

Calorie Restriction – An Approach towards Obesity Management

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Abstract

Obesity is increasing worldwide and has become a public health concern due to associated degenerative diseases and morbidity. Even though overweight and obesity are not life threatening, they qualify themselves as a disease entity. The bulk of literature on obesity says that the external environment largely influences the increase in food intake and is termed scientifically as “obesogenic environment”. A “dual approach” that uses both traditional and holistic health can be used to curb this rising trend. Dietary approaches like low calorie diets and increased physical activity are recommended for weight management and prevention of diseases. A number of studies indicate that there is an increased interest in enhancing the use of herbs, bioactive components of foods, traditional diets; owing to their wide spectrum of therapeutic properties for obesity and for the armed forces personnel (under the hypocaloric rations in the field). Therefore, taking the existing scenario of obesity into consideration and the protective role of calorie restriction, this paper provides an insight into the highly convoluted process of dietary restriction and highlights the implications of hypocaloric diets.

Keywords: Obesity; Food; Environment; Nutrition; Calorie

Introduction

Obesity is now widely accepted as a complex interplay between environmental and genetic factors and is associated with significant morbidity and mortality. Overweight and obesity both independently and in association with other diseases cause and aggravate a large number of health problems. The rise in obesity in the last 20 years has accelerated thinking about the study of food intake stimulated by the external environment. The term “obesogenic environment” has entered into scientific discourse and implies that the influence of the external environment is largely responsible for the increase in food intake [1]. Along with the physical and dietetic focused approaches there are a range of other factors that can impact weight management (Figure 1).

Need to Eat vs. Want to Eat

In the past, oral urges have been confused with eating behaviours and hunger with appetite. Appetite was often referred to in the same sense as hunger [2]. Earlier, they both were seen as psychic links of the actual mechanisms which control nutrient balance. With clinical observations, the concepts of hunger and appetite can be distinguished from each other now. Later on, Bruce and Kennedy [3] and Anand [4] conceptualized that there are two types of urges to eat, “hunger” located in the hypothalamus and the other “appetite” located in the cerebral cortex where the effect of the hypothalamic factor may be modified by the cortical influence. The two words – Hunger and Appetite, if taken together would rather be an ill-defined phrase. More recently, Egger [5] gave a lucid distinction between the terms and mentioned that appetite is a function of the brain and the psychological desire to eat. It is intertwined with sensory experiences and determined by neuroanatomic associational experiences. Appetite integrates the nutritional realities of the environment such as the sight and smell of food, emotional cues, social situations, and cultural conventions with the internal metabolic demands of hunger. It can go away when distracted and is therefore generally easier to deal with than genuine hunger when trying to reduce one’s food intake. Hunger, on the other hand is an instinct. Basically, hunger is the biological need to have to eat. It is a constant, urging drive to seek out food, which doesn’t go away with distraction.

The implication is that “liking” may be important for provoking the motivation towards food consumption, but once these are retained it is the upregulation of “wanting” in an obesogenic environment along with insensitivity to homeostatic signals but over-reactivity to external

cues – that promotes over consumption. These changes in the food environment have stimulated food intake beyond what is required to match energy expenditure, and consequently have resulted in weight gain. Hence, need of the hour is to adopt a “dual approach” using both traditional and holistic health practices in order to curb this rising trend in obesity. Low calorie diets have consistently shown to be an effective strategy for losing weight [6], though strict behavioural efforts are needed to maintain the acquired weight loss [7]. In connection, Harvey-Berino [8] highlighted that energy-dense diets rich in fats and refined sugars promote weight gain. Dietary fat restriction alone does not exert effects superior to calorie restriction, thus strengthening the public health message that calories do count.

Calorie Restriction (CR) is a major form of dietary restriction

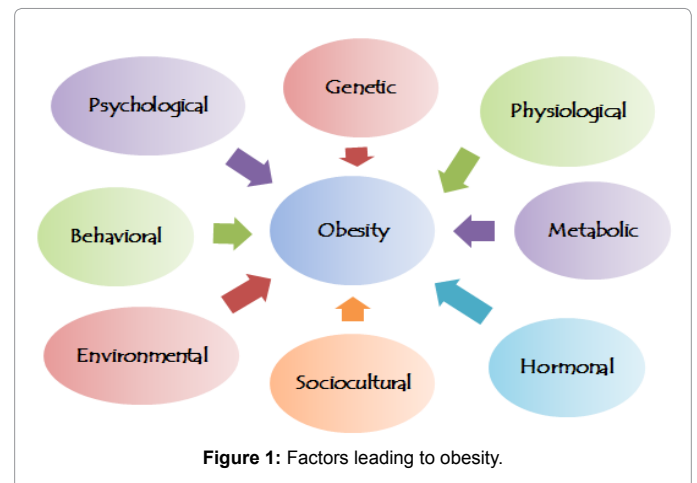


Figure 1: Factors leading to obesity.

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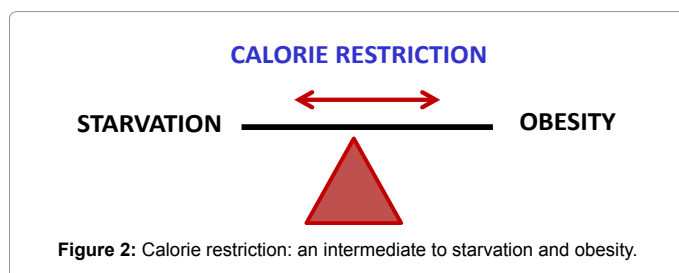
which consists of decreasing daily energy intake by 15-40% of baseline needs. Although, the intake of calories is reduced, sufficient intake of vitamins, minerals and other essential nutrients must be maintained. The amount of food that can be consumed has two extremes: i) low enough to cause death from starvation, and ii) high enough to lead to obesity, CR lies between these two extremes (Figure 2). CR is the only non-pharmacological intervention known to date, with the potential to extend longevity and improve health parameters and indicators of diseases [9].

Research on CR began much earlier than the twenty first century. A considerable amount of research in the first decade of twenty first century has been an extension to the explorations done in the nineteenth century itself. Restricting energy intake has been explored since 1914, when Francis Peyton Rous reported how reducing food intake inhibited the occurrence of cancers in rodents [10]. A few years later, Osborne and Mendel [11], demonstrated that decreasing food intake led to increased life span of rats. This relationship got stronger scientific basis when McCay et al. [12] reported that retarding the growth of rats by reduction of calorie intake extended their life. This research group pioneered the classic calorie restriction studies on the laboratory rat, which showed that long term 40% CR without malnutrition reduces body weight and prolongs the life span. In animal experiments, CR is measured as a percentage of food given to an experimental group compared to the amount of food eaten by its own basal food intake or the control group that eats either without restriction or ad libitum e.g., 30% less, etc. So, the first observations were on rodents which were later on observed across wide range of species like yeast, worms and fish [13]. Data from long term prospective trials on humans are lacking, however, there is a lot to infer from a handful of epidemiological and cross-sectional observations in longer-lived humans and individuals who self-impose CR.

History has many examples where during military missions and for local population, food availability was restricted. Both, armies and general population faced starvation on scarcity of food since maintenance of normal food supply was difficult. The World War II reduced the food intake of many people living in Europe which resulted in anti-aging benefits and fewer cases of hypertension, heart disease and diabetes were reported [14]. Surveillance data from Norwegian population exposed to energy restriction during World War II showed reduced breast cancer risk later in life in association with acute (< 1 year) energy restriction (about 50 % CR without major changes in diet quality) [15]. Similarly, in 1940s Scandinavians who were surviving on a semi-starvation diet equivalent to about 20% CR were found to have a reduced incidence of cardiovascular disease [16]. In the fifteenth century, an Italian nobleman Luigi Cornaro reasoned and related his improvement in health to dietary restriction and eventually lived to be a centenarian.

Classical Views and Various Hypotheses on How CR Works

Even though there has been research on CR for over 70 years, the



mechanism by which CR works is still not fully understood. Some of the explanations include reduced cellular divisions, lower metabolic rates, reduced production of free radicals and hormesis. The most widespread theory points to a significant protection from DNA damage due to a reduction of metabolism [17]. Various hypotheses have been proposed to explain the effect of dietary restriction on life span, predominantly in short-lived rodent species, but the role of oxidative stress has attracted the greatest research attention [18]. Recent findings have identified a few molecular pathways that appear to regulate the aging process. Libert and Guarente [19] beheld the view that understanding the molecular mechanisms of CR may lead to the development of novel therapies to combat diseases of aging and thereby improve the quality of life.

Body fat hypothesis

Berg and Simms [20] came up with their hypothesis somewhat 25 years after McCay et al. gave the retardation of growth hypothesis. Their theory came as a challenge wherein they proposed that CR causes life extension by reducing body fat content; based on the growing obesity rates and therefore it was quite reasonable to think that CR would decrease the body fat content. This view was however, mainly supported by nutritionists only. Subsequently, in early 1980's this hypothesis was discredited for many years. A study by Redman and Ravussin [21], demonstrated that a 6 month CR intervention induced a decline in body weight but no alteration in abdominal fat was observed. In support of this contention, a new perspective of fat hypothesis lies with the ability of CR to improve insulin action primarily by reducing visceral fat [22].

Pituitary function and CR

Everitt [23] proposed that pituitary function and CR are linked. He viewed that while pituitary has a role in the regulation of food intake, it is also responsible to cause CR induced decrease in the secretion of an aging factor. The latter view was widely taken up and is still a portent of the current debate on a possible role of the Growth Hormone-IGF-1 axis in the life-extending action of CR. CR induces lower levels of pituitary growth hormone in animals [17]. However, Kenny et al. [24], are the first ones to investigate the effects of chronic mild CR on HPA axis response, and found a slight beneficial effect on stress response. In the midst of the studies, reporting positive findings, there is a dearth of parallel studies reporting the effects of CR on HPA axis.

Metabolic rate hypothesis

Another hypothesis that gained favour over the leading McCay's retardation of growth hypothesis was proposed by George Sacher in 1977. He presented that CR retards aging by reducing the metabolic rate per unit of body mass [25]. Although Sacher had not measured the metabolic rate, this hypothesis was promoted. There are conflicting views surrounding this; McCarter et al. [26] stated that if CR were to slow metabolism, the production of ROS would decrease consequently, which is not the case as observed in various studies. This placed the beginning to bring up research on how to normalise findings on metabolic rate for differences in body size. Sohal and Forster [27] highlighted in their recent review that the effect of CR on metabolic rate is not brief but long lasting.

Biosphere 2 experiment

Further on, in the 1990's Walford et al. [28], reported the effect of CR on primate model, Homo Sapiens. Roy Walford, Lisa Walford, and Brian M. Delaney (founders of CR Society International, 1994) developed a nutrient-rich, very low calorie diet known as CRON-diet

(Calorie Restriction with Optimal Nutrition). The concept of CRON-diet involved the practice of calorie restriction that will improve health and retard aging, along with providing the recommended daily amounts of various nutrients. The CRON-diet was a result of the decades of animal experiments performed by Walford and the Biosphere 2 study [28] and is associated with many physiological, biochemical, and metabolic alterations coherent with CR rodents [21].

Oxidative damage theory

Currently, this hypothesis is the one approved by most biological gerontologists. In 1990's, Lee and Yu [29] documented that oxidative damage is reduced in CR animals. Later on in 1996, researchers Sohal and Weindruch [30] expanded this view and proclaimed that CR extends life by attenuating oxidative damage.

It is certain that CR delays the age-associated accumulation of cellular oxidative damage. However, it is not yet established that oxidative damage plays a major role in the aging process. One of the possible explanations of this hypothesis could be the increased efficiency in transport of electrons through the respiratory chain. This might reduce the production of ROS and slow aging [31]. A different explanation is that CR poses an increased ability to detoxify ROS which in turn slows oxidative damage. There is lower ROS generation observed in isolated tissue mitochondria from CR rodents, which subsequently leads to lower tissue oxidative stress. However, the data relating CR to detoxification of ROS is inconsistent. For example, the expression of sulphur oxide dismutase enzyme (SOD) increases on lifelong CR, but in genetically altered mice there is no consistent correlation in the expression levels of SOD and life span [32].

Hormesis hypothesis

The word "hormesis" is derived from the Greek word "hormaein" which means "to excite". The term "hormesis" was coined by Southam and Ehrlich [32] who described this as any beneficial action resulting from the response of an organism to a low-intensity biological stressor. Research has indicated "hormesis" as an explanation for CR. In the year 1998, investigators Turturro et al. [33] independently proposed this hypothesis. This hypothesis provides a basis for studies aimed at understanding the complex nature of the processes that underlie the anti-aging actions of CR. The view mainly gained support during the twenty first century, as it is increasingly apparent that an interaction of multiple processes underlies the life-extending and anti-aging actions of CR.

Based on the concept of Hormesis, Michael Ristow's group in 2007 postulated mitochondrial hypothesis of CR. They proposed that diet imposes a low-intensity biological stress on the organism, which elicits a defensive response and helps to protect it against the causes of aging and improved health. Perhaps the first experimental evidence for hormesis was presented by this group, on a worm *Caenorhabditis elegans*, which suggested that the restriction of glucose metabolism extends life span mainly by increasing oxidative stress that stimulates the organism into exhibiting an increased resistance to further oxidative stress [34].

Protein turnover

This theory suggests that reduction in protein turnover and accumulation of oxidatively damaged proteins which are also potentially harmful may cause aging [35,36]. Experimental evidences in previous studies led to the conclusion that CR related increase in longevity are associated with enhanced protein turnover [30]. During CR, as there is

reduction in fat biosynthesis, the degradation of proteins is triggered, thereby increasing their turnover. The data suggest an increase in protein turnover during CR, but the elevated turnover during CR is not uniform; although some damaged proteins were degraded, others continued to accumulate [37].

Like all other effects of CR, this is also surrounded with differing results [38,39].

Metabolic Effects of Calorie Restriction

Metabolic changes occur as a result of a two phase mechanism of CR in mammals- i) an adaptive period immediately after the regimen is imposed ii) steady state period, which can last till the lifetime of the animal.

Adaptive Phase: An array of changes takes place during the adaptive phase. Glucose metabolism regulates secretion of insulin from the pancreatic β -cells. As an immediate response to low levels of glucose, the glycogen stores begin to degrade upon the secretion of glucagon from the pancreas. After the carbohydrates have been depleted, lipolysis begins to compensate for the lack of glucose in the blood [40]; also resulting in loss of fat mass in calorie restricted animals [41]. Degradation of fat and protein leads to ketogenesis. Also, liver up-regulates the expression of enzymes involved in gluconeogenesis and down-regulates those in glycolysis [42]. During this phase of CR, metabolism rate as measured by oxygen consumption also declines [43].

Steady State: During this phase, β -cells sense the low glucose levels, and correspondingly produce less insulin, as the blood glucose levels are still below normal level during the steady state resulting in lowered blood insulin levels [44,45]. The organism reaches a steady state in which ketones help meet energy needs of the brain. An increase in the coupling of oxidative phosphorylation to ATP synthesis, by a reduction in levels of uncoupling proteins also takes place leading to a reduction in body temperature [46].

Changes in the Neuroendocrine System

The endocrine system is extremely integrated where a change in one factor affects the other hormone. Neuroendocrine system has long been thought to play a role in aging and many changes observed in the CR mammals indicate a direct or indirect association with the neuroendocrine system. CR alters expression of hormones significantly, resulting in delayed senescence. There is evidence that anterior pituitary hormones - growth hormone (GH), prolactin, thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), impinge on life span and age related pathology. All these hormones contribute to complex physiological functions such as growth, reproduction, mitochondrial function and stress resistance, which have an effect on aging processes. Characteristically, CR mammals have lower levels of GH, TSH, IGF-1, and gonadotropins [47]. Conversely, glucocorticoids, catecholamines, and glucagon increase [48]. Han et al. [49] reported that secretion of most hormones is greatly reduced by CR except corticosterone. The most constant response observed on a CR regime across species and strains has been suppressed circulating insulin levels and increased insulin sensitivity [50].

However, the degree and extent of CR induced is a major determinant for the levels of regulatory peptides. Long term, short term and intermittent dietary restriction feeding regimens may produce different effects on the biomarkers. A study from our laboratory showed

that short term CR (25%) regime when induced for 5 days demonstrated significant effects on appetite regulatory peptides. Plasma levels of orexigenic peptides like ghrelin and NPY were found to be increased with reduction in CCK, IGF-1 and circulating T3 levels, with no change in the insulin levels. Leptin decline has an appetite stimulating effect which explains the lower than the detectable concentrations of leptin observed on short term dietary restriction in rats [51].

Besides, hypocaloric diets are an implication of combat situations also. The soldiers' ration is hypocaloric in energy content relative to their daily expenditure in short term assault situations. This is a limitation imposed by ration design and mission constraints. Research group led by Shukitt-Hale [52] and the committee of IOM [53], articulated some basic ideas about the soldiers' diet and health during the missions (Box-1). As the state of negative energy balance proceeds performance is compromised and appetite is increased, even under stressed conditions [54]. The nutritional composition of ration would be optimized to best sustain physical and cognitive performance and to prevent possible adverse health consequences. The rations designed for short term use by the warfighters must be adequate for the nutritional needs of the extremely intense and highly mobile combat situations [55].

BOX-1
Ration Constraints during Assault Mission

- During combat operations the expected daily energy expenditure is 4000-4500 Kcal, through intermittent periods of high energy expenditure mixed with longer periods of low intensity movement.
- Soldiers possibly have an average energy intake of 2400 kcal/day.
- Assault rations take care of only 60% of the energy needs of the combat soldiers.
- The daily ration must fit in 0.12 cubic feet and weigh 3 pounds or less.
- The soldiers rely on this ration for 3-7 days followed by 1-3 days of recovery when they would have access to more nutritionally complete meals.
- During combat these troops will therefore experience an energy deficit of 1600-2100 kcal/day.

Energy restriction results in a constant feeling of hunger. In concert, Redman and Ravussin [21] in their review indicated the participants on CR regimen, reported an increased desire to eat and a decreased satisfaction of appetite after 6 months. Furthermore, mood and Quality of Life (QOL) indicators are imperative, as a factor to assess the feasibility of CR in humans. While the Minnesota Semi Starvation study [54] indicated that CR can negatively affect mood, the results of the CALERIE and MAEDS trials depict no negative effect on mood; instead found a decline in the symptoms of depressed mood in the CR group. Experimental evidence suggests that that increased appetite has been known to interfere with the ability to perform maximally [55]. Researchers- Gibson and Green [56] reported that it is the psychological preoccupation of food and feelings of hunger that are associated with afflicted performance than by a physiologic effect of low energy intake. Training soldiers to ignore the hunger feelings may be a very challenging task. However, reducing the appetite by hypohydration or stress to the extent that the thoughts of food even are eliminated is not beneficial [57]. A study by Laessle et al. [58] presented that during the low calorie periods the subjects reported stronger hunger pangs, thought more about food and exhibited difficulties concentrating, had greater fatigue than during the *ad libitum* periods even on minimal

weight loss. Therefore, altering the appetite by causing its reduction might be beneficial in elevating mood and cognitive performance. Indeed, Fischer et al. [59] has reported declining hunger sensations to be associated with being more energetic. However, disagreement revolves around the effect on cognitive performance under CR in humans.

To reduce the negative psychological and physiological impact of restricted eating like hunger pangs, a satiety based approach / use of pharmacologic appetite suppressants may be considered [60]. Drugs- the pharmacological agents control or reduce weight by altering the fundamental processes of the human body, like altering appetite, metabolism or absorption of calories [61]. Also, appetite suppressants have found their way already, in suppressing appetite for those under the hypocaloric rations in the field. As reviewed above, the physiological and mental status of the soldiers determine the success of a military operation and maximize performance and effectiveness. Use of appetite suppressants dates back to the First World War, when the drug- MDMA was experimented as an interrogation tool in Project MKUltra by the US Army [62]. British military used 72 million amphetamine tablets in the Second World War. At that time, diets of the soldiers were supplemented with the compound amphetamine, in order to reduce the hunger and to increase their fighting capacity [63].

Soldiers also consume other bio-actives (L-carnitine, creatine) and substances that are already consumed at liberty in either the sports community or the general population (e.g., Ginkgo biloba and Ginseng extracts) with the goal of increasing physical endurance. In recent years, there has been an increased interest among sports community in enhancing the use of herbs, bioactive components of foods and traditional diets to optimize physical and mental performance. These include a variety of substances ranging from essential and nonessential amino acids, metabolites, energy enhancers, muscle builders and stimulants such as caffeine. Recent research has shown that *Hoodia gordonii*, herb of African origin works as an appetite suppressant under short term calorie restriction [64]. Taking into consideration, the extent of physical burden the soldiers go through during operations, developing operation- suitable ration is of importance to enhance soldier's performance. During sustained operations (SUSOPS), combat foot soldiers carry loads in excess of 50 kg for 3-7 days under weather conditions that vary from cold, mountainous to humid, tropical climates. In view of the fact, that the physiological and nutritional status of soldiers can markedly affect the success of military operations discernibly, frontline soldiers might gain a performance edge with the use of non-traditional food components, stimulants, and herbals that might act as ergogenic aids [53,65].

Conclusion

Given that exercise and diet remain the interminable basis for weight control, their use should be collective i.e. with regular exercise as well as dietary and behavioural modifications weight loss can be achieved. Research has shown that use of multiple phytochemicals might result in a synergistic and enhanced effect. Nonetheless, there is lack of evidence to demonstrate that the phytochemicals used as appetite suppressants and anti- obesity agents are effective and safe. Regardless of this, several natural appetite suppressants are available as non-prescription herbal preparations. Even though some plants have shown promising results in the short term, there is still a need for more human clinical trials and longer duration studies to substantiate the traditional claims for these plant extracts. Most importantly, whether the effect is achieved at an appropriate and safe dose remains a matter of investigation. In light of the existing controversy, further research

is needed to determine the actual picture of feasibility and safety of CR in humans for adherence to hypocaloric diets. Nonetheless, this review highlights the importance of calorie restriction in conditions like obesity and combat operations.

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