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The Potential Benefits of Fasting Do Not Include Regenerative Stem Cells

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ABSTRACT

Tracing back to the first civilizations, there has always been a drive to live longer healthier lives, to cheat death. As potions and prayers gave way to science, deeper understanding of the body's chemicals and processes encouraged people to manipulate them in a quest to avoid disease. With the awareness and comprehension of stem cells, new questions arose, many of which were directed at how we might control stem cells that exist throughout the body to our benefit, or how we might utilize them to prevent or manage illness. An increasing number of studies appear to point to the ability of stem cells to regenerate through fasting, which could have potentially far-reaching implications in future approaches towards medical applications. The beneficial effects of fasting – though numerous – do not, however, include stem cell regeneration; instead, it is the cumulative effects of many of our body's other mechanisms that tend to work together in rejuvenating cells of all types. Further, it is misleading to think that fasting will benefit every person in every situation, as it comes with its own complications and as such, is only recommended in very specific circumstances.

Keywords

Fasting, Calorie restriction, Stem cells.

Abbreviations

ALS: Amyotrophic Lateral Sclerosis, AMPK: Adenosine Monophosphate-activated Protein Kinase, ATCH: Adrenocorticotropic Hormone, ATP: Adenosine Triphosphate, β-HB: β-Hydroxybutyrate, DNA: Deoxyribonucleic Acid, DR: Dietary Restriction, FMD: Fasting-Mimicking Diet, GI: Gastrointestinal, GLUT4: Glucose Transporter type 4, hASMCs: Human Aortic Smooth Muscle Cells, HFD: High-Fat Diet, hGH: Human Growth Hormone, HUVECs: Human Umbilical Vein Endothelial Cells, IGF-1: Insulin-like Growth Factor–1, IR: Interventional Radiology, mTOR: Mammalian Target of Rapamycin, NAD+/NADH: Nicotinamide Adenine Dinucleotide, Nox2: NADPH oxidase, NSC: Neuronal Stem Cell, ROS: Reactive Oxygen Species.

Introduction

Does fasting increase stem cell regeneration? This topic could direct a wide range of future research, not only looking at how stem cells are impacted by various mechanisms, but also the potential benefits of fasting in general. The problem which presents itself is that there's a push to find a miracle cure against aging and disease, and people have turned to stem cells as a prospective answer [1-7]. Particularly because we've come a long way in understanding concepts like unraveling telomeres [8] and have used stem cells to generate new tissues and organs [7,9], there's a hope that stem cells might just be the solution we're looking for.

There are limitations, however, not the least of which is that not every patient is created equal. What works for one will not work for all [10,11]. Even if fasting did lead to somehow enhanced or regenerative stem cells across all types, that simply cannot be a standardized method of treatment or prevention. Fasting can be extremely challenging to do correctly and without side effects, and it does not have the same effect on everyone – either at the same rate or in the same ways [1].

The purpose of this study is to understand that there is an unparalleled value in understanding all the mechanisms that affect our health and that chasing after stem cells is not the magic solution

many hope it to be. Instead, this report encourages the medical community to look at everyone as an individual, considering his/her specific biochemistry, genetics, lifestyle, etc., and that a patient and the healthcare team can make educated decisions together based on this full picture.

Background

What is a stem cell and where are they found in the body?

Unspecialized stem cells give rise to all the other cells and tissues in our body that have specialized functions [12]. Found in both embryos and adults, stem cells can differentiate into any cell of an organism under the correct physiological conditions [12]. Stem cells are found throughout the body, highlighting the important role they play in the maintenance of our body's cells and, ultimately, our overall health. In adults, they can be found in bone marrow, the gut, hair follicles, the brain, the blood, and the skin [9,12]. The discovery of the ability to undifferentiate stem cells has led to many diverse studies that attempt to reprogram adult stem cells, in the effort to create cell lines that are compatible with the patient's immune system, avoiding rejection [12]. That they are found in many places – ranging from the digestive tract, the central nervous system, circulatory system, musculoskeletal system, and skin – should also highlight that not all stem cells exist in the same environments or are subject to the same chemicals or processes equally [12].

Defining Fasting and Its Effects on the Body

Because there exist a multitude of diets and eating habits – some of which have varied purposes, from weight loss to muscle-building, observing religious practices, and more – it's important to define what is meant by fasting, as opposed to simply restricting calories or introducing/limiting different levels of diverse metabolic building blocks. Of the myriad studies observing the benefits and limitations of fasting, many distinguish short-term periods of fasting as "periodic" and lasting less than two days, while periods lasting longer than two days as 'intermittent' [13]. This is distinct from starvation, in which a person experiences a chronic nutritional insufficiency that typically results in degeneration and death [14]. Studies discussed here also use variations on traditional fasting, including calorie restriction [3], a very-low-carb "keto" diet [2], and a "fasting-mimicking diet" (FMD) [5], while others use the term "dietary restriction" (DR) to indicate a caloric restriction or intermittent fasting in general [1]. Some attempt to relate the results of their animal studies to human equivalents, believing the effects of 24 hours of fasting to equate to a week of fasting in humans [11].

Given that fasting requires an extended period with either limited or no food, it's helpful to recognize what stages the body goes through leading up to the point of inducing stress within the body, and what it is that's physically occurring. This becomes especially important when considering potential patient populations and what challenges they might face by attempting to fast. The progression is as follows:

Missing one meal (roughly 8 hours) - one day: Excusing other potential complications, a person can reasonably expect to experience low blood sugar, leading to irritation, confusion, fatigue, light-headedness, and nausea. The initial slowing of metabolism leads to temporary weight gain as the body tries to hold onto whatever fuel is provided. After glucose is depleted around the 12-hour mark, the liver switches to producing ketone bodies to fuel the brain, and hormones are released, signaling the breakdown of glycogen and fats into useable forms [15]. As ketones increase, inflammation decreases, and DNA repair is encouraged [1-5]. As Human Growth Hormone (hGH) increases, learning and focus improve [5]. Autophagy – the process by which the body consumes its own tissues in a state of starvation – begins around 18 hours, serves as a sort of 'forced clean up' of the body's systems, recycling parts of old cells when no new building blocks are being introduced through ingestion, and resulting in potential benefits for the immune system.

24 hours: The body is forced into gluconeogenesis using glycerol fatty acid breakdown and hGH increases so that protein isn't pulled from the muscles as a fuel source [14]. An increase in Adenosine Monophosphate-activated Protein Kinase (AMPK) signals the body to enter both a very low energy state and to burn fat/continue autophagy [14]. It also lowers the protein Mammalian Target of Rapamycin (mTOR), reducing the anabolic processes of the body, so that no energy or resources are wasted in trying to build compounds [5, 14]. Lastly, there is an increase in Nicotinamide Adenine Dinucleotide (NAD+) because there is not enough energy to convert it back into NADH for reuse in glycolysis [16].

48 hours: The overall stress state on the body can be avoided by doing aerobic exercise, so that it doesn't appear like an emergency that would require carbohydrate reserves, but the general debilitating and run-down feelings persist. At this point, the very low levels of insulin mean lessened inflammation [5,14].

3 days: The beneficial effects of fasting continue to improve and there are some reports of disease reversal – including type 2 diabetes, cardiovascular, high blood pressure, and cancer [2-4,11] – tumors shrink, hematopoietic stems cells evidently regenerate and rejuvenate [14]. All of this strengthens both red and white blood cells, thereby strengthening the immune system [14].

In most arguments in favor of fasting, it is somewhere between the 2- and 3-day mark where most benefits are reported and is considered the goal if the person's aim is to prevent cancer, increase overall immunity against disease, or even to offset the toxicity of chemotherapy [2,11,14]. It is also helpful to recognize that many of the effects of fasting happen both faster and to an increased level with the addition of exercise [17], which may not be advisable for all individuals. In nearly all cases, it is recommended that fasting be supported by some levels of nutrient intake, including sodium and potassium, as well as electrolytes to avoid headaches [18] and dehydration [15,18].

Discussion

There is very little information that directly correlates fasting with a tangible effect on stem cells; instead, either fasting or various

targeted diets are associated with mechanisms not necessarily directed at the stem cell, but through which the body benefits, such as reducing oxidative stress [1,2], reversing an over-response from the immune system [3,5], or altered gene expression [1,4,5,10]. The following studies are only a few of many that have shown that it is these other systems and processes that convey the benefits of fasting, rather than to claim that fasting somehow regenerates stem cells and that they might be considered a target for anti-aging or anti-disease simply through fasting.

In their 2013 study on restricted calories and ketogenic diets, Paoli et al. provided a list of the potential therapeutic uses and the evidence for use in a wide array of therapy/treatments. Among remedies for weight loss, Type 2 diabetes, and epilepsy, they offer some unexpected suggestions that fasting might help against cancer, polycystic ovary syndrome (PCOS), neurological disorders, Alzheimer's, and Parkinson's, among others. Their argument, like many others, is that once the brain runs out of glucose (roughly 3-4 days into fasting), it must rely on ketone bodies provided by the liver, namely β-hydroxybutyric acid; then, because ketones "are able to produce more energy compared with glucose," the body essentially becomes more efficient. Given this information, it should be clear why fasting seems to affect the body in so many ways, benefiting multiple body systems. In addition, the authors offer that it is this increase in circulating ketone bodies that not only inhibit hunger by reacting with hormones ghrelin and leptin, but lower the hepatic glucose output, reversing the insulin resistance that accompanies diabetes, and reducing the neuronal excitability seen in epilepsy. This all points to the idea that the more effective the ongoing biochemistry is within the body, the more efficient normal processes will be. In the discussion that follows, it's clear that these biochemical effects continue to be relevant in research today, and it is such mechanisms that impart the benefits of fasting. Paoli et al. also noted in their discussion on neural disorders, that "Although these various diseases are clearly different from each other, a common basis potentially explaining ketogenic diet efficacy could be a neuroprotective effect in any disease which the pathogenesis includes abnormalities in cellular energy utilization" [2]. While they are referring to neural diseases, it can be valuable to realize that this is also true across the other diseases in the discussion that follows, and to be mindful that the same mechanisms that affect one disease in this way may affect another in a completely different way. This becomes especially helpful in the analysis of the effects of fasting on stem cells, as they too respond differently in different situations.

To study the effects of fasting on neuroinflammation and Alzheimer's, Rangan et al. offered a "fasting-mimicking diet," where mice were cycled between standard rodent chow and a 5-day FMD twice a month [5]. The diet, consisting of "a low-calorie/low-protein but high-unsaturated fat," meant that it simulated water-only fasting in humans, but additionally minimized the stress of prolonged fasting where macro-/micro-nutrients are missing. The results of this study of neuronal stem cells (NSCs) – among other factors – showed that while this diet did seem to "promote stem cell-dependent regeneration in the nervous and other systems" and "FMD cycles increase the expression and generation of NSC's (as indicated by BrdU+Sox2+ expression)," it is still, however, the case that "the contribution of NSC's to the cognitive improvements or connection with Nox2 remains to be investigated" [2]. NADPH oxidase (Nox2) is an enzyme that helps to regulate inflammation [19]. Importantly, while there may be resulting NSC regeneration present, it's because FMD "results suggest that part of the protective effects of the FMD cycles are associated with reduced microglial and Nox_2 activation/levels and therefore reduced O_2- and ONOO- generation and toxicity, which may contribute to cognitive decline by damaging neurons, increasing tau phosphorylation but potentially also by interfering with synaptic plasticity" [5]. This would seem to indicate that toxic products of oxidative stress are the issue and that the FMD reduces their effect. Oxidative stress refers to the radical Reactive Oxygen Species (ROS) that are produced because of multiple cellular processes, including oxidative phosphorylation, whereby mitochondria generate a major source of energy – Adenosine Triphosphate (ATP) [20]. Other studies included in the research by Rangan et al. "concluded that both [calorie restriction] and [intermittent fasting] dietary regimens ameliorate age-related behavioral deficits by mechanisms that may or may not be related to Aβ and tau pathologies" [5].

Another study by Han et al. investigated ketone bodies – which generate in the absence of glucose [15] – on vascular senescence through upregulating Oct4 expression [4]. The references included in the study show that "fasting and caloric restriction extend both the average and the maximal lifespan and prevent age-related diseases through energy sensors dependent on Sirtuin1 or Forkhead box O3 activation... Additionally, calorie restriction-mediated moderation of all senescence... However, it is unknown whether alternative metabolic fuels generated during energy deficit, such as the ketone bodies β-hydroxybutyrate and acetoacetate, affect cell senescence and quiescence, nor what the underlying mechanisms may be" [4]. By introducing β-HB, Han et al. were able to show that the ketone did slow premature cellular aging brought on by stress, but that there's still not conclusive evidence that the products of fasting alter the pathways that bring on cellular aging in vascular cells. Importantly, "Quiescence not only avoids initiation of the senescent program but also contributes to the maintenance of stemness, allowing cells to be resistant to genotoxic stress, a major trigger of cellular senescence" [4]. The authors make it clear that we don't know if ketones alter the aging process, but the claim here is that fasting-acquired ketones cause cellular inactivity, thereby inhibiting vascular cells from a cessation in both division and growth, and it does so by stabilizing Oct4 mRNA and thus its expression. Among the stressors discussed, toxic oxidative stress appears again, specifically hydrogen peroxide (H_2O_2), which activates senescence in cells, causing them to stop dividing and growing. Elevated ketone bodies, like β-HB, are believed to be "anti-aging and this study showed that it is β-HB specifically that stops H_2O_2 from senescence-effects on cells, by suppressing H_2O_2 from causing expression of [Interleukin-6] and [Interleukin-1α]" [4]. This means that a ketone resulting from fasting caused the apparent benefit, but within this study, it was acting on Human

Umbilical Vein Endothelial Cells (HUVECs) and Human Aortic Smooth Muscle Cells (hASMCs). Here again, the results give a two-fold argument that while stem cells do appear to benefit from fasting, it's due to other mechanisms in play, and the cells being studied are not actually stem cells, diminishing any claims we might make as to the effectiveness of fasting on stem cells. By comparing the addition of β-HB to stressed and non-stressed umbilical vein cells, this study showed that β-HB suppressed the negative effects of oxidation marker genes and upregulated 'inactivity' markers when no stressors were present. Ultimately, while the β-HB generated through fasting reverses the growth arrest brought on by the products of oxidative stress, it is not proof of stem cell regeneration. As Han et al. state, "Cellular quiescence is a crucial process for maintaining the stemness of embryonic stem cells through inducing autophagy. We did not show sufficient results to prove β-HB induces autophagy..." [4].

Mikirova et al. chose to investigate the effects of losing weight through a low-calorie diet on cardiovascular disease, particularly looking at the CD34+ progenitor cells circulating through the blood [3]. Though the low-calorie/supplement approach is not true fasting, it offered a look at any potential change in progenitor cells resulting from a significant change in body weight and body composition in human subjects. As per their discussion, obesity leads to many cardiovascular issues and "All of these abnormalities create a state of constant and progressive damage to the vascular wall, manifested by a low-grade progressive inflammatory process and endothelial dysfunction" [3]. Additionally, they offer other studies showing that proinflammatory cytokines and dyslipidemia damage endothelial cells and lead to disease. The presence of the CD34 phosphoglycoprotein is a marker for progenitors and proliferation across many cell types [21]. The circulating CD34+ progenitors in question – which give rise to endothelial cells and maintain vessels – could then potentially serve as a measure of improving/worsening vascular health. At the conclusion of the study, all participants showed a decrease in white blood cell counts, along with an increase in circulating CD34-positive cells "by an average of forty percent" [3]. This lends to the claim that there was an "improvement of circulatory progenitor cell numbers" and "that the improvement of body composition affects the number of stem/progenitor cells in circulation" [3]. Though the authors suggest that "increasing the number of CD34-positive cells during [cardiovascular] treatment may provide an indicator of improvement of vascular health," their study not only utilized a dietary regimen other than true fasting but was also directed at enhancing weight loss to improve cardiovascular health overall. CD34+ progenitor cells circulating in the blood should be a good indication of stem cell function, and those that experienced weight loss in the study saw an increase in these cells, but the concern that obesity leads to oxidative stress – to which hematopoietic stem cells are sensitive – means that the apparent goal is to reduce oxidative stress, which does not act exclusively on stem cells.

In a study exploring another end of the dietary spectrum – a chronic high-fat diet (HFD) – Perbellini et al. were able to induce a pre-diabetic state in mice, allowing them to look at how the mesenchymal cell population was affected in both cardiac and adipose tissue. Though the study was designed to answer questions about the potential use of self-stem cells in treating myocardial infarction and prevention of heart failure, it proposed that the number of fibroblasts and adipose-derived hematopoietic cells increase on an HFD, while cardiac progenitors are left unaffected [10]. This points to an extremely relevant insight: not all stem cells across the body are affected in the same ways by diet (or lack thereof). At the time of the study, mesenchymal cells looked promising for treatment after heart attack, so by providing mice with either a rodent chow high in carbohydrates, protein, and oil, or a control chow, the authors were able to differentiate between fasting groups that had been subject to high fat intake over time versus those who had had a standard diet prior to fasting. The HFD increased the fibroblasts and hematopoietic cells in fat tissue but left the cardiac progenitors unchanged. When looking at the two cell types – cardiac and adipose – from both HFD and standard diet, the study looked to the clonogenic capacity of each, stating that it "is usually associated with stemness in cell populations," however, "...No differences were noticed between the clonogenic capacities of cells from the two diet groups" [10]. Interestingly, the adipose cell populations showed a low capacity for making colonies, which decreased over time, while the cardiac stemness was slightly better and increased over time, but the authors still point out that it was not to a significant level. In the explanation, it becomes clear that a HFD led to "genes expressed earlier in differentiation" in those cells, some of which include GATA4 and Desmin, suggesting that they become expressed earlier to make up for the damage that's being done through poor diet. GATA4 is a transcription factor that plays a role in cardiac cell differentiation, as well as preventing apoptosis of cardiac cells post-infarction [22], and Desmin is a muscle-specific intermediate filament that's essential for proper muscular structure and function [23]. In both cases, the early expression of these genes with a diet high in fat indicates an attempt at genetic recovery against cellular damage. Further investigation into the diabetic phenotype showed that the HFD mice had elevated plasma glucose, with "greatly reduced cardiac [glucose transporter type 4] GLUT4 protein levels" meaning "reduced insulin-mediated glucose uptake in [mice] hearts...suggesting that this metabolic disturbance plays a causative role in the cardiac dysfunction seen in diabetes" [10]. That GLUT4 expression fell with the high-fat diet meant that metabolizing glucose – the most efficient form of breaking down materials for energy – suffered, and instead the mice were forced to use fatty acid oxidation. Once again, though stem cells may be affected, it is the course of metabolic processes that are directly altered through changes in diet. At the conclusion of their study, Perbellini et al. offer that there's no reason that obese patients can't use cardiac cells in post-infarction treatment, however, "syndromes such as diabetes can alter the progenitor cell populations and their functionality in various tissues" when considering adipose cells [10]. This further lends to the idea that a poor diet can negatively affect some types of stem cells, and how essential it is to recognize that not all stem cell types are created equal; this is certainly also true about fasting, that it has the potential to be beneficial, detrimental, or neutral.

In addressing the effects of meal size and frequency on neuronal cells, Mattson et al. claim that "DR [dietary restriction; either caloric restriction or intermittent fasting, with maintained vitamin and mineral intake] can stimulate the production of new neurons from stem cells (neurogenesis) and can enhance synaptic plasticity, which may increase the ability of the brain to resist aging and restore function following injury" [1]. By examining how caloric intake affected the lifespan and development of disease in mice, they offered many avenues through which the body reacts to an altered diet. Among their explanations are changes in 1) genetic expression due to lessened oxidative stress, 2) the levels and sensitivity to neurotransmitters, 3) a hormesis cellular response, whereby 'injury' to the cells encourages genesis of that cell type in a sort of survival mechanism, 4) mutated enzymes, 5) upset calcium homeostasis, and 6) diminished energy metabolism. Ultimately, they state that "it appears that a major contribution of the beneficial effects of DR on neurons comes from a cellular stress response in which level of protein chaperones and neurotrophic factors are increased" [1]. In contrast – and regarding an unrestricted diet – they offer that the prevalence of disease also comes from many factors, potentially including damage through excessive ATP production, genetic and environmental factors, and "increased levels of cumulative oxidative stress as the result of increased glucose metabolism and consequent superoxide production" [1]. Interestingly, the authors note through studies on the benefits of DR, that fasting was still more successful in neuroprotective effects than reduced calories alone, even though the mice consumed twice the amount of food when released from a fasting cycle. "These findings suggest that increasing the time interval between meals is beneficial, even when the size of the meals is increased to a level that results in no overall decrease in caloric intake" [1]. In addition to the basic challenges fasting produces, Mattson et al. also address studies where "Caloric restriction did not prevent the age-related decrease in the density of inhibitory synapses and, surprisingly, decreased the density of excitatory synapses," [1] lending to the argument that diet affects cell types differently. Other studies reported that mice with mutated endocrine receptors resulted in death because they were unable to regulate glucocorticoid/blood glucose in response to fasting, and studies on Amyotrophic Lateral Sclerosis (ALS) models were also an exception because "Disease onset was unaffected by DR, and once the mice became symptomatic the progression of the disease was accelerated" [1]. This should make anyone wary about the effects of fasting on all cell types, including stem cells. Without further discrete research specifically directed at all types of stem cells, it is dangerous to ignore all the supplemental factors present in an individual. To this point, the authors were able to gather from across studies that "the stress associated with DR appears to be fundamentally different than that induced by other stressors such as psycho-social stress, restraint stress, etc." [1]. By looking at the expression of glucocorticoid and mineralocorticoid receptors in neurons, they saw that dietary stress activates mechanisms not seen in other stressors. This may be why it's so appealing – and oftentimes useful – to use changes in diet as a cure or preventative measure. As other authors mention, it may be that fasting leads to cell death but the feeding that follows results in high proliferation due to the introduction of growth factors [14]. This points to the idea that stem cells do not truly regenerate during fasting, but rather that the feeding afterwards encourages cellular regrowth.

Another study by Bonilla et al. compared the effects of radiation on the intestinal crypts of both fed and fasted mice, with the aim of seeing whether the change in diet might influence the effectiveness of radiotherapy against pancreatic cancer. The results indicated that – after a 24-hour fast, the equivalent to one week in humans – there was "improved intestinal stem cell regeneration" [11]. As noted in multiple studies above, fasting does not affect all cells in equal measure, and it's worth noting that, because the intestinal stem cells are directly subject to changes in diet by virtue of being part of the digestive tract, they may or may not be affected in ways that other stem cells are not. At the conclusion of the study, the authors relate that fasting resulted in the dual benefits of improved intestinal crypts post-radiation and causing increased radiosensitivity to the induced tumors, as compared to mice who were fed normally in the 24 hours prior to radiotherapy. It is very important to keep in mind that the point of the study was to look at potential protective effects gained through fasting prior to radiotherapy, and that the aim of the study was not simply to explore regeneration of stem cells. While the results are certainly instrumental in working towards more-effective, less-damaging radiotherapy against tumors, the study specifically examined stem cells after they'd been bombarded with radiation. As a result of the improved crypts – perhaps among other mechanisms activated through fasting – fasted mice showed intestinal recovery after only 10 days, whereas the fed-mice perished due to the radiotoxicity. This meant that the study was unable to look at the intestinal stem cell generation over the long-term, to compare it to fasted mice 180 days post-radiation.

While these results seem encouraging, Bonilla et al. clarify "These results indicate that in [small intestine] crypts, fasting on its own did not induce Deoxyribonucleic Acid (DNA) damage, nor did it significantly impact the generation or resolution of DNA damage following radiation" [11], highlighting once again, that – while there may be some correlation between fasting prior to pancreatic radiation and improved intestinal recovery – fasting does not actually fix the damage that the radiation caused. The authors offer that perhaps "fasting may protect SI crypt cells from IR-induced [Interventional Radiology] apoptosis or that apoptotic cells were cleared more readily in fasted animals" [11]. In accord with previous studies, fasting-induced autophagy may play a role in 'cleaning up' after cell damage. However, Bonilla et al. clearly state "Fasting alone did not significantly affect the median survival of unirradiated tumor-bearing mice" meaning that, without radiation, fasting had no effect on the stem cells present in the intestine, though it did "[reduce] the capacity of pancreatic tumors to repair the DNA double strand breaks induced by IR" [11]. The authors also admit that the study could not be fully examined due to the die-off of the fed-irradiated cohort, having been euthanized for the sake of GI toxicity. Bonilla et al. go on to offer outside studies that show intestinal cells "de-differentiating" when crypts are damaged, and so-called "revival stem cells" that activate following radiation; at the time of writing (2020), the

authors could only recommend that further research explore these cell types under fasted or fed conditions, as well as apply their methods of study to other stem cell types found elsewhere in the body. Lastly, the authors note that one theory about why fasting imparts some sort of protection against radiotherapy does not hold true in every case: through downregulating circulating Insulin-like Growth Factor 1 (IGF-1) – a mechanism meant to protect normal tissue while sensitizing tumors – made mice more sensitive to the damage of etoposide treatment for lung/testicular cancer.

Conclusion

It would seem common sense that fasting, which puts the body into a stressed state and ultimately denies cells access to energy once stores are depleted, would be detrimental to all cell types, including stem cells. Recent evidence suggests that fasting slows the aging process [4,13] but is this another hopeful attempt to find a miracle cure against disease and death? Fasting has the potential to cause a number of negative side effects, including: 1) affected mental state, leading to anxiety and depression due to the release of the "stress hormone" cortisol, 2) because the brain can use glucose as a fuel-source, denial of glucose can lead to reduced reaction times and general feelings of malaise and illness, 3) you may lose the ability to respond to the hormonal cues of leptin and ghrelin, making hunger and satiety difficult to decipher, perhaps leading to psychological disorders like binge eating, 4) a serious risk of nutrient deficiencies if supplements are not monitored, and 5) irregular digestion could lead to nausea and diarrhea, leading to higher risk of other disorders [2,11]. Importantly, Longo et al. offer that fasting results in a relatively immediate decrease in glucose, insulin, and IGF-1, which causes cell death or atrophy in many tissues, but it is followed by an unusually high rate of cellular proliferation driven by growth factors during feeding following a fast; equally important is that if carcinogens are introduced during this feeding, there's an increased level of carcinogenesis [14]. Even with these potential negative effects, there is currently a wide range of research looking to discover if fasting offers benefits beyond weight loss, pointing to instances of decreased inflammation, improved blood pressure, the prevention of neurodegenerative disorders and cancer, and delaying the aging process [13-15].

Many of our population's current disorders come from our inability to balance what we eat and how often, against our body's energy needs, along with inactive lifestyles [1,13,14]. Traditionally, humans have had to rely on getting food when they could, so it made sense to store glucose. In fact, there are seven hormones that raise blood sugar (glucagon, cortisol, epinephrine, thyroxine, hGH, and Adrenocorticotropic Hormone (ATCH)) and only two that lower it (insulin and somatostatin) [24]. That there exist so many avenues for our body to get the energy needed for performing millions of daily processes, should serve as an indicator as to just how important it is that when our body needs energy, it's going to find a way to get it. It's the sudden lack of glucose that signals our body to experience hunger, however, there is evidence that the brain prefers ketones – the fuel produced by the chemical breakdown of fat in the liver – and many people report better sleep and mental clarity during a ketogenic state [6,14].

For some, there are undoubtedly benefits to a change in diet. It should never be the case that someone fasts without the recommendation and guidance of a medical or nutritional professional. As Bonilla et al. recognized, "we do not envision that fasting beyond 24 hours would be advisable in pancreatic cancer patients, many of whom are already underweight and/or cachectic" [11]. Beyond the challenges of fasting, there's simply not enough research currently to claim that fasting causes stem cell regeneration [4-6]. This claim is both misleading and potentially dangerous when considering patient therapies. As Perbellini et al. remind us, no one diet is going to affect every stem cell the same in every instance [1,2,10]. It is my hope that further research will singularly examine the effects of altered diets on all stem cells, with minimal confounding factors, and with the objective of better patient health overall, both preventative and restorative.

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