DIETARY RESTRICTION (DR) AND ITS ADVANTAGES

M. N. Astagimath and Shrinivas B. Rao

Department of Biochemistry, Kasturba Medical College, Bejai, Mangalore

ABSTRACT

Dietary restriction (DR) also called dietary control or calorie restriction is reported to have many advantages with regard to human health. It leads to suppression of obesity, mitigates free radicals and increases available antioxidants which are accounted for extending the life span of individuals. DR is also reported to induce synthesis of heat shock proteins in animals as a control mechanism against stress. Further, it is known to play a significant role in decreasing toxicity and lethality due to a variety of toxic chemicals and drugs by stimulating tissue repair damaged by the toxicants leading to restoration of intact organ and its functions. Moreover, extensive work done on animals indicate DR has an important role in suppressing certain types of cancer. In this review an effort is made to highlight the various advantages of DR from the point of human health perspective.

KEY WORDS

Calorie restriction, hepatocellular regeneration, obesity, cancer, reactive oxygen species, dietary restriction, aging, toxicity

INTRODUCTION

Dietary control, which may also be called as dietary restriction (DR), is an important aspect of food consumption where nutritionally essential components of the diet are not restricted. However, unnecessary intake of food which is more likely to be stored as fat is avoided. DR which is also synonymous with calorie restriction has major health benefits. Experimentally it has been shown that DR consistently decreases the physiological changes associated with aging of mammals (1). DR has also been shown to significantly reduce the incidence of cancer in experimental animals compared to those exposed to unlimited food (2). Further it has been reported (3) that diabetes state of certain obese persons can return to normal after weight loss due to DR. The benefits of DR are far too many but it has not touched the Indian health scenario to the extent seen in advanced countries. Under the circumstances the aim of this review is to highlight the various advantages and beneficial aspects of DR.

a) Obesity and DR

Obesity generally defined as an increase in total body fat is a chronic disease, which poses a serious risk for the development of diabetes mellitus, hypertension, heart disease, gall bladder disease and certain forms of cancer (4). Genetic determinants have been

indicated in some individuals to play a role in the pathogenesis of obesity (5). There is also another group of obese individuals who tend to increase body weight with fat storage due to their uncontrolled eating habits (6). The disposition to obesity in such individuals is more a physiological process than any pathologic attribute (7). It is now well established that obesity needs to be controlled and suppressed. Exercise (8) and vegetarian diet (9) have been suggested to be the most ideal treatment for obesity. Further, modulation in life style strategies (10) have a role in suppressing obesity. Work has also been reported (11) on anorexigenic agents which are indicated to suppress uncontrolled eating habits in mammals leading to obesity. Suppression of obesity extends life in a variety of species (12) attributed to a decrease in reactive oxygen species (13). DR has also been shown to improve immunologic function, neuroendocrine system and glucose homeostasis all of which are due to a decrease in adipose cells and their products (12). A close link has been established between obesity and hypertension (14) and it has been shown that DR lowers blood pressure and improves response to antihypertensive medications (15). Moreover, there is a marked reduction in secretion of growth hormone in obese individuals, which is completely reversed by normalization of body weight by DR (16). Further, it is well established that obesity is the primary causative factor for various types of tumours (17). Thus it is clear that obesity is responsible for many health problems (18,19) and needs to be suppressed by DR taking care to avoid any deleterious effects on the general health of an individual.

Author for Correspondence :

Dr. Shrinivas B Rao
*Department of Biochemistry,
Kasturba Medical College, Bejai,
Mangalore-575 004.*

b) DR and ozone induced lung inflammation.

It is well known that ozone inhalation by humans and animals lead to inflammatory response indicated by oxidative damage (20). However, using rats as a model, it was shown that DR protects the lungs against ozone toxicity by increasing antioxidant ascorbate in bronchoalveolar lavage of rats exposed to ozone, which is responsible for detoxification of reactive oxygen species (21). Further, the role of DR to increase antioxidant status of the body of different species has also been reported by other workers (21,22) and accounts for suppression of oxyradicals generated during metabolic processes. However, the mechanism by which specific antioxidants is increased still remains unclear.

c) Decreased drug toxicity in DR

The drug isoproterenol is a beta-adrenergic agonist, which in low doses is prescribed for certain heart diseases. However, high dose of this drug leads to maximum cardiac output, arrhythmias, cardiac arrest and mortality (23). Experimentally it was shown that rats having uncontrolled access to food when injected this drug intramuscularly at 15 mg/kg body weight, died due to cardiac arrest. However, DR rats injected 300 mg/kg body weight of this drug survived (24). This protective effect in DR rats against isoproterenol was explained as due to rapid onset of hypothermia in these rats which results in an increase of heat shock proteins which protects against cardiac cell damage and mortality (25). Another drug ganciclovir, an antiviral agent is clinically used for a number of cytomegalovirus infections (26). A single dose of 400 mg/kg body weight of this drug fed to mice showed 22 fold lower mortality in DR mice than those who had free access to food (26). The gastrointestinal tract (GIT) injury was responsible for death due to ganciclovir and DR mice showed decreased toxicity due to cell replacement and repair of GIT not seen in animals having access to unlimited food (26). Aspirin and other non steroidal anti-inflammatory drugs are known to cause various gastric mucosal injuries in humans (27) and animals (28). Aspirin caused significant gastric mucosal lesions in rats exposed to unlimited food compared to DR rats who are protected due to higher levels of gastric GSH and ATP which prevent mucosal injury due to peroxidative changes caused by aspirin (29).

d) DR and hepatocellular toxicity

Studies done (30) on carbon tetrachloride potentiation of hepatotoxicity by a pesticide chlordane indicated compromised levels of liver polyamines and ATP necessary for hepatocellular regeneration an event important for recovery from hepatotoxicity. Injecting these rats with fructose-1,6 diphosphate (31, 32) to

increase ATP and polyamine synthesis only delayed mortality without any recovery. This led to the realization that sugars and sugar phosphates suppressed cellular proliferative activity (33). Hepatic tissue repair, damaged by toxicants is absolutely necessary for recovery of animals from hepatotoxicity, lack of which leads to mortality of animals (34-37). This concept was further supported and confirmed by experiments done exposing hepatotoxin thioacetamide to DR rats with sugar levels within limits. Increased hepatotoxic injury due to thioacetamide was seen in these rats but were protected by enhanced liver tissue repair (38) contrary to the lethal outcome seen in animals with uncontrolled food exposure. Earlier onset and higher repair in DR rats allow these animals to escape lethal consequence (39). This is the general mechanism proposed for DR rats for recovery irrespective of the chemicals that cause hepatotoxicity leading to hepatocellular damage (40,41).

e) Cancer and DR

The role of DR and its influence to suppress cancer suggest its reduction of oxidative damage with induction of selective cell growth (42, 43). There is extensive literature suggesting DR modifies neoplastic development primarily during the stage of promotion (44). This was also believed to be due to an increase in antioxidative enzymes leading to modulation of oxidative DNA damage and enhancing DNA repair processes thus affecting various aspects of gene expression in DR rats (45). Further, it has also been shown (2) that insulin like growth factor-1 and its associated regulatory apparatus are involved in endocrine, autocrine and paracrine signaling system in mediating the anti-carcinogenic activity in DR. It has been repeatedly demonstrated that calorie restriction inhibits growth of transplanted or induced tumors in mice or rats (46). A 36 % of restriction in caloric intake dramatically decreased the radiation induced solid tumors and leukemias in animal models though the exact mechanism involved remains unclear (45, 47). In general it is now believed that dietary intake may modulate the basal turnover rates of cell death and proliferation in a direction consistent with a cancer-protective effect in DR mice and cancer promoting effect in mice with free access to food (48). Moreover, there are reports that DR suppresses a wide variety of cancer in animals like breast cancer (46), myeloid leukemia (47), hepatic tissue cancer (48), colon cancer (49) and pancreatic carcinogenesis (50).

CONCLUSION

Animal models controlled by DR results in increased ability to extract energy from food with key metabolic enzymes becoming more efficient (23). DR alters the isoforms of many enzymes collectively called as drug metabolizing enzymes in the liver, kidney, lung, intestine

and endocrine tissues (23) with their enhanced activity. Further under DR certain enzymes like glucose-6-phosphatase, an enzyme of gluconeogenesis functions unhindered at full efficiency (20). DR also induces increased metabolic rate with respiratory quotient indicating direct utilization of food stuffs (20). Suppression of generation of free radicals (51) is known in DR which also enhances the supply of antioxidants (21), thus limiting injury to cellular components. Further, DR also increases heat shock proteins considered as cellular reaction to stress by some (25) while others suggest that they are involved at the central regulatory level to coordinate the response to stress (52). Moreover, all the above-mentioned changes brought about by DR have a profound impact on the animal's ability to preserve the integrity of the genome (20). No significant gender differences are indicated in acute toxicity studies involving DR regimen (20) with biological advantages of DR only reflected in survival. In spite of a fund of information available on the beneficial effects of DR it needs to be practiced with supervision and caution particularly because of various deleterious effects observed when there is an absence of a balanced intake of nutrients and non nutrients (53, 54). It is reported that supplementation of a nutrient against the backdrop of a poor diet does not yield the desired results (55). Further, trace amount of certain food components have a critical role in the ultimate outcome of DR (56). Finally in the Indian context it is unfortunate that the formulation and practice of DR from health perspective has received very little attention and needs greater work efforts in future.

REFERENCES

- Masaro, E.E. (1988) Food restriction in rodents: An evaluation of its role in the study of aging. *J. Gerontol.* 43, 59-64.
- Kari, F.W., Dunn, S.E. French, J.E. and Barrett, J.C. (1999) Roles for insulin-like growth factor-1 in mediating the anti-carcinogenic effects of caloric restriction. *J. Nutr. Health Aging* 3, 92-101.
- Skillman, T.G. and Tzagournis, M. (1978) Diabetes mellitus. College of Medicine, Ohio State Uni. Upjohn publishers.
- Flier, J.S. (2001) Obesity in Harrison's principles of internal medicine, Eds Braunwald, E., Fauci, A.S., Kasper, D.L., Hauser, S.L., Longo, D.L. and Jameson, J.L. 15th Ed, Vol. 1 Mc Graw - Hill N. York pp 479-490.
- Lissner, L. and Heitmann, B.L. (1995) Dietary fat and obesity. Evidence from Epidemiology. *Eur. J. Clin. Nutr.* 49, 79-85.
- Vasudevan, D.M. and Shreekumari, S. (2001) Textbook of Biochemistry. 3rd Ed. Jaypee Brothers Medical publishers Ltd., New Delhi, pp 95-102.
- Kovach, M.K., Hermann, M. and Winick, M. (1999). The psychological ramnification of weight management. *J.Women's Health, Gender Based Medicine.* 8, 477-482.
- Zachwieja, J.J. (1996) Exercise as treatment for obesity. *Endocrinol. Metab. Clin. North Am.* 25, 965-988.
- Kennedy, E.T., Bowman, S.A., Spence, J.T., Freedman, M. and King, J. (2001) Popular diets: correlation to health, nutrition and obesity. *J.Am.Diet. Assoc.* 101, 411-420.
- Cowburn, G., Hillsdon, M. and Hankey, C.R. (1997) Obesity management by life style strategies. *Br. Med. Bull.* 53, 389-408.
- Narasimhaswamy, K.N., Ramaswamy, C., Rao, S.B. and Vasudev, R. (1995) Anorexigenic effect of fecal extract from ventro medial hypothalamic lesioned rats on normal rats. *Indian J. Expt. Biol.* 33, 101-104.
- Barzilai, N. and Gabriely, I. (2001) The role of fat depletion in the biological benefits of caloric restriction. *J. Nutr.* 131:903-906.
- Lindsay, D.G. (1999) Diet and Aging: The possible relation to reactive oxygen species. *J. Nutr. Health Aging.* 3, 77-83.
- Nicolas, A.S., Lanzmann – Petithory, D. and Vellas, B. (1999) Caloric restriction and aging. *J. Nutr. Health Aging.* 3, 77-83.
- Landsberg, L. (1999) Weight reduction and obesity. *Clin. Exp. Hyperten.* 21, 763-768.
- Scacchi, M., Pincelli, A.J. and Cavagni, F. (1999) Growth hormone in obesity. *Int. J. Obes. Related Metab. Disorders.* 23, 260-271.
- Shephard, R.J. and Shek, P.N. (1998) Associations between physical activity and susceptibility to cancer, possible mechanisms. *Sports. Med.* 26, 293-315.
- Levin, B.E. (2000) The Obesity epidemic: Metabolic imprinting on genetically susceptible neural circuits. *Obes. Res.* 8, 342-347.
- Hermansen, K. (2000) Diet, blood pressure and hypertension. *Br. J. Nutr.* 83, 113-119.
- Ramaiah, S.K., Apte, U. and Mehendale, H.M. (2000) Diet restriction as a protective mechanism in non-cancer toxicity outcomes: A review. *Int. J. Toxicol.* 19, 413-424.
- Kari, F., Hatch, G., Slade, R., Crissman, K., Simeonova, P.P. and Luster, M. (1997) Dietary restriction mitigates ozone induced lung inflammation in rats: A Role for endogenous

- antioxidants. *Am. J. Respir. Cell Mol. Biol.* 17, 740-747.
22. Feners, R.J., Duffy, P.H., Leykey, J.E.A., Turlutto, A., Mittelmaedi, R.A. and Hari, R.W. (1989) Effects of chronic caloric restriction on hepatic enzyme of intermediary metabolism in the male F344 rat. *Mech. Ageing Dev.* 48, 179-189.
23. Leakey, J.E.A., Seng, J.E., Barnas, C.R., Baker, V.M. and Hart, R.W. (1998) A mechanistic basis for the beneficial effects of dietary restriction on longevity and disease. Consequences for the interpretation of rodent toxicity studies. *Int. J. Toxicol* 17, 5-56.
24. Duffy, P.H., Feuers, R.J., Pipkin, J.L., Berg, J.F., Leakey, J.E.A., Turturro, A. and Hart, R.W. (1995). The effects of dietary restriction and aging on the physiological response of rodents to drugs. In dietary restriction: Implications for the design and interpretation of toxicity and carcinogenicity studies Eds. Hart RW, Neumann DA, Robertson RT, ILSI Press, Washington DC, pp 127-140.
25. Aly, K.B., Pipkin, J.L., Hinson, W.G., Feuers, R.J., Duffy, P.H., Lyn Cook, L. and Hart, R.W. (1994) Chronic caloric restriction induces stress proteins in the hypothalamus of rat. *Mech. Aging Dev.* 76, 11-23.
26. Berg, T.F., Breen, P.J., Feuers, R.J., Oriaku, E.T., Chen, F.X. and Hart, R.W. (1994) Acute toxicity of ganciclovir, effects of dietary restriction and chronobiology. *Food Chem. Toxicol.* 32, 45-50.
27. Soll, A.H., Weinstein, W.M., Kurata, J. and McCarthy, D. (1991) Nonsteroidal anti inflammatory drugs and peptic ulcer disease. *Ann. Intern. Med.* 114, 307-319.
28. Kauffman, G. (1989) Aspirin induced gastric mucosal injury: Lessons learned from animal models. *Gastroenterology* 96, 606-614.
29. Lee, M. and Devi, B.G. (1996) Effects of dietary restriction on experimental gastric mucosal injury in Fischer 344 rats. *Mech. Aging Dev.* 89, 11-20.
30. Rao, S.B., Young, R.A. and Mehendale, H.M. (1989) Hepatic polyamines and related enzymes following chlordecone potentiated CC1₄ toxicity in rats. *J. Biochem. Toxicol.* 4, 55-63.
31. Rao, S.B. and Mehendale, H.M. (1989) Protective role of fructose 1, 6 – biphosphate during CC1₄ hepatotoxicity in rats. *Biochem.J.* 262, 721-725.
32. Rao, S.B. and Mehendale, H.M. (1989) Protection from chlordecone(kepone) – potentiated CC1₄ hepatotoxicity in rats by fructose 1,6 – diphosphate. *Int. J. Biochem.* 21, 949-954.
33. Dajani, O.F., Refsnes, M., Guren, T.K., Horn, R.S., Thoresen, G.H. and Christoffersen, T. (1994) Elevated glucose concentrations inhibit DNA synthesis and expression of C-myc in cultured hepatocytes. *Biochem.Biophys.Res.Comm.* 202, 1476-1482.
34. Mehendale, H.M. (1991) Role of hepatocellular regeneration and hepatobular healing in the final outcome of liver injury. A two stage model of hepatotoxicity. *Biochem. Pharmacol.* 42, 1155-1162.
35. Soni, M.G. and Mehendale, H.M. (1998) Role of tissue repair in toxicological interaction among hepatologic organics. *Environ. Health Perspect.* 106, 1307-1317.
36. Calabrese, E.J. and Mehendale, H.M. (1996). A review of the role of tissue repair as an adaptive strategy: Why low doses are often non-toxic and high doses are fatal. *Food Chem. Toxicol.* 34, 301-311.
37. Mehendale, H.M. (1994) Amplified interactive toxicity of chemicals at non toxic levels: mechanistic considerations and implications to public health. *Environ. Health Perspect.* 10, 139-149.
38. Ramaiah, S.K., Soni, M.G., Seng, J., Leakey, J.E.A. and Mehendale, H.M. (1999) Molecular players in increased thioacetamide hepatic injury and decreased mortality following diet restriction. *Toxicol. Sci.* 48, 164-171.
39. Ramaiah, S.K., Warbritton, A., Bucci, T.J., Soni, M.G. and Mehendale, H.M. (1998). Temporal changes in tissue repair response permit survival of diet restricted rats from an acute lethal dose of thioacetamide. *Mechanism of survival. Toxicol. Sci.* 45, 233-241.
40. Soni, M.G., Ramaiah, S.K., Mumtaz, M.M., Clewell, H. and Mehendale, H.M. (1999). Toxicant inflicted injury and stimulated tissue repair are opposing toxicodynamic forces in predictive toxicology. *Regul. Pharmacol. Toxicol.* 29, 165-174.
41. Hart, R.W., Leakey, J., Duffy, P.H., Feuers, R.J. and Turturro, A. (1996). The effects of dietary restriction on drug testing and toxicity. *Exp. Toxicol. Pathol.* 48, 121-127.
42. Barrett, J.C. (2000). Molecular and environmental causes of cancer. *Drug Metab. Rev.* 32, 139-142.
43. Klaunig, J.E. and Kamendulis, L.M. (1999). Mechanism of cancer chemoprevention in

- hepatic carcinogenesis: modulation of focal lesion growth in mice. *Toxicol. Sci.* 52, 101-106.
44. Hikita, H., Vaughan, J., Babcock, K. and Pitot, H.C. (1999). Short term fasting and the reversal of the stage of promotion in rat hepatocarcinogenesis: role of cell replication, apoptosis and gene expression. *Toxicol. Sci.* 52, 17-23.
45. Kritchevsky, D. (1999). Caloric restriction and experimental carcinogenesis. *Toxicol. Sci.* 52, 13-16.
46. Kritchevsky, D. (1997). Caloric restriction and experimental mammary carcinogenesis. *Breast Cancer Res. Treat.* 46, 161-167.
47. Yoshida, K., Inoue, T., Nojima, K., Hirabayashi, Y. and Sado, T. (1997). Caloric restriction reduces the incidence of myeloid leukemia induced by a single whole body radiation in C3H/He mice. *Proc. Nat. Acad. Sci.* 94, 2615-2619.
48. James, S.J. and Muskhellshvili, L. (1994). Rates of apoptosis and proliferation vary with caloric intake and may influence incidence of spontaneous hepatoma in C57BL/6xc3HFI mice. *Cancer Res.* 54, 5508-5510.
49. Steinbach, G., Heymsfield, S., Olansen, N.E., Tighe, A. and Holt, P.R. (1994). Effect of caloric restriction on colonic proliferation in obese persons: Implications for colon cancer prevention. *Cancer Res.* 54, 1194-1197.
50. Roebuck, B.D., Baumgartner, K.J. and MacMillan, D.L. (1993) Caloric restriction and intervention in pancreatic carcinogenesis in the rat. *Cancer Res.* 53, 46-52.
51. Weindruch, R. and Sohal, R.S. (1997). Caloric intake and aging. *N Engl. J. Med.* 337, 986-994.
52. Duffy, P.H., Feuers, R.J., Leakey, J.E.A., Nakamura, K., Turturro, A. and Hart, R.W. (1989). Effect of chronic caloric restriction on physiological variables that modulate energy metabolism in the male Fischer-344 rat. *Mech. Aging Dev.* 48, 117-133.
53. Youngman, L.D. (1993) Protein restriction (PR) and caloric restriction (CR) compared: Effects of DNA damage, carcinogenesis and oxidative damage. *Mutat. Res.* 295, 165-179.
54. Rogers, A.E., Zeisel, S.H. and Groopman, J. (1993). Diet and carcinogenesis. *Carcinogenesis* 14, 2205-2217.
55. Weindruch, R., Albanes, B. and Kritchevsky, D. (1991). The role of calories and caloric restriction in carcinogenesis. *Hematol. Oncol. Clin. North Am.* 5, 79-89.
56. Krishnaswamy, K. and Polasa, K. (2001) Non-nutrients and cancer prevention. *ICMR Bull* 31, 1-9.