Maturitas 79 (2014) 275–278

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review

The health pros and cons of continuous versus intermittent calorie restriction: More questions than answers

Malgorzata E. Skaznik-Wikiel*, Alex J. Polotsky

University of Colorado Anschutz Medical Campus, Department of Obstetrics and Gynecology, 12631 E 17th Avenue, B198-3, Aurora, CO 80045 United States

ARTICLE INFO

Article history:
Received 2 August 2014
Received in revised form 7 August 2014
Accepted 9 August 2014

Keywords:
Intermittent fasting diet
Caloric restriction
Fertility

ABSTRACT

Beneficial effects on health of limiting food intake for certain periods of time have been recognized for a long time. While many diets can produce short-term weight loss, most fail to result in a long-lasting impact. Current data suggest that intermittent fasting may be beneficial for overall health and wellbeing. However, the lack of properly designed clinical studies makes it challenging to formulate evidence-based practice recommendations. Potential health risks of drastic changes in food intake are often ignored and might only be revealed after extensive follow-up. This review summarizes the popular intermittent dieting methods and their potential impact on fertility and reproduction.

Contents

1. Introduction 275
2. What is intermittent fasting? 275
3. Evidence for intermittent fasting in animal studies 276
4. Evidence for intermittent fasting in human studies 276
5. What is known about overall health effect of intermittent diets? 276
6. Intermittent diets and reproductive health 277
7. Summary of evidence 277
Contributors 277
Competing interest 277
Funding information 277
Conflict of interest statement 277
Provenance and peer review 277
References 277

1. Introduction

Beneficial effects on health of limiting food intake for certain periods of time have been recognized for ages. First scientific study assessing the influence of restricted caloric intake on lifespan was conducted almost 80 years ago in rats. It indicated that limited food intake dramatically extended lifespan in these animals [1]. Since that time many other studies confirmed these results in other species [2]. It must be emphasized that it is prudent to exercise caution when attempting to translate animal model data on weight reduction to humans. While many diets can produce short-term weight loss, most fail to result in a long-lasting impact. Potential health risks of drastic changes in food intake are often ignored and might only be revealed after extensive follow-up. This review will be devoted to describing the popular intermittent dieting methods and their potential impact on fertility and reproduction

2. What is intermittent fasting?

Several nutritional strategies exist to facilitate weight loss. The two most popular diets are caloric restriction (CR) and intermittent fasting (IF). CR typically involves limiting daily caloric intake for up to 10–30% of energy needs [3]. IF is a regimen that has gained considerable popularity in the past decade and involves significant

* Corresponding author. Tel.: +1 3037246515.
E-mail addresses: malgorzata.skaznik-wikiel@ucdenver.edu, mskaznik22@yahoo.com (M.E. Skaznik-Wikiel).

http://dx.doi.org/10.1016/j.maturitas.2014.08.007
0378-5122/

restriction of calories (75–90% of energy needs) on only one or two days per week [4]. The combination of the two methods is also frequently used and sometimes results in a greater reduction in weight. Significant CR is known to ameliorate age-related decline of many organs, including those of the female reproductive axis in animal models [5]. On the other hand, involuntary CR during the infamous Dutch famine has been associated with younger age at natural menopause [6].

It is well known that female reproductive ability is impaired in undernourished women which is demonstrated by menstrual irregularity or amenorrhea and decreased fertility [7–9]. Such adaptations protect women against the hazards of pregnancy and motherhood during situations where food availability is limited. During undernutrition the pattern of hypothalamic GnRH secretion usually returns to prepubertal state.

IF and CR diets are popular in the general population since they usually result in prompt weight loss. Currently, the fast diet, also known as 5:2 diet appears to be the most popular [4]. The diet consists of five days of normal eating, followed by eating a quarter of the recommended daily calorie quota. That works out at 500 kcal for women and 600 for men. However, it is usually impossible to keep such lifestyle modifications forever because of their unbalanced content. Nonetheless, it is imperative to evaluate if there are any detrimental consequences of such drastic CR, even if only temporary.

3. Evidence for intermittent fasting in animal studies

Several physiological effects of CR and IF that may contribute to their ability to improve health and increase lifespan have been demonstrated [2]. The most striking findings are increased insulin sensitivity [10,11], reduced levels of oxidative stress [12], enhanced immune function [13], and increased resistance to oxidative stress [14]. Rodents maintained on CR diet are generally smaller and leaner and have less body fat [15]. The amount by which lifespan is extended has been shown to increase progressively as caloric intake is reduced.

It has recently been reported that moderate CR in adult mice can significantly extend function of the female reproductive axis into advanced age. Significant benefits include the higher survival rates of the offspring conceived by aged CR females once returned to an ad libitum (AL) diet [16]. There is an increasing body of evidence indicating that CR produces many of the same physiological, metabolic and hormonal adaptations in aging nonhuman primates [17,18], and humans [19] that are observed in rodents. Recent data from mice demonstrate the beneficial effects of prolonged ovarian function on the female body with age [20]. Therefore, sustaining the ovarian function by adult-onset CR may have an important role in improving the overall quality of life of aging females.

In other studies litter size as well as regularity of estrous cycle of CR then AL fed aging females was similar to those of young adult females. This implies that CR can postpone age-related reproductive failure in mice [21]. While the mechanisms by which CR sustains fertility with age remain to be fully characterized, studies in rodents have shown that the oocyte complement appears to be higher in CR females when compared to the age-matched AL-fed controls [21]. These findings suggest that the beneficial effects of CR on female reproductive function are at least partly mediated via maintenance of the ovarian follicle reserve in aging animals. Other work has shown that CR also alters the release patterns of many hormones produced by the hypothalamus and pituitary gland, including those involved in the control of ovarian function [22]. Consequently, the ability of CR to affect reproductive performance probably reflects a very complex process involving modulation of the entire hypothalamic–pituitary–gonadal axis.

4. Evidence for intermittent fasting in human studies

To date, there have been no randomized clinical trials to determine the effects of long-term CR and IF on humans. The largest studies assessing this topic thus far were conducted retrospectively based on the Dutch famine data. During the winter of 1944–1945, residents of the western part of the Netherlands experienced severe food shortage. The famine was a result of an embargo on the food transports imposed by the Germans as a revenge for a strike of the Dutch railways. The daily rations dropped precipitously to as little as 400 to 800 kcal per day during the 5 to 6 months of famine. The famine was associated with an acute increase in mortality and morbidity [23]. This gruesome experience has afforded an opportunity to study the effects of severe CR on human health in later life, including the effects of undernutrition in utero or during early childhood. Women exposed to famine in early gestation had a higher overall adult, cardiovascular, cancer, and breast cancer mortality risk than did women not exposed to famine [24]. In addition, famine exposure in childhood for several months was found to be associated with an increased CHD risk in adult life, in a dose-dependent manner [25].

Another socio-cultural phenomenon that approximates IF is Ramadan. One of the five pillars of Islam is that healthy adult Muslims are obligated to fast from dawn to sunset during the holy month of Ramadan. Over the past few decades emerging evidence from epidemiologic studies has supported health-related benefits of IF during Ramadan. In patients who observed fast during Ramadan, studies have shown improved insulin sensitivity [26], improved glycemic control, and improvement in lipid profiles [27,28].

The effect of IF combined with CR on weight loss and coronary heart disease (CHD) risk was evaluated in a prospective study of 60 obese women. The combination of both methods was shown to be effective for reducing body weight, visceral fat mass, and CHD risk in these women [29]. In a trial conducted by Williams et al. of IF, obese patients consumed less than 500 kcal a day one day per week and ate ad libitum every other day of the week. After 20 weeks of this regimen, body weight decreased by 9% from baseline [30].

Yet another relevant study was the biosphere 2 trial. This uniquely designed experiment assessed the influence of consuming low-calorie nutrient-dense diet by persons sealed inside a closed ecological space. Over the two year period the participants exhibited significant weight loss, decrease in blood cholesterol level, blood pressure, fasting blood sugar, and low white blood cell counts, mirroring the effects demonstrated in rodents [31].

5. What is known about overall health effect of intermittent diets?

Recently, an increasing number of physiological effects of intermittent fasting (IF) have been documented in studies on rodents, monkeys, and humans [2]. The most important among these are increased lifespan [32], decreased mortality from cancers and cardiovascular diseases[33], improved insulin sensitivity [34], and reduced oxidative stress and inflammation [35]. The amount by which lifespan is extended increases progressively as calorie intake is reduced as well as the duration of the diet (the later the diet begun, the less lifespan is increased). Interestingly, IF can also increase lifespan, even when there is little or no overall decrease in calorie intake [36]. Most studies have shown that CR and IF have been shown to diminish severity of risk factors for diseases such as diabetes and cardiovascular disease [37].

6. Intermittent diets and reproductive health

The data from the Dutch famine study suggested that in utero exposure to famine was not associated with subsequent subfertility, including age at first pregnancy, completed family size, and inter-pregnancy interval [38]. Another study showed that women who were exposed to Dutch famine in utero had more children, more twins, and were less likely to remain childless. The famine had a direct influence on menstruation patterns. Severe famine exposure was associated with increased risk of irregular menses. CR in childhood was associated with a higher risk of prolonged time for menses to become regular after menarche [39].

CR has also been shown to reduce age at menopause. Women who were severely exposed to the famine during World War II experienced natural menopause on average 0.36 years earlier [6]. This finding may have significant health implications since earlier age at menopause has been associated with increased risk of morbidity due to osteoporosis [40], cardiovascular disease [41], and cognitive decline [42]. It is particularly and perhaps alarmingly problematic that higher burden of osteoporosis has been documented in some of the published studies. Bone is particularly sensitive to prolonged oligoovulation and resultant hypoestrogenism. The impact of such diet as IF on bone function may escape easy and reliable detection since the after effect of acute energy availability may not be observed for decades. This is especially relevant for adolescents as adequate build-up of bone mass in women takes place during the early reproductive years.

The energy availability hypothesis has been proposed recently. It postulates that reproductive function in women is regulated not by the actual amount of body mass and body fat, but rather by available energy [43]. Experiments that imposed a high volume of aerobic exercise in an abrupt fashion caused a large prevalence of anovulation in the first and second month after starting the exercise [44]. The period after bariatric surgery represents another example of potential low energy availability due to CR. A recent study of 29 women undergoing bariatric surgery found that more than 90% of studied cycles were ovulatory [45]. In contrast, an earlier study reported that women in the rapid phase of weight loss after bariatric surgery exhibit transient anovulation [46], presumably due to low energy availability.

7. Summary of evidence

Current data suggest that IF may be beneficial for overall health and wellbeing. However, the lack of properly designed clinical studies makes it challenging to formulate evidence-based practice recommendations. Potential detrimental impact of IF diet on reproduction and particularly bone health ought to be studied. The fast diet is currently popular, however individuals desiring to adapt IF as a consistent nutritional strategy should be forewarned that there is scant research on its efficacy and long-term influence on general health.

Contributors

Malgorzata E. Skaznik-Wikiel is the first author. She and the senior author made an outline for the manuscript together. Dr. Skaznik-Wikiel did most of the literature search and wrote the first draft of the paper. She also did the final editing to the paper.

Alex Polotsky is the senior author. He and the first author did the outline for the paper together. He assisted with the literature search and edited the draft of the manuscript. He also approved the final draft of the paper.

Competing interest

The authors Malgorzata E. Skaznik-Wikiel and Alex J. Polotsky have no actual or potential conflicts of interest including any financial, personal or other relationships with other people or organizations that could inappropriately influence (bias) their work.

Funding information

The authors have received no funding for this article.

Conflict of interest statement

None.

Provenance and peer review

commissioned; externally peer reviewed

References

[1] McCay CM, Crowell MF, Maynard LA. The effect of retarded growth upon the length of life span and upon the ultimate body size. 1935. Nutrition 1989;5(3):155–71. Discussion 172.
[2] Varady KA, Hellerstein MK. Alternate-day fasting and chronic disease prevention: a review of human and animal trials. Am J Clin Nutr 2007;86(1):7–13.
[3] Lee SH, Min KJ. Caloric restriction and its mimetics. BMB Rep 2013;46(4):181–7.
[4] Barnosky AR, et al. Intermittent fasting vs daily calorie restriction for type 2 diabetes prevention: a review of human findings. Transl Res 2014 Jun 12 [Epub ahead of print].
[5] Masoro EJ. Overview of caloric restriction and ageing. Mech Ageing Dev 2005;126(9):913–22.
[6] Elias SG, et al. Caloric restriction reduces age at menopause: the effect of the 1944–1945 Dutch famine. Menopause 2003;10(5):399–405.
[7] Warren MP. Effects of undernutrition on reproductive function in the human. Endocr Rev 1983;4(4):363–77.
[8] Wynn A, Wynn M. The effects of food shortage on human reproduction. Nutr Health 1993;9(1):43–52.
[9] Harlow SD, Ephross SA. Epidemiology of menstruation and its relevance to women's health. Epidemiol Rev 1995;17(2):265–86.
[10] Anson RM, et al. Intermittent fasting dissociates beneficial effects of dietary restriction on glucose metabolism and neuronal resistance to injury from calorie intake. Proc Natl Acad Sci USA 2003;100(10):6216–20.
[11] Heilbronn LK, Ravussin E. Calorie restriction and aging: review of the literature and implications for studies in humans. Am J Clin Nutr 2003;78(3):361–9.
[12] Sohal RS, Weindruch R. Oxidative stress, caloric restriction, and aging. Science 1996;273(5271):59–63.
[13] Ahmed T, et al. Calorie restriction enhances T-cell-mediated immune response in adult overweight men and women. J Gerontol A: Biol Sci Med Sci 2009;64(11):1107–13.
[14] Walsh ME, Shi Y, Van Remmen H. The effects of dietary restriction on oxidative stress in rodents. Free Radic Biol Med 2014;66:88–99.
[15] Weindruch R, Sohal RS. Seminars in medicine of the Beth Israel Deaconess Medical Center. Caloric intake and aging. N Engl J Med 1997;337(14):986–94.
[16] Selesniemi K, Lee HJ, Tilly JL. Moderate caloric restriction initiated in rodents during adulthood sustains function of the female reproductive axis into advanced chronological age. Aging Cell 2008;7(5):622–9.
[17] Ingram DK, et al. The potential for dietary restriction to increase longevity in humans: extrapolation from monkey studies. Biogerontology 2006;7(3):143–8.
[18] Bodkin NL, et al. Mortality and morbidity in laboratory-maintained Rhesus monkeys and effects of long-term dietary restriction. J Gerontol A: Biol Sci Med Sci 2003;58(3):212–9.
[19] Walford RL, et al. Calorie restriction in biosphere 2: alterations in physiologic, hematologic, hormonal, and biochemical parameters in humans restricted for a 2-year period. J Gerontol A: Biol Sci Med Sci 2002;57(6):B211–24.
[20] Perez GI, et al. Absence of the proapoptotic Bax protein extends fertility and alleviates age-related health complications in female mice. Proc Natl Acad Sci USA 2007;104(12):5229–34.
[21] Nelson JF, Gosden RG, Felicio LS. Effect of dietary restriction on estrous cyclicity and follicular reserves in aging C57BL/6J mice. Biol Reprod 1985;32(3):515–22.
[22] Martin B, et al. Caloric restriction: impact upon pituitary function and reproduction. Ageing Res Rev 2008;7(3):209–24.
[23] Lumey LH, Van Poppel FW. The Dutch famine of 1944–45: mortality and morbidity in past and present generations. Soc Hist Med 1994;7(2):229–46.
[24] van Abeelen AF, et al. Survival effects of prenatal famine exposure. Am J Clin Nutr 2012;95(1):179–83.
[25] van Abeelen AF, et al. Cardiovascular consequences of famine in the young. Eur Heart J 2012;33(4):538–45.

[26] Shariatpanahi ZV, et al. Effect of Ramadan fasting on some indices of insulin resistance and components of the metabolic syndrome in healthy male adults. Br J Nutr 2008;100(1):147–51.
[27] Al-Shafei AI. Ramadan fasting ameliorates oxidative stress and improves glycemic control and lipid profile in diabetic patients. Eur J Nutr 2014 Jan 19 [Epub ahead of print].
[28] Shehab A, et al. Favorable changes in lipid profile: the effects of fasting after Ramadan. PLoS One 2012;7(10):e47615.
[29] Klempel MC, et al. Intermittent fasting combined with calorie restriction is effective for weight loss and cardio-protection in obese women. Nutr J 2012;11:98.
[30] Williams KV, et al. The effect of short periods of caloric restriction on weight loss and glycemic control in type 2 diabetes. Diabetes Care 1998;21(1):2–8.
[31] Walford RL, Weber L, Panov S. Caloric restriction and aging as viewed from Biosphere 2. Receptor 1995;5(1):29–33.
[32] Mattson MP, Wan R. Beneficial effects of intermittent fasting and caloric restriction on the cardiovascular and cerebrovascular systems. J Nutr Biochem 2005;16(3):129–37.
[33] Buschemeyer 3rd WC, et al. Effect of intermittent fasting with or without caloric restriction on prostate cancer growth and survival in SCID mice. Prostate 2010;70(10):1037–43.
[34] Lu J, et al. Alternate day fasting impacts the brain insulin-signaling pathway of young adult male C57BL/6 mice. J Neurochem 2011;117(1):154–63.
[35] Castello L, et al. Alternate-day fasting protects the rat heart against age-induced inflammation and fibrosis by inhibiting oxidative damage and NF-kB activation. Free Radic Biol Med 2010;48(1):47–54.
[36] Goodrick CL, et al. Effects of intermittent feeding upon body weight and lifespan in inbred mice: interaction of genotype and age. Mech Ageing Dev 1990;55(1):69–87.
[37] Wan R, Camandola S, Mattson MP. Intermittent food deprivation improves cardiovascular and neuroendocrine responses to stress in rats. J Nutr 2003;133(6):1921–9.
[38] Lumey LH. Reproductive outcomes in women prenatally exposed to undernutrition: a review of findings from the Dutch famine birth cohort. Proc Nutr Soc 1998;57(1):129–35.
[39] Elias SG, et al. Menstruation during and after caloric restriction: the 1944–1945 Dutch famine. Fertil Steril 2007;88(4 Suppl):1101–7.
[40] Sowers MR, La Pietra MT. Menopause: its epidemiology and potential association with chronic diseases. Epidemiol Rev 1995;17(2):287–302.
[41] van der Schouw YT, et al. Age at menopause as a risk factor for cardiovascular mortality. Lancet 1996;347(9003):714–8.
[42] Wise PM, et al. Minireview: neuroprotective effects of estrogen-new insights into mechanisms of action. Endocrinology 2001;142(3):969–73.
[43] Loucks AB. Energy availability: not body fatness, regulates reproductive function in women. Exerc Sport Sci Rev 2003;31(3):144–8.
[44] Bullen BA, et al. Induction of menstrual disorders by strenuous exercise in untrained women. N Engl J Med 1985;312(21):1349–53.
[45] Legro RS, et al. Effects of gastric bypass surgery on female reproductive function. J Clin Endocrinol Metab 2012;97(12):4540–8.
[46] Di Carlo C, et al. Hypogonadotropic hypogonadism in obese women after biliopancreatic diversion. Fertil Steril 1999;72(5):905–9.