes impaired production of endothelium-derived relaxing factor [22], stimulates the proliferation of smooth-muscle cells [23], and increases the expression of thrombomodulin, as well as activating protein C [24]. Another important mechanism to explain homocysteine-induced atherosclerosis is its growth-promoting effect on vascular smooth-muscle cells and its inhibitory effect on endothelial cell growth [23].

Plasma homocysteine increases when folate is deficient [25]. The active form of folic acid, 5-methyltetrahydrofolate, functions as a cosubstrate in the remethylation of homocysteine to methionine. Plasma homocysteine reaches a stable low concentration with folate intakes of 400 μg/day or more. Folate supplements of 1 to 2 mg/day are usually sufficient to reduce or normalize a high homocysteine [26]. It has been shown that 5 mg folic acid and suprophyllologic doses of B-vitamins may be required to correct hyperhomocysteinaemia in dialysis patients [27].

It has been suggested that homocysteine might be atherogenic by inducing the oxidation of low-density lipoprotein. Lupo et al. [28] showed that the incubation of native low-density lipoprotein with increasing amounts of homocysteine resulted in significantly increased oxidation. Oxidation was most pronounced at 50 μM homocysteine, which corresponds to concentrations found in uremic patients.

In uraemia, the elevated plasma and red-cell homocysteine causes an accumulation of the toxic compound S-adenosylhomocysteine, a potent inhibitor of methyltransferase, in erythrocytes [29]. In vitro, the reaction adenosine + homocysteine → S-adenosylhomocysteine proceeds in the direction of hydrolysis, since the products are rapidly removed. An increase of erythrocyte homocysteine concentration favours the accumulation of S-adenosylhomocysteine. In chronic renal failure, S-adenosylhomocysteine can be considered as a storage form of homocysteine in the intracellular compartment. Inhibition of methyl-esterification is the primary mechanism for hyperhomocysteinaemia in uraemia. The increase in the intracellular concentration of S-adenosyl-homocysteine is associated with a decrease in enzymatic protein methylation in uraemia. Methyl esterification of erythrocyte membrane proteins, a reaction involved in the recognition and repair of specifically damaged proteins, is impaired in uraemia [30].

Role of cytokines

Cytokines promote muscle protein degradation. Interleukin-1 (IL-1) and tumor necrosis factor (TNF) inhibit amino acid and protein synthesis in muscle [31]. Anti-TNF treatment decreases protein degradation rates in skeletal muscle, heart, and liver of tumor-bearing rats [32]. Amino acids released from muscle are needed for protein synthesis in the liver during acute inflammation. In vivo, cytokines stimulate amino acid uptake by the liver [33].

Cachexia is associated with hypertriglyceridaemia. Cytokines enhance plasma triglyceride levels [34], probably by inhibition of lipoprotein lipase activity, inhibition of VLDL clearance and/or stimulation of fatty acid synthesis [35].

Cytokines are also involved in carbohydrate metabolism. IL-1 and IL-6 stimulate glycogenolysis and glycolysis, and inhibit glycogen synthesis and gluconeogenesis [36]. IL-6 stimulates the release of glucose from the liver.

Cytokines may affect food intake. McCarthy et al. [37] reported reduced intake of a liquid diet in rats given recombinant murine IL-1α. Recombinant human IL-1β administered to ad libitum fed mice was reported to decrease food intake by 10–15% [38]. The study of Hellerstein et al. [39] demonstrates that IL-1 is anorexigenic in the rat, but this is influenced by the structural form of IL-1, the route and chronicity of
administration, the source of diet, and the age of the animal.

References


