

The Assessment of Dietary Interventions on Stem Cell Fate, Homeostatic Mechanisms, and Disease

Carolyn Lee

German Swiss International School

ABSTRACT

Economic growth and globalisation have increased food availability and disposable income, causing people to rely on nutrient-poor fast foods due to their low price and wide availability instead of nutritious produce. Global statistics show the population consumes exponentially more fats and carbohydrates than proteins, vegetables, and fruits. This dietary pattern negatively impacts public health, increasing prevalence of obesity and diet-related diseases like diabetes, heart disease, and hypertension. When used appropriately, dietary interventions have a profound effect on stem cell regeneration and homeostasis, hormone signaling, and prevalence of disease and obesity, posing strong potential in regenerative medicine and non-communicable disease treatment. This review studies caloric restriction, prolonged fasting, the ketogenic diet, and the high fat diet and outlines their effect on stem cell fate and numbers, hormone and metabolism levels, and prevalence of disease and discusses the advantages, disadvantages, and future directions of each dietary intervention.

Introduction

Our diets have evolved over time due to factors such as changing food availability, food prices, level of income, and urbanization [1]. Although the specific changes differ for each country, we can see a negative global trend where traditional, nutritious, whole food-based diets are replaced by high sugar and high-fat diets that lack dietary fibre and essential micronutrients [2]. This is because countries widely import and produce ultra-processed, nutrient-poor foods, which take the place of fruits and vegetables in the population's diet [3]. The effect of this nutrition transition is mainly negative, increasing global obesity and diet-related diseases like diabetes, insulin resistance, hypertension, and even cancer [4], [5].

Recent studies provide evidence that stem cell regeneration and homeostasis is closely linked to organismal diet. Our body is composed of cell and tissue, and the type and amount of food we consume can impact their function and homeostasis [6]. In context of the nutrition transition, cell and tissue health are compromised, reducing cell stemness and causing an imbalance in homeostasis, which leads to the harmful diseases mentioned previously [7]. However, stem cell numbers in certain areas, such as the blood, increase, showing the possible potential of a high-fat diet [8]. Contrastingly, other dietary interventions such as the ketogenic diet, fasting, and calorie restriction have emerged, advocated to increase longevity, cell stemness, and regenerative capacity, and are commonly used to treat obesity and diabetes [9].

In this review, I will discuss the effect of various dietary interventions on stem cell function and homeostasis in different adult tissues, as well as hormone levels, metabolism, and prevalence of disease.

The Role of Dietary Interventions in Stem Cell Behavior and Disease

A dietary intervention is classified as any alteration or treatment in an individual's diet with a planned goal,

usually to improve the individual's overall health. Diet has a profound effect on tissue regeneration. Macroscopic dietary interventions such as caloric restriction, prolonged fasting, ketogenic diets, and high-fat diets alter an organism's metabolic state and stem cell fate in different ways, but they share the commonality of enhancing self-renewal [6].

Caloric Restriction

Caloric restriction (CR) is a dietary regime where daily energy intake is reduced by >20% through ad libitum feeding or lengthening the time between meals without causing malnutrition [6]. CR generally has a positive effect on cell biology and homeostasis (Table 1). It reduces circulating system factors, such as growth factors and hormones, and induces ketogenesis, which may protect against cancer, enhance lifespan, increase insulin sensitivity, and delay ageing [10] (Figure 1). Moreover, CR led to increased stem cell renewal and enhanced adult stem cell functionality in multiple areas, such as the intestine, skeletal muscle, and blood. In the intestine, CR increases intestinal stem cell (ISC) self-renewal and proliferation by enhancing the ability of intestinal crypts to form organoids in vitro [11] and regenerate crypts after damage in vivo [12]. In skeletal muscle stem cells (MuSC), CR preserves their functionality during ageing and enhances the frequency of proliferation and myogenic function in both young and old mice [10].

Additionally, CR may modulate the stem cell environment to regulate stem cell biology. This can be seen from how MuSC from ad libitum-fed mice had a higher engraftment frequency into injured CR mice than injured ad libitum-fed mice [13], which is likely caused by a metabolic shift to more mitochondrial oxidative phosphorylation and ketogenesis (Table 1). Furthermore, even short-term CR significantly enhanced stem cell availability and activity in the muscle of young and old animals. Not only did this improve muscle regeneration, but it increased mitochondrial numbers and induced conserved metabolic and longevity regulators [13]. Therefore, CR has potential medical applications, for example enhancing stem cell transplant efficiency.

Prolonged Fasting

Fasting is a dietary intervention defined as the abstinence of food for periods of 12 hours to multiple days [14]. It can be divided into three main types: prolonged fasting (PF), which lasts for 2 or more days, intermittent fasting (IF), which is applied chronically, or fasting-mimicking diet (FMD) [15], which is a specific meal plan formulated to simulate the fasting state while providing nutrients and calories. This review will focus on PF. Although the body is also in an energy-deficient state, this is different from caloric restriction, where food is chronically restricted and meal frequency is maintained. However, they share the commonality of promoting lifespan and overall health by enhancing the function of stem cells, which rejuvenates the immune system and lowers visceral fat and cancer risk [16] (Table 1). In the hematopoietic niche, PF for 48 hours led to increased hematopoietic stem cell (HSC) numbers, hematopoietic multipotent progenitor, and myeloid precursor proliferation while maintaining the total number of the stem and progenitor cells compared to non-fasted animals [10]. Cycles of PF restore the balance between aged and young blood cell populations and reduce the bias towards myeloid lineage, as observed in young mice [10]. Moreover, a study performed on young and aged mice showed that a 24 hour fast increased ISC function by generating a fatty acid oxidation (FAO) mechanism where cells break down fatty acids instead of glucose for energy [17] (Table 1) (Figure 1).

Furthermore, PF promotes stress resistance against DNA damage, presenting itself as a potential alleviator for chemotherapy side effects [18]. A recent study [14] showed that fasting for more than 3 days reduced more than 30% of insulin, glucose, and insulin-like growth factor (IGF-1) levels which decreased risks of cancer development, DNA damage, and ageing. Furthermore, differential stress resistance (DSR) was activated, protecting mice from a variety of chemotherapy drugs [14] (Table 1). Additionally, PF increases ketone body levels

and creates a protective environment for stem cells, while generating hostile conditions for tumour and pre-cancerous cells [14].

Therefore, PF has potential in cancer treatment and regenerative medicine. However, the safety of PF (2 weeks or longer) in cancer treatments still needs to be tested and carefully implemented into clinical trials to avoid malnourishment, weakened immune system, and increased risks to certain infections [14].

Ketogenic Diet

Ketogenic diets (KDs) have high fat, moderate protein, and low carbohydrate contents, with 70-80% of calories coming from fat, and the remainder from protein and carbohydrates. Because glucose is not readily available, a metabolic shift away from carbohydrates and towards fatty acid oxidation occurs (Table 1) (Figure 1). This increases circulating ketone bodies, a water-soluble molecule produced in the liver, which is used as an alternative energy source [19]. Moreover, the low carbohydrate content may induce greater glycemic control and lower blood glucose levels, which is helpful for obese or diabetic patients [20].

The KD can also positively impact stem cells in the intestinal niche. A study done on mice exhibited that ones undergoing KD had increased ISC regeneration and faster recovery from intestinal lining damage (Table 1) compared to mice on a normal diet [21]. The intestine already produces ketone bodies to use as fuel in the absence of carbohydrates and sustains its own stemness through specialised pathways that determine cell lineage and fate. The KD further increases ketone body levels, enhancing this effect – mice were able to better regenerate intestinal tissue due to increased ISC pools which formed organoids more readily. This is crucial for maintaining intestinal lining health and homeostasis and could be useful for cancer patients as intestinal lining damage can result from radiation or chemotherapy treatments [21]. Furthermore, recent studies suggest that a stem cell's decision to activate or remain quiescent is regulated by glucose utilisation [6]. For instance, HSCs are thought to reside in hypoxic areas of their niche and increase glycolysis during periods of quiescence. Since the KD induces higher rates of glucose utilisation, it is suggested that it will increase stem cell activation (Table 1).

Additionally, the KD is associated with improved mitochondrial and cellular metabolism [9] (Table 1). This contributes to the ability of neurons to resist metabolic stress, as well as conferring neuroprotective properties, such as battling against late-stage disorders like Alzheimer's and Parkinson's disease [10], [22]. However, the KD's impact on adult tissue stem cell function requires further investigation because ketone-induced stem cell activity could be linked to cancer development, evident by tumours derived from KD stem cell activity [21]. Moreover, individuals who are intolerant to the diet can experience potential side effects, such as nausea, lethargy, vomiting, and gastrointestinal discomfort [20]. Some patients also show deficiencies in trace minerals such as selenium, copper, and zinc. Therefore, appropriate supplementation of these minerals is necessary while on the KD [21].

High Fat Diet

The high-fat diet (HFD) is a diet where at least 35% of total calories are consumed from fats, both unsaturated and saturated. The remainder of the diet is made up of 20-25% protein and carbohydrates. This form of chronic overnutrition promotes obesity, demonstrated in a study where mice undergoing a HFD became obese within months [23]. Furthermore, the imbalance in metabolic, hormonal, and cytokine signalling leads to metabolic syndrome, type 2 diabetes, heart disease, and even certain types of cancer [10].

The effect of the HFD on stem cell biology is complex and differs between different tissues and niches, but an increasing number of studies show it could enhance self-renewal of ISCs by increasing their numbers, proliferation, and function, but also increase carcinogenesis [7], [8], [24] (Table 1). The intestine is responsible

for nutrient uptake and responds to diet-induced signals. A long-term HFD increases ISC numbers and decreases the number of their niche Paneth cells [6]. This forces the intestine to adapt and acquire niche dependence to maintain or enhance self-renewal, no longer relying on Paneth cells to initiate ex vivo organoids [6]. However, intestinal progenitors simultaneously acquire properties of stemness, leading to higher risks of tumour formation. Additionally, the HFD changes the hematopoietic system. A short-term HFD, lasting a few weeks, leads to reduction in hematopoietic stem cell (HSC) numbers, while a long term HFD, lasting a month or more, increased HSC numbers and function and led to more myeloid cell colonies forming units [10]. Contrasting to other dietary interventions, the HFD does not induce ketogenesis. In fact, it reduces insulin sensitivity and the efficiency by which glucose enters tissues [25] (Figure 1). Despite increased glucose availability, it was not necessarily utilised, and certain types of unsaturated fatty acids were circulated more, which may act as ligands for various signalling pathways, ultimately resulting in insulin resistance. Although a HFD has clear positive impacts on HSC progenitor numbers and differentiation, the mechanisms controlling these effects are unclear. Moreover, the HFD promotes obesity and imbalances in circulating factors and metabolic signalling. More studies must be done to understand these mechanisms and gauge the safety of the HFD.

Table 1. Comparison of dietary interventions on stem cell fate, hormone levels, and metabolic response

	Insulin Sensitivity	Stem Cell Fate	Ketogenesis	Impact on Health and Risk of Disease	Effects on Levels of Circulating Factors and Hormones	Metabolic Response
Caloric Restriction	Increased [10]	Increased ISC numbers and regeneration [10], [12]	Yes [10]	Protect against cancer, enhance lifespan, delay ageing [10]	Reduced [10]	More mitochondrial oxidative phosphorylation [12]
Prolonged Fasting	Increased [10]	Increased HSC numbers and regeneration [10], [12], [16]	Yes [15]	Reduces DNA damage and carcinogenesis [14], [15]	Reduced more than 30%. Increased ketone levels [14]	Fatty acid oxidation instead of glucose utilisation [17]
Ketogenic Diet	Increased [10]	Increased ISC numbers and regeneration [21]. Regulates stem cell activity [6].	Yes [19]	Greater glycemic control and lower blood glucose levels [20]. Neuroprotective properties [22]	N/A	Glycolysis and fatty acid oxidation [19]. Improves mitochondrial and cellular metabolism [9].
High Fat Diet	Decreased (caused insulin resistance) [25].	Increased ISC and HSC numbers, stemness and carcinogenesis [7], [8], [24]	Yes [25]	Promotes obesity and cancer [23]	Imbalance in hormone levels [10]. Blood glucose levels increase but are not utilised [25]	Causes an imbalance in metabolic, hormonal, and cytokine signalling [10]

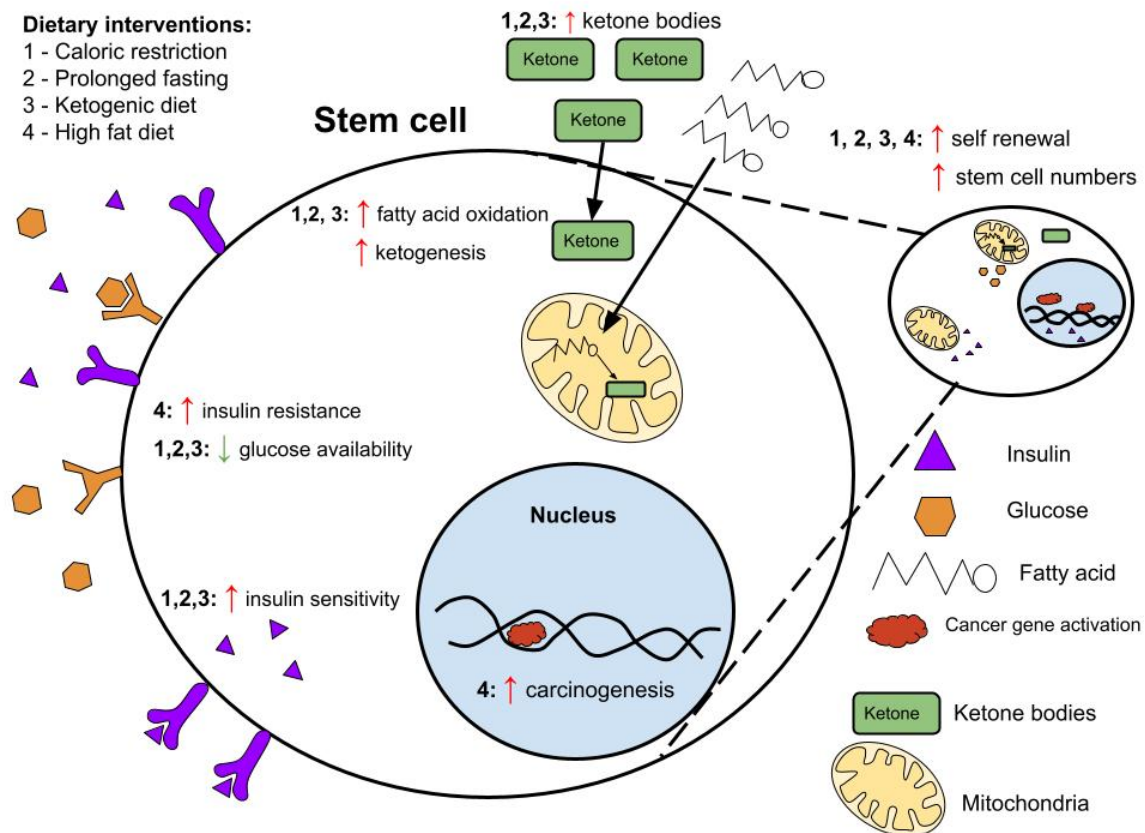


Figure 1. Cellular representation comparing the effect of dietary interventions on stem cell numbers, insulin sensitivity, glucose availability, and ketogenesis. The dietary interventions – caloric restriction, prolonged fasting, the ketogenic diet, and the high fat diet – are numbered from 1 to 4, respectively. The annotations indicate the effect of the dietary intervention in the corresponding regions of the cell. A red arrow denotes an increase, while a green arrow denotes a decrease. Caloric restriction, prolonged fasting, and the ketogenic diet (dietary interventions 1, 2, and 3) increase fatty acid oxidation, insulin sensitivity, and stem cell renewal and regeneration, hence inducing ketogenesis, and decreasing glucose availability. The high fat diet (dietary intervention 4) also increases stem cell renewal and regeneration but simultaneously increases insulin resistance and carcinogenesis.

Limitations and Future Considerations

The studies used to investigate CR only focused on reducing calories by 20-40% without causing malnutrition [6] and did not specify macronutrient composition. Therefore, individuals could theoretically consume all their calories from only one macronutrient, for example fats, mirroring the HFD, while remaining in an energy deficit. The HFD is associated with increased risks of carcinogenesis and obesity [24], so it is unknown whether the benefits of CR, such as longevity, ketogenesis, and fatty acid oxidation, would still be seen.

A study done by Solon-Biet et al [26] shows that CR is highly dependent on macronutrient composition. CR achieved by replacing protein with carbohydrates optimised longevity and health the most [26]. This contrasts the basis of the KD, where carbohydrate consumption should be extremely limited and replaced by fats to achieve longevity and other health benefits [19]. More research may be done in this area to explore this contradiction.

Although significant research has been devoted to understanding the underlying mechanisms of the studied dietary interventions, none have yet investigated it from different nutrient composition standpoints. Further studies are required to understand how CR changes stem cell function and homeostasis, and how the macronutrient composition plays a role.

Contrasting to other dietary interventions, PF may be one of the easiest to implement. It does not call for specific macronutrient or calorie compositions, only requiring restricted feeding time [14]. The benefits and potential it has are immense - PF increases fatty acid oxidation and stem cell proliferation in the intestine while reducing DNA damage and carcinogenesis [17], [18], posing as potential regenerative medicine or cancer treatments for chemotherapy patients [14]. Moreover, it would be highly beneficial for individuals to incorporate periodic fasting to promote health and reduction of disease, especially for those who are overweight and sedentary. However, it must be noted that there are no studies of fasting performed on children, underweight individuals, women during pregnancy, and the elderly [14]. Since PF likely simultaneously causes CR, it may be harmful to the above groups by impacting growth and development. Before undergoing any dietary regime, one should consult a healthcare practitioner.

In the medical field, KDs are most used for diabetic or obese patients to effectively lower insulin, blood glucose, and body weight [19], [27]. Recent studies have discovered its neuroprotective properties and disease modifying effects [22], so the application of KDs may begin to evolve towards the regenerative and therapeutic field of medicine as more studies and research contribute to this hypothesis. However, since KDs drives stem cell proliferation, this intervention could possibly increase carcinogenesis [21]. This is supported by a study done by Massachusetts Institution of Technology, showing that elevated ketone activity due to KDs lead to tumour development [21]. In future studies, some questions to be considered are the role ketone bodies play in early tumour formation, and whether overpromotion of this pathway can impact carcinogenesis.

Of the four dietary interventions, the HFD has the least benefits and most consequences, promoting obesity, carcinogenesis, and imbalanced metabolic signalling [7], [24]. Although HFDs enhance ISC and HSC numbers, it simultaneously promotes niche independence, creating opportunities for tumorigenesis because progenitors in these niches acquire properties of stemness [8]. Moreover, this is the only intervention that does not induce ketogenesis, and increases insulin resistance instead of sensitivity, leading to metabolic syndrome, type 2 diabetes, heart disease, and even certain types of cancer [6]. In the medical field, HFDs are not recommended due to the adverse impacts on health and metabolism. More studies must be done to understand these mechanisms and gauge the safety of the HFD.

Conclusion

Diet is a major part of lifestyle that can largely impact organismal health, metabolism, stem cell fate, and disease. CR, PF, and the KD all mainly benefit health and stem cell fate. Moreover, they protect against cancer and other NCDs, induce ketogenesis, and increase metabolic responses through elevated insulin sensitivity and circulating hormones. In the studies reviewed, CR and the KD increased ISC numbers and regeneration while PF increased that of HSCs. Contrastingly, a HFD has more adverse impacts than benefits. Although it increases ISC and HSC numbers, it simultaneously increases carcinogenesis, insulin resistance, imbalance in hormones and metabolic signalling, and promotes obesity. In the medical world, PF, CR, and KDs are seen as dietary interventions with significant potential for regenerative medicine or NCD treatment, while HFDs are not recommended. Furthermore, PF is easiest to implement because it does not require specific macronutrients, but implementation of CR and KDs are equally feasible due to increasing food variety and availability, which makes it easy to tailor diets to such guidelines. Increasing understanding for these dietary interventions can significantly contribute to dietary management and disease prevention, building a healthier future population.

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