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Kalori Kısıtlaması ve Sağlığa Faydalı Etkilerine Bir Bakış

A Review of Calorie Restriction and Beneficial Health Effects

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ÖZ

Kalori kısıtlaması yıllardır araştırmalara ve çalışmalara konu olmuştur. Kalori kısıtlaması geniş bir tanım olması ile beraber kısıtlamanın uygulanma şekli, zamanı, miktarı ve hangi durumlarda yapılacağı oldukça önemlidir. Kısıtlama yapılırken karbonhidrat, yağ ve protein dengeleri iyi değerlendirilmelidir. Ancak bu kısıtlama, yetersiz beslenmeye sebep olmaksızın uygun koşullarda yapıldığı zaman çeşitli olumlu etkileri göstermektedir. Kalori kısıtlaması ile serbest radikallerin üretimi ve sebep oldukları oksidatif stres azaltılır. Yaygın olarak görülen kronik hastalıklarda uygulanan medikal tedavilere ek; alternatif bir yöntem olarak hastalığa özgü gerekli kalori kısıtlamaları ile yaşamsal fonksiyonlarda düzelmelerin meydana geldiği görülmektedir. Sağlığın yaşam boyu sürdürülmesi ancak dengeli beslenme, düzenli ve sürekli egzersiz programı ile birlikte mümkündür. Beslenme hayatın her döneminde dikkat edilmesi gereken bir konudur. Uzun ve sağlıklı bir yaşam sürmede en önemli kilit noktalardan birinin beslenme olduğu unutulmamalıdır. Bu nedenle bu derlemenin amacı; güncelliğini korumakta olan ve araştırmaları süren bir konu olarak kalori kısıtlamasının bazı faydalı etkilerine yapılan çalışmalardan örnekler ile değinerek dikkat çekmektir.

Anahtar Kelimeler: Kalori kısıtlaması, Diyet, Beslenme, Sağlık.

ABSTRACT

Calorie restriction has been the subject of research and studies for years. Although calorie restriction is a broad definition; the way, time, amount and situations of restriction are very important. While restricting, carbohydrate, fat and protein balances should be well evaluated. However, this restriction shows various positive effects when done under suitable conditions without causing malnutrition. With calorie restriction, the production of free radicals and the oxidative stress they cause are reduced. In addition to medical treatments applied in common chronic diseases; as an alternative method, it is seen that improvements in vital functions occur with the necessary calorie restrictions specific to the disease. Maintaining health throughout life is only possible with a balanced diet, regular and continuous exercise program. Nutrition is an issue that needs attention in every period of life. It should not be forgotten that one of the most important key points in living a long and healthy life is nutrition. Therefore, the purpose of this review; is to draw attention to some beneficial effects of calorie restriction, as a topic that is still up-to-date and researches, by giving examples from studies.

Key Words: Calorie restriction, Diet, Nutrition, Health.

1. INTRODUCTION

Calorie restriction is the reduction of food intake to below the ad libitum level without malnutrition. With calorie restriction, the production of free radicals and the oxidant damage they cause are reduced (1). For the first time in 1935, Clive McCay and his colleagues found

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that the maximum and average life expectancy of mice increased due to growth retardation by reducing the amount of consumption (2). Today, the numerous beneficial effects of calorie restriction on health can be listed as follows; reducing the risk of cardiovascular disease, improving insulin sensitivity in diabetes, reducing oxidative stress and improving cognitive function. Calorie restriction (CR) reduces calorie intake by 30-40% while preserving protein, vitamin, mineral, water intake to ensure proper nutrition.

In a study, rats were divided into 2 groups as ad libitum and calorie restriction, the calorie restriction group was given enough food tosupply 65% of their daily energy needs. After 6 weeks, each group was divided into two and half were given saline and the other half were given acetate. Superoxide dismutase and GSH-Px (Glutation peroxidase) activities were significantly increased in the livers of rats, and lipid peroxidation levels were decreased in the calorie restriction group (3).

In a randomized trial of calorie restriction, calorie restriction was applied for six months. Positive physiological changes such as fat distribution, body temperature, fasting insulin, T3 and T4 and ghrelin levels were observed as a result of the study (4). In calorie restriction; while glycolysis decreases, gluconeogenesis and transamination pathways accelerate. And thus, the oxidation of nutrients that are out of the glycolytic pathway is expedited. For example, fructokinase enzyme, which is effective in fructose metabolism, was found to be more active in calorie-restricted mice compared to control groups (1). Some changes observed as a result of calorie restriction are shown in Table 1(5).

Table 1. Some of the changes observed as a result of calorie restriction (5).

Decreased effects as a result of calorie restriction	Increased effects as a result of calorie restriction
Glycolysis ↓	Gluconeogenesis ↑
Oxidative stress ↓	Mitochondrial respiratory rate ↑
DNA damage ↓	Glycogenolysis ↑
Synthesis of cholesterol, fatty acid and triglyceride ↓	Protein and fatty acid catabolism ↑
Inflammation ↓	

Calorie Restriction and its Effects on Aging

Caloric restriction acts as an anti-aging in old age and aging process or as a preventive effect on age-related diseases such as chronic nephropathies, cardiomyopathies, diabetes, autoimmune diseases and respiratory diseases (6).

Studies in monkeys have reported that calorie restriction reduces brain atrophy and age-related diseases. The application of caloric restriction to aged mice for 10 days resulted in suppression of age-related oxidative stress and inflammatory processes, which lead to impaired brain functions. In adult rodents, dietary restriction for 6 months resulted in better consolidation and memory. In studies conducted on volunteers, it has been shown that 30-20% calorie restriction for 3 months provides an increase in word memory values (7).

Mechanisms of therapeutic and neuroprotective effects of calorie restriction; has been reported that reducing reactive oxygen species, improving mitochondrial function, which increases energy production, decreasing the expression of proapoptotic factors and increasing the expression of neuroprotective factors such as neurotrophic factors (8). Long-term calorie restriction that does not cause malnutrition and reduction in function mutations in the insulin/IGF-1(Insulin Like Growth Factor-1) signaling pathway have been shown to be the strongest attempts known to prolong maximum lifespan in rodents. IGF-1 plays an important role in the regulation of cellular processes. In the nervous system, IGF-1 neurotrophic effects are associated with the correction of age-related cognitive impairment and is a potent regulator of glutamate receptor levels (9). Calorie restriction reduces serum IGF-1 concentration in rodents by approximately 40%, and the reduction in IGF-1 level associated with this calorie restriction is believed to play a key role in regulating its antiaging and anticancer effects (10). But in another study; plasma IGF-1 levels were measured in animals fed ad libitum and calorie restricted. It has been shown that the level of IGF-1 decreases slightly with age, that the level of IGF-1 is lower in calorie-restricted animals compared to animals fed ad libitum, and this level is fixed throughout life (9). Increase in insulin sensitivity, increase in the levels of hormones that suppress inflammation (such as cortisol, adiponectin, ghrelin), decrease in the levels of anabolic hormones (such as insulin, testosterone, leptin), decrease in the levels of hormones that regulate thermogenesis and cell metabolism (such as triiodothyronine, norepinephrine) contribute to the anti-aging effects of calorie restriction are important metabolic adaptations related to calorie restriction that have been shown to play an important role in mediation. It has been observed that calorie restriction has effects such as delaying aging and preventing various pathologies related to aging, as well as preventing obesity. Certain regions of rodent models of both aging and obesity, particularly the corpus callosum, fornix, and hypothalamus, are characterized by inflammation. Microglia, which is the main component of the central nervous system, is important for brain development, nerve support and homeostasis. Diet and lifestyle also affect microglia during aging (11).

In a study on mice, the effects of high-fat diet (HFD) or low-fat diet (LFD) on changes in microglia phenotype and functions in different brain regions of mice during aging were investigated. Expression levels in genes associated with immune response, phagocytosis and metabolism in the hypothalamus of 6-month-old HFD and LFD mice and 24-month-old mice, and finally, the effect of diet, physical exercise and caloric restriction were investigated. In conclusion, it was observed that phagocytic markers in white matter microglia of the 24-month-old brain were significantly reduced in calorically restricted LFD mice, where changes in diet caused morphological changes in microglia. As a result, LFD caused a decrease in microglia activation. This may be an underlying mechanism for the protective role of aging-associated calorie restriction. The detrimental effect on the brain created by HFD is predominantly seen in the hypothalamus. The hypothalamus has an active and important role in nutritional behaviors and neuroendocrine/autonomic outputs (11).

In another study, the effect of diet on oxidant and antioxidant markers was investigated in rats who underwent calorie restriction by reducing the calorie intake by 60% for 10 weeks. As a result, while calorie restriction reduces lipid peroxidation, it also reduces antioxidant enzyme consumption. Again, it can reduce the formation of free radicals; so calorie restriction

can be a protective measure against many diseases in which free radicals play a role and the negativities in the aging process (12).

Resveratrol use and calorie restriction are powerful treatment options that can be used to delay aging. Resveratrol is a plant polyphenol and is commonly found in a variety of plants such as strawberries, grapes, and peanuts. Using resveratrol in dietary supplements or incorporating it into foods can be a powerful option to delay aging. Some reports show that resveratrol therapy produces beneficial effects similar to those produced by calorie restriction.

Resveratrol and calorie restriction demonstrated similar anti-aging activities, proven in a combined study by inhibiting aging and apoptosis, restoring cognitive impairment and oxidative damage (13).

Calorie Restriction and its Effect on Depression

Calorie restriction is receiving increasing attention with its effects on the neuroendocrine system and state of mind. It has been shown by both basic and clinical studies that calorie restriction triggers the intracellular signaling pathway including the stress response and neuron metabolism. Many of these have been recognized as important regulators of depression. At the same time, the question of whether calorie restriction has positive or negative effects on neuropsychological conditions is still controversial. Moderate exercise, when added to short-term and mild calorie restriction, enhanced its antidepressant effects by activating neuroendocrine hormones to compensate for energy deficiency. However, severe dietary restriction in long-term calorie restriction or fasting inevitably damaged neurons and caused exaggerated depressive behaviors (14).

Decreased neurogenesis affects the occurrence of depression and anxiety. Hippocampal neurogenesis may be presented as a potential new strategy in the treatment of depression. It has also been reported that the antagonistic hormones leptin and ghrelin play a role in determining the mental state. Levels of acyl-ghrelin, an orexigenic gastrointestinal hormone, increase for a while during fasting. Both ghrelin and leptin are transported across the blood-brain barrier in order to implement their central effects. In hippocampus, ghrelin is a growth hormone secretagogue receptor ligand. Studies have shown that; caloric restriction applied for 8 days lowers leptin levels. Studies in rodent models have shown that fasting increases brain use of tryptophan and serotonin. Interestingly, reducing the number of calories consumed ensures the survival of newly formed cells in the hippocampus. Moreover, chronic mild food restriction activates AMPK (AMP-activating protein kinase) after reduced hypothalamic malonyl-CoA, inhibitor of fatty acid oxidation (15).

Decreased cerebral blood flow is associated with the occurrence of anxiety and depression. Calorie restriction in young 5-6 month old mice increased cerebral blood flow and blood-brain barrier function in mice and has been shown to be protective for cerebral blood flow in older adult rodents. It has been shown that acute, short-term and long-term calorie restrictions activate the HPA axis (hypothalamic pituitary adrenal axis), cause an increase in glucocorticoid levels and improve depressive symptoms. The mechanism by which this increase in glucocorticoids triggers neuronal survival and enhances BDNF (brain-derived neurotrophic factor) is not fully known (15). The most likely mode of action of energy restriction in neurological disorders is via BDNF signaling. BDNF is associated with brain health, food intake, and glucose metabolism. It is known to increase the amount of neuronal

glucose transporter (GLUT-3) and glucose utilization in the brain. Increased BDNF level has been associated with decreased symptoms of depression. The goal of dietary restriction is to increase BDNF levels. Studies have shown that glycemia and high-fat diets have negative effects on BDNF levels (16).

Implementation of 25% calorie restriction in energy intake for six months reduced depressive symptoms. In another uncontrolled study by Michalsen et al., the effects of calorie intake of 250 kcal/day for 2 weeks were examined in patients with chronic pain. In conclusion, improvement in depressive mood disorder was seen in more than 80% of patients (17). Antidepressant effects of this type have been found to result from increased neurotransmitters such as serotonin and endogenous opioids (14).

In a study conducted to investigate the effect of low-calorie diet therapy on the degree of depression and eating behavior in overweight and obese individuals, the mean score of the BDS (Beck Depression Scale) pre-test was found to be 13.0±8.3, while the BDS post-test the mean was found to be 11.6±7.2. A decrease was observed in the BDS after diet treatment. The difference between these two measurements was statistically significant (18).

Calorie Restriction and its Effects on the Cardiovascular System

Lifestyle changes are generally recommended in cardiovascular diseases. Implementation of calorie restriction among lifestyle changes and regular endurance-enhancing exercises delay the signs of vascular aging. It has been reported that this delay is mediated by increasing sirtuin levels, PGC-1α (Peroxisome proliferator activated receptor gamma coactivator-1 alpha)-dependent mitochondrial biogenesis, and eNOS (Endothelial nitric oxide synthase) functions (19).

Increase in body weight and presence of obesity; It is known as risk factors for many weight problems such as hypertension, especially visceral adiposity. Minimizing the harmful effects of these risk factors through calorie restriction usually lowers blood pressure. Studies have shown that systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure can be reduced by applying calorie restriction. Medically supervised studies of fasting and calorie restriction tend to be shorter and often yield beneficial results regardless of sodium intake (5). In the study of Blumenthal et al., it was shown that the addition of exercise in addition to calorie restriction reduced blood pressure by an average of 16.1 / 9.9 mmHg over four months in hypertensive subjects. This finding was greater than the effect of a high antihypertensive drug on blood pressure. At the end of the treatment, the calorie restriction group was still found to be hypertensive at a higher rate than in the calorie restriction + exercise group, suggesting that the effects of calorie restriction and exercise may contribute to blood pressure in hypertensives (20).

In a study in mice, the possible effects of calorie restriction (feed) on body weight of basic biochemical values such as blood LPO (lipid peroxidation), HDL (High density lipoprotein) and LDL (Low density lipoprotein), TG (triglyceride), AST (aspartate amino transferase) and glucose were investigated. The study was carried out for 60 days in 3 different groups, as 1st control, 2nd calorie restricted (40%) group, 3rd calorie restricted (60%) group. A significant decrease was observed in LPO values and triglyceride levels in the 2nd and 3rd groups. It was determined that especially the 2nd group, which was applied 40% restriction, showed the lowest LDL and highest HDL rates. The blood glucose levels were the lowest, especially in the 3rd

group (21). CRP (C-reactive protein) and other cytokine levels were observed to be low in individuals with calorie restriction. Considering this decrease as an indicator of decrease in proliferation and inflammation, it shows that calorie restriction can prevent vascular endothelial thickening, loss of elasticity and atherosclerosis (22).

Subcutaneous abdominal fat is browner in women than in men with obesity. Caloric restriction reduces browning properties in subcutaneous abdominal fat (23).

A prospective intervention study was conducted with 27 obese type 2 diabetes patients with coronary artery disease. In this study, patients were followed on a very low calorie diet (VLCD, 450-1000 kcal/day) for 16 weeks. As a result, calorie restriction was found to improve cardiovascular function when added to optimal pharmacological treatment for glycoregulation in patients with advanced type 2 diabetes (24).

Weight loss has a positive effect on improving endothelial functions. In studies on calorie restriction, it is known that weight loss can be achieved with lifestyle changes and exercise. It has been proven in studies that increased physical activity provides regeneration of coronary vessels and improvement of aortic endothelial dysfunction in mice with type 2 diabetes (22).

In the case of heart failure, nutritional deficiencies ranging from mild to cachexia can be seen depending on the course of the disease. There is no special diet for heart failure. Excess weight loss is not recommended in these patients. The effects of diet in heart failure are evaluated by insulin activity and insulin like growth factor-1 levels. Moderate calorie restriction is recommended in obese heart failure patients (25).

Effects of Calorie Restriction on Weight Management, Obesity and Insulin Resistance Cycle

Achieving an energy deficit by applying calorie restriction is a common strategy in the management of obesity in the clinic. It has been reported that weight loss induced by calorie restriction reduces insulin resistance and ameliorates many of the metabolic abnormalities seen in obesity and reduces the risk of diabetes (23). Lifestyle modification through calorie restriction and increased physical activity is the most commonly used method in the treatment of obese people with insulin resistance. In recent studies, it has been observed that a 5-7% weight loss occurs with lifestyle changes, and the risk of developing diabetes mellitus is reduced by 58% in people with glucose intolerance (22).

Recent findings suggest an association between obesity, loss of gut barrier function, and changes in microbiota profiles. Therefore, when the effect of caloric restriction in obese women and the effect of subsequent weight loss on intestinal permeability were examined, a 4-week caloric restriction resulted in significant weight loss, improvement of the intestinal barrier, and reduction of systemic inflammation in obese women (26).

A study was conducted to examine the effects of Ramadan fasting and calorie restriction on growth hormone / insulin like growth factor-1 and insulin resistance in obese women (n=23). At the end of the two years follow-up period, it was observed that weight loss was higher in women in the calorie restriction group (27).

While there is a decrease in glycolysis in calorie restriction, there is an increase in the rate of gluconeogenesis and transamination mechanisms. Accordingly, oxidation of other nutrients increases rather than glycolytic mechanisms. For example; It has been stated in the study that

the fructokinase enzyme, which is effective in the use of fructose, is more active in calorie-restricted mice compared to control groups (22).

In a study examining the effect of high fructose food restrictions in obese school-age children, restriction of high fructose foods with reduced calorie and carbohydrate intake did not result in weight loss in school children at the end of 6 weeks; however, triglyceride levels and hepatic steatosis were decreased (28). Again, in a study on young obese mice, mild and short-term calorie restriction prevented obesity-induced cardiomyopathy independent of cardiac metabolic profile (29). Some of the studies examining BMI (Body mass index) with calorie restriction are given in Table 2 (30).

Table 2. Some of the studies examining BMI with calorie restriction (30).

Reference, year and study design	Subjects	Duration	Calorie restriction or dietary calorie	BMI
Shaver et al., 2019, Randomized Controlled Trial	Intervention: 47 Control: 48 Older adults with obesity	24 weeks	Data in the form of total intake of 1100-1300 kcal/day. Type: low calorie restriction (low calorie diet) Estimated reduction of 500-1000 kcal	Intervention Start: 35.2 ± 3.5 Control Start: 35.5 ± 3.0
Ruggenenti et al., 2017, Randomized Controlled Trial	Intervention: 37 Control: 37 Type 2 diabetes	24 weeks	25% restriction of calories	Intervention Start: 30 ± 3.9 [(Obese group (BMI ≥ 30: 33.7(2.4)] End: 28.4 ± 3.8 [(Obese group) Obese (BMI ≥ 30: 31.6(3.0)] Control Start: 29.6 ± 3.8 [(Obese group (BMI ≥30: 32.7(2.9)] End: 29.3 ± 3.7 [(Obese Obese (BMI ≥ 30: 32.5(2.7)]
Ghachem et al., 2017, Observational Study	With Metabolic Syndrom: 20 Without Metabolic Syndrom: 53 Obese postmenopausal women with and without the metabolic syndrome	24 weeks	Calorie restriction (500 to 800 kcal) Energy intake; Carbohydrates: 55%, Total fat: 30%, Protein: 15%	With Metabolic Syndrom Start: 34.5 ± 4.7 End: 31.8 ± 4.4 Without Metabolic Syndrom Start: 31.7 ± 4.3 End: 29.7 ± 4.2
Joris et al., 2016, Randomized Controlled Trial	Intervention: 21 Control: 25 Abdominally obese men	8 weeks	500 kcal/day continued each week for 4 weeks until the target waist circumference was reached. A diet of 1000 kcal/day was applied for 1-2 weeks. The diet was continued according to the maintenance of body weight in the 7th and 8th weeks.	Intervention: Start: 30.2 ± 1.5 End: 27.1 ± 1.3 Control: Start: 29.9 ± 2.5 End: 30.0 ± 2.5
Beleslin et al., 2007, Observational Study	Women: 77 Men: 33 In morbid obesıty women and men	3 weeks	500-800 kcal /day	Women Start: 43.9±0.8 End: 39.5±0.8 Men Start: 48.8±1.7 End: 43.9±1.6

2. CONCLUSION

There are numerous animal experiments and human studies on calorie restriction on aging, obesity, cardiovascular disease, diabetes, and depression. Antioxidant and anti-inflammatory effects caused by calorie restriction are one of its health-promoting properties. It reduces vascular oxidative stress that develops with aging, helps prevent inflammation and improves endothelial function (30). When applying calorie restriction, care should be taken to avoid malnutrition, because its various positive effects emerge when done under appropriate conditions. It is also known that calorie restriction applied by reducing food intake below the ad libitum level without causing malnutrition reduces free radical production. Although there is not enough information about its positive and negative effects on health, it has become a popular topic. Today, studies on the subject of calorie restriction maintain their continuity. It should be well known how much calorie restriction is made, in which situations it is applied, and its metabolism.

Compliance with the Ethical Standard

Conflict of interests: The authors declared that there are no actual, potential, or perceived conflicts of interest for this article.

Ethical permission: Due to the nature of the research, it is not subject to ethical permission.

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