Good fat in, excess fat out

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THE NEW PERSPECTIVE ON BODY LIPIDS AND NUTRITIONAL FAT

The quantity and composition of lipids in the body is one of the foremost factors deciding metabolic health. Lipids play an important role in the evolutionary origins of life as basic components of the cell membranes separating primordial organisms from their environment. The molecular structure of lipid membranes is considered by scientists dealing with theories of life origins as capable of storing biological information, predating RNA and DNA in that function. Omega-6 and omega-3 polyunsaturated fatty acids (omega-3 or omega-6 aka n-3 or n-6 means 3rd or 6th carbon from the non-acidic omega end of fatty chain has double-bond, i.e. bond unsaturated with hydrogen atoms) are important structural components of phospholipids in human cell membranes regulating metabolism via their lipid metabolites, endocannabinoids. Once incorporated into the cell membranes, n-3 or n-6 fatty acids affect cell membrane properties such as fluidity, flexibility, permeability, the activity of membrane-bound enzymes and metabolic activity. The difference between content of n-6 vs. n-3 fatty acids in the cell membrane can be decisive in metabolic response of the cell, i.e. n-6 derived endocannabinoid overproduction may lead to metabolic health deterioration and obesity, whereas n-3 will prevent overproduction of metabolism-deteriorating endocannabinoids.

The increase in prevalence of obesity in the USA during the 20th century and accelerating in the first two decades of the current century has been postulated, in part, due to a marked increase in consumption of high fat processed food rich in polyunsaturated n-6 fatty acid, linoleic acid, a precursor to arachidonic acid (1). Linoleic acid is classified as an essential fatty acid (has to be supplied with food and cannot be produced by the human organism, i.e. endogenously) for human health with a typically recommended daily dose of 3 g. However, this essential nutrient is commonly found in most processed foods and is overconsumed in the Western diet by 5 to 30 times – causing a dramatic imbalance. The concern with the excess dietary linoleic acid is that its consumption may increase content of the cell membrane-bound n-6 arachidonic acid and contribute to chronic overproduction of endocannabinoids.

The new evidence emerges that saturated fat of animal origin, which is an energy "white" storage fat, may not necessarily be the culprit in obesity but rather certain vegetable oils, e.g. safflower, sunflower, corn, soy and peanut oils, which are rich in n-6 linoleic acid and are omnipresent in our daily food. Conversely, the flax seed, rapeseed, hemp seed and marine life oils exemplify oils with high content of n-3 fatty acids and little n-6 variety fatty acids; olive oil, rapeseed oil and sesame seed oil are not viable sources of n-3 but they have high content of omega-9 variety of fatty acids (oleic acid) which may protect n-3 from oxidation and spoilage.

The animal saturated fat may or may not be a source of n-6 vs. n-3 fatty acids depending on feed received by the animals. For example, beef from grain (corn) fed animals would have higher proportions of n-6 to n-3 fatty acids while grass fed animals would provide meat high in n-3 fatty acids. Therefore animal fat, eggs, dairy and butter from nutritionally sound stock will provide healthy storage fat with healthy proportion of n-3/n-6 fatty acids, which eaten in moderation and combined with a sensible life style, will not contribute to obesity – giving credit to the Atkins diet. Therefore n-6, n-3 fatty acids, saturated fatty acids and contained fat-soluble vitamins A, D, E and K2 are all important to maintain metabolic health, however their excessive and unbalanced consumption will contribute to metabolic deterioration, overweight and obesity conditions.

THE BODY FAT THAT MATTERS: RISK FACTORS VS. CAUSE OF OBESITY

Obesity and overweight conditions in pandemic proportions resemble unmanageable health problem from another time in human history: before the discovery of antibiotics when infectious diseases decimated populations due to the disease process that was poorly understood and left without effective treatment. The cause was unknown and therefore the treatment was unknown. Similar to times when bacteria and

antibiotics were unknown and blood-letting was a common and a futile practice to treat infectious diseases, so now we are presented with an urgent need to discover a true cause and the equivalent solution to the pandemic proportions of obesity and metabolic deterioration.

There are many promising nutritionals in the field of fighting overweight and obesity but they need to be systematically and consistently researched to arrive at a safe and effective weight management product. The reason "why" we are losing battle with obesity may be as simple as the lack of distinction between the cause of obesity, and the risk factors that increase the likelihood of developing overweight or obese conditions. The calorie-dense Western-type diet, super-sizing meals, overeating, snacking and sedentary life style qualify as the risk-factors. However, a common cause of obesity may ultimately be not in the calories, carbs and fats but in the mechanism that directly and actively promotes obesity.

Each of us has a natural protective metabolic mechanism against obesity which can be overwhelmed when the body is frequently barraged by food. When we arrive to that turn-around point the body can respond with misguided pathological mechanisms, which in time become the cause of obesity and/or type 2 diabetes mellitus. One such mechanism is due to excess dietary fatty acids that gradually incapacitate hepatocytes (liver cells), and compromise one of the major functions of the liver, oxidation and utilization of fat for energy. A liver burdened with accumulated fat clinically is referred to as non-alcoholic fatty liver disease (NAFLD), and can be compared to a vacuum cleaner clogged with excess dirt. As a result of the "clogged" liver condition nutritional fat is deposited throughout the body, leading to a characteristic central or abdominal obesity pattern. Typically, people with NAFLD present several co-morbidities along with obesity, e.g. adult-onset diabetes mellitus and metabolic syndrome.

TARGETING THE CAUSE: FAT REGULATING FAT

Although NAFLD was discovered and named in 1980, only recently it is increasingly recognized as a leading cause of chronic liver disease in the western world (2-5). Nutritional intervention such as balanced diet is well-known as the first line of defense against NAFLD. However, the emerging target mechanisms in dietary intervention against NAFLD and co-morbid conditions is the endocannabinoid system (ECS) and its role regulating metabolic functions, satiety and energy homeostasis (6). The ECS, which also regulates mood, memory and pain sensation, owes its name to *Cannabis indicis*, since it mediates the psychoactive effects of cannabis.

The ECS consists of circulating endocannabinoids derived from cell membrane n-6 fatty acids, mainly arachidonic acid, and the corresponding network of cannabinoid receptors 1 and 2, i.e. CB1 and CB2 scattered throughout the body especially in some of the oldest parts of the central nervous system (CNS) i.e. limbic system, hypothalamus and medulla oblongata (7). Those brain structures command the most basic functions of the organism like motivation and drive, e.g. compulsive behavior, functions of the autonomic nervous system and endocrine system. The ECS is well recognized in the literature for its appetite-promoting or orexigenic effects utilized in *Cannabis* medical applications in terminally ill and cachectic patients. The CB1 receptors are among the most important receptors in the central nervous system, but also found in metabolic organs such as the liver, adipose tissue, gut, pancreas and skeletal muscle. The CB2 receptors are predominantly operating in the immune and haemopoietic systems, but also present in the brain, liver, pancreas, adipose tissue and cardiac muscle.

The high-fat diet and obesity stimulate the ECS and upregulate CB1 and B2 receptors by increasing synthesis of endocannabinoids activating CB1 and CB2 receptors (8). Therefore, circulating endocannabinoids could be considered the markers of the nutritional status and they tend to be significantly higher in overweight and obese individuals as compared to non-obese individuals. The two main endocannabinoids operating the ECS are anandamide or AEA and 2-arachidonoylglycerol or 2-AG, activating CB_1 and CB_2 receptors but also PPAR (peroxisome-proliferator-activated receptor) α and PPARγ, which play important roles in obesity and diabetes.

The overactive ECS increases appetite, builds up insulin resistance, slows down glucose metabolism and increases storage fat production (lipogenesis and adipogenesis) by exerting its action in the CNS, the liver (hepatocytes), adipose tissue (adipocytes), skeletal muscle and pancreatic islet cells. The overactive ECS and accumulating liver fat result in shutting off metabolic functions of hepatocytes and beta-oxidation of fatty acids for vital energy, reduced sensitivity to insulin, glucose intolerance, further increase the appetite levels and fuels NAFLD (9). The activation of CB2 receptors and the immune system compounds the NAFLD pathology, generating the pro-inflammatory interleukin IL-6 and (tumor necrosis factor alpha) TNF-alpha, leading to chronic inflammation and metabolic deterioration of the liver. The increase in circulating endocannabinoids, activation of CB1 and CB2 receptors and NAFLD positively and significantly correspond with increased body mass index, waist circumference, abdominal adiposity, overweight and obesity, pre-diabetes, diabetes and metabolic syndrome.

THE FIRST STEP: HEALTHY-FAT DIET

As the endocannabinoids are predominantly products derived from dietary fats, the healthy diet consisting of eating whole, unprocessed foods, low in polyunsaturated n-6 and high in polyunsaturated n-3 fatty acids, is – and should be considered to be – the first line of approach to down-regulate the overactive ECS and its metabolic consequences (10-14). Providing metabolic health-promoting n-3 fatty acids and replacing n-6 fatty acids also serves the purpose to gradually diminish synthesis and availability of endocannabinoids. The stress is on "gradually diminish synthesis" as opposed to the pharmacological approach of blocking of overactive ECS and CB receptors – the latter mechanism being known to effectively reverse metabolic deterioration and obesity but also to negatively affect the mood – e.g., Rimonabant®.

The task of gradual nutritional intervention to normalize the ECS is accomplished in two ways by:
i) consuming an n-3 fatty acids rich diet that would compete with n-6 fatty acids for enzymes (desaturase and elongase) in the gastrointestinal tract; and ii) providing n-3 long chain polyunsaturated fatty acids, i.e. EPA and DHA, which would directly substitute long chain polyunsaturated n-6 fatty acids, e.g. arachidonic acid in the cell membrane. Dietary n-3 polyunsaturated fatty acids are known to improve NAFLD and related overweight and obesity conditions presumably by slowing down metabolic pathways leading to synthesis of endocannabinoids (15-18). Regular consumption of fish, fish oil or krill oil and plant sources of n-3 fatty acids may competitively replace arachidonic acid in the liver cell membrane bilayers and gradually diminish availability of arachidonic acid as a substrate for production of endocannabinoids, thus preventing an overactive endocannabinoid system.

The n-3 long-chain polyunsaturated fatty acids, which may directly replace n-6 long-chain polyunsaturated fatty acids in

the cell membrane phospholipids, refer primarily to 20-carbon eicosapentaenoic acid (EPA) and 22-carbon docosahexaneoic acid (DHA) found in fish, krill and microalgae. Besides the marine food source "long chain" fatty acids can be obtained from "short chain" or 18-carbon fatty acids, like alpha linolenic acid (ALA), found in chia seeds, flax seeds, rapeseeds and forage – this "replacement" is accomplished through the action of gastrointestinal enzymes desaturase and elongase. The healthy-diet effect to enrich cell membranes with n-3 fatty acids is further enhanced when DHA and EPA are supplemented as phospholipids rather than triglycerides – krill oil's DHA and EPA are predominantly in the form of phospholipids and are potentially more efficient in building cell membrane phospholipids than fish oil's DHA and EPA that are in the form of triglycerides.

The influence of dietary EPA and DHA from krill and fish on levels of circulating endocannabinoids in overweight and obese individuals was evaluated in a 4-week, randomized, double-blind clinical trial conducted at two research sites (19). The study included 63 healthy overweight and obese men and women, 35 to 64 years old who were randomly assigned to receive 2 g/day of either krill oil, fish oil, or olive oil (control). The short duration study did not produce changes in body weight or body mass index (BMI), however it lowered circulating endocannabinoids, indicating a positive change in body metabolism. At baseline, plasma AEA levels were significantly higher in obese subjects, whereas plasma 2-AG levels were significantly higher only in overweight subjects. At the conclusion of the study supplementation with krill oil resulted in a significant decrease in 2-AG levels in the obese subjects with a trend to decrease 2-AG in overweight subjects. The decrease of 2-AG correlated well with the decrease of plasma n-6/n-3 ratio, and krill oil supplementation was more effective in reducing endocannabinoid plasma levels than in the fish oil supplemented group. The relatively low doses of supplemental EPA and DHA for a relatively short period of time can significantly decrease circulating endocannabinoids and improve plasma n-6/n-3 ratio in obese and overweight subjects.

PREVENTING EXCESS DIETARY FAT ABSORPTION

While healthy lifestyle and diet that includes n-3 polyunsaturated fatty acids may be a cornerstone targeting overactive ECS, the intervention to prevent excess gastrointestinal fat absorption may provide an additional and critically important synergistic effect.

Inhibition of pancreatic lipase in dietary fat digestion and absorption has been utilized in weight management and has been proven an effective strategy in metabolic health. This strategy has been supported with the 24-week pilot study of known pancreatic lipase inhibitor Orlistat® (120 mg tid) vs. placebo in obese subjects and evaluating weight loss, glycemic control and composition of n-3 fatty acids in skeletal muscle (biopsy) (20). At the conclusion of the 24-week clinical protocol, the Orlistat® group showed significant weight loss in comparison with the untreated control – 3.9 kg vs. + 2.2 kg ($p < 0.05$), improved glycemic control over placebo, and improved composition of n-3 polyunsaturated fatty acids in skeletal muscle over control, i.e. DHA 51% vs. 17%, EPA 34% vs. 32% and total n-3 polyunsaturated fatty acids 31% vs. 14%. Despite the small sample and the preliminary findings, this study is important to show that pancreatic lipase inhibitor may improve polyunsaturated n-3 fatty acids status and improve glycemic index while decreasing body weight in obese individuals over the untreated control; presumably selectively preventing dietary fat absorption.

However, excessive pancreatic lipase inhibition e.g. tetrahydrolipostatin (Orlistat, Alli) has also several known side effects, i.e. unpleasant gastrointestinal issues – steatorrhea (oily, loose stools with excessive intestinal putrefaction and flatus due to unabsorbed fats reaching the large intestine), fecal incontinence, frequent bowel movements and urgency, compromised absorption of fat-soluble vitamins and nutrients, increased appetite, and diminished effectiveness over time (21).

Therefore, to safely and effectively control an overactive endocannabinoid system, there is a continuous need to develop safe and effective regimens preventing gastrointestinal absorption and accumulation of excess dietary fat. The herbal composition FB^{3}® Fusion Ingredient that features *Coleus forskohlii*, *Salacia reticulata*, and *Sesamum indicum* – standardized for diterpene forskolin, kotanol and salacinol, and sesamin respectively – has been shown to inhibit pancreatic lipase with differing degrees and dynamics. In a placebo-controlled, 6-week clinical study the daily intake of 1000 mg *C. forskohlii* stand-alone standardized for 10% diterpene forskolin, showed statistically significant lowering of total body fat vs. baseline and placebo group. The computerized tomography showed a decrease of total body fat and visceral fat in the *C. forskohlii* group in comparison to the baseline. In the placebo group caloric intake was higher by the end of six weeks and in the *C. forskohlii* group caloric intake was significantly lower in that same duration. The potential of three herbal extracts in FB^{3}® Fusion Ingredient preventing dietary fat absorption has been emphasized by the *in vitro* synergy between *C. forskohlii* and *S. reticulata* inhibiting pancreatic lipase at a higher rate than the fat-blocking activity generated by each component alone. The *in vitro* addition of *S. indicum* to the formula has been found to synergistically assist inhibition of the pancreatic lipase in a lower dose range, while moderating the pancreatic lipase inhibition in a higher dose range. This dual mechanism of *S. indicum* has been postulated as a safety mechanism preventing any potential side effects resulting from excessive inhibition of pancreatic lipase activity.

Based on the preclinical and clinical evaluation, FB^{3}® Fusion Ingredient shows potential for safe and effective prevention of excessive dietary fat absorption (21).

THE METABOLIC HEALTH STRATEGY

What becomes apparent in the field of research for a universal safe and effective weight loss strategy is that healthy living and nutrition alone will not prevent the pandemic proportions of obesity and diabetes. A strategy addressing the cause rather than risk factors is required that would, like the aforementioned antibiotic comparison, prevent and stop obesity and related metabolic conditions regardless of geography of affected population. Clearly "fat" is not only proverbial in describing obesity but a key to finding a cure for obesity and co-morbid conditions. Addressing body fat with a "fat solution" rather than addressing risk factors alone emerges as viable approach potentially solving the epidemic of obesity. Conversely, addressing the risk factors alone would likely have negligible impact on obesity with the outcome comparable to the results of new-year fitness resolutions.

The endocannabinoid system in the human body operates via one of the oldest structures in the brain, the limbic system, which regulates most basic functions commanding our daily life. Therefore, normalizing the ECS preventing excess fat intake and body fat build-up may prevent metabolic deterioration. Pharmacological blocking of the ECS has been found effective in sustained weight loss, including normalizing excessive food consumption and independently preventing body fat accumulation. However, the detrimental effect on mood by blocking endocannabinoid receptors

rules out ECS blocking as a viable strategy for metabolic health.

On the other hand, the aforementioned strategy for a gradual substitution of the most commonly consumed fatty acid, linoleic acid, with n-3 fatty acids to prevent NAFLD and obesity emerges as a plausible cause-oriented strategy normalizing the overexpressed ECS. The proposed strategy in addition to healthy lifestyle and diet is based on incorporating consumption of the botanical food supplement FB^{3}® Fusion Ingredient to prevent excess dietary fat absorption based upon the safe and effective pancreatic lipase inhibition mechanism. Based on emerging experimental data, such a strategy would not only prevent build-up of excessive storage "white" fat but may also enhance absorption of n-3 polyunsaturated fatty acids while synergistically helping to normalize the overactive ECS. To sum up, improving cell membrane composition with lipids, the oldest class of information biomolecules, may help upregulate the oldest parts of the brain, limbic system, to regain the metabolic health.

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