



## Editorial

## Religious fasting and the vascular health

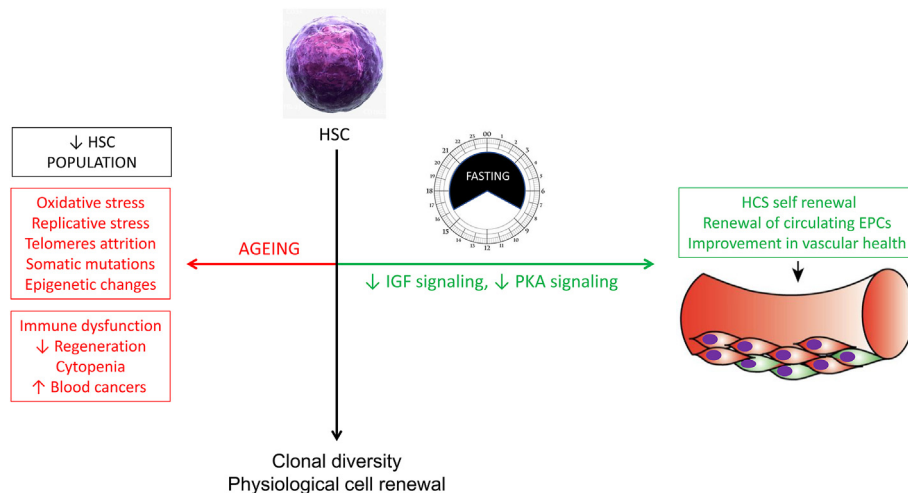
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**1. Preamble**

Prof. Rakesh Yadav, Editor-in-Chief of the Indian Heart Journal, during his interview with Prof. Jagat Narula complimented the legendary alum. Three major discussion points stood out. First, how did the Indian medicine influence the modern western medicine, and cardiology in particular?" Prof. Narula claimed that even

the name HEART was derived from **Hridaya** that conveyed a complete physiological meaning, comprising 3 verbs- **HRU** for harati (to receive from or to abduct), **DA** for dadati (to give or to donate), and **YA** for either yagati (control through self-generated rhythmicity) or Yama (maintaining balance for contraction and relaxation, to circulate).<sup>1</sup> **Second** discussion point focused on the relevance of tradition of **Upavasa**, practiced in India for thousands of years. Prof. Narula highlighted a potentially strong association of fasting with exaggerated release of endothelial progenitor cells and consequently superior vascular health. The circulating levels of endothelial progenitor cells are manifold greater in women of reproductive age offering them a protection against endothelial injury and rendering them to be more resilient against heart disease. Supported by his 4 colleagues, he discusses global religious practices and the basis of improved vascular health resulting from **fasting**. During the **third** discussion point, Prof. Yadav lauded Dr. Narula's editorial contributions to the field of cardiovascular medicine, and asked about the inspiration for his editorial prowess which the Indian Heart Journal would publish in a subsequent issue.



**Fig. 1. Fasting, hematopoietic stem cells (HSC) and vascular health.** HSC contribute to clonal diversity and physiological cell renewal in various organ systems such as GI and respiratory tracts, endometrium and vascular endothelium. HSC population decreases with ageing (left) and is associated with increasing cellular loss and decreasing cell replenishment; somatic mutations are also associated with blood malignancies and vascular inflammation. Intermittent and/or prolonged fasting has been demonstrated experimentally to influence Insulin-Like Growth Factor-1 (IGF-1) signaling (right) and at least partially restore HSC integrity leading to superior vascular health, amongst other stem cell and non-stem cell-based beneficial consequences.

**2. Upavasa and vascular endothelium**

**Abbreviations:** HSC, hematopoietic stem cells; EPC, endothelial progenitor cells; IGF, insulin-like growth factor; PKA, protein kinase A; NAD, nicotinamide adenine dinucleotide.

The global burden of atherosclerotic cardiovascular disease continues to grow, and is the most important cause of mortality worldwide.<sup>2</sup> The deteriorating lifestyle behavior, including eating

patterns and lack of indulgence in physical exercise have contributed immensely to the growing burden of disease. The increasing prevalence of obesity is associated with increased incidence of metabolic disease, diabetes, hypertension, and fatty liver, all of which contribute to atherosclerotic cardiovascular disease. The need to reduce this global atherosclerotic burden is imperative. Caloric restriction has been demonstrated to be associated with improvement in physical endurance, blood pressure, heart-rate variability, and glucose metabolism.<sup>3–8</sup> This review will focus on the potential role of stem cells in mediating the benefits of decreased caloric intake in prevention of atherosclerotic disease.

Since prehistoric times, more than 12,000 years ago, abstinence from food or drinking or both have been a part of human living. In pre-agricultural era during Paleolithic times, our prehistoric ancestors were exposed to undeliberate intermittent fasting for various periods of time while searching for food, between hunting and gathering. These factors have compelled the human body to incorporate fasting as a physiological (rather than a pathological) process, and to adapt and thrive during both fasting and eating. About 10,000 years ago, during agricultural revolution in Neolithic era, when humans started to domesticate animals such as goats and sheep, and started farming and growing crops, undeliberate fasting disappeared from diurnal human life. At this time, humans learned to store food, and arguably initiated a culture of scheduled meals through the day. *Ayurveda* (science of life, Sanskrit) has its roots in the *Ajur-veda* (science of longevity)- an appendage to the *Atharvaveda*, was compiled around 5000 BC, by the priests and the scholars of Ayurveda, including *Dhanwantari*, *Charaka*, *Sushruta*, and *Vagbhata*. Deliberate fasting was first introduced; in ancient India with an aim to strengthen the spirit and ensure health wellness; Ayurveda claims *Langhanam param aushadham*, or that fasting is the best medicine.

When Alexander invaded India in 326 BC, he brought the *vaidyas* (Ayurvedic practitioners) with him to Greece, who in turn further influenced the evolution of Greek Medicine.<sup>1,9</sup> There is no evidence that *Hippocrates* had proposed *thy food to be thy medicine and thy medicine to be thy food*,<sup>10</sup> even though he has been credited for it. Ancient Greek philosopher, *Pythagoras* promoted fasting (abstinence from all food for a certain period) as a way to enhance physical strength, energy level and concentration in his students.<sup>11–13</sup> Over the last decade, various types of fasting have gained popularity as a dietary modification for weight loss and as a part of the non-pharmacological strategy for primary prevention of cardiovascular disease.<sup>14</sup>

*Intermittent fasting* where food intake is restricted to a certain time period, has long been present in many cultures around the world and has been a part of all major religious beliefs and practices. Most prominent religions such as Christianity, Islam, Hinduism, Judaism, Buddhism, Jainism and Taoism promote different types of fasting for spiritual purposes as also for known health benefits and longevity. Numerous health benefits of fasting have been supported by experimental<sup>15</sup> and clinical studies.<sup>16,17</sup> Decreased inflammation, neuroendocrine activation, reduced mitochondrial oxidative stress,<sup>11</sup> and activation of autophagy in endothelial cells that accompany intermittent fasting prevent cell death<sup>18</sup> and promote proliferation, regeneration, and activation of endothelial progenitor cells.<sup>18</sup> Fasting has beneficial effects on cardiovascular health through modification of common risk factors such as better blood pressure control,<sup>11</sup> increased insulin sensitivity and better control of blood glucose level. The direct beneficial effects of prolonged fasting on the vasculature could be exerted through activation of endothelial progenitor cells (EPC) and promotion of endothelial cell regeneration. Caloric restriction has been demonstrated to impart cardiovascular benefits to fruit flies,<sup>19</sup> rodents<sup>20–24</sup> and humans.<sup>25–29</sup>

It is important to review different religious practices of fasting and their relationship with direct health benefits through promotion of EPC activity and vascular regeneration.

### 2.1. Different types of religious fasting and cardiovascular effects

Different types and durations of nutrient restrictions has been a part of cultural and religious practices all around the world.<sup>30–33</sup> Fasting in Hinduism is commonly practiced, more so during religious festivals as an offering of self-sacrifice to pleasing the Gods. Ayurveda advocated fasting to cleanse the body of toxic materials and eliminating disease. Gandhi practiced fasting as an instrument of advocacy, to resolve moral dilemmas or during periods of self-reflection, and on many occasions fasting unto death during the pursuit for freedom of India from the British. He wrote “*Food should be taken as one takes medicine in measured doses, at measured times and as required. A ‘full’ meal is a crime against God and humanity. Hence the need for total fasts at intervals and partial fasts forever. What is enough [food] is a matter of conjecture, therefore, of our own mental picture. What we often think is spare or meager is likely more than enough. More people are weak through over-feeding or wrong feeding rather than underfeeding*”.<sup>34</sup> Communal fasts in Hinduism are typically associated with religious events such as *Ram Navami*, *Shivaratri* and *Janmashtami*, some Hindus fast on the eleventh day of the lunar fortnight called *Ekadashi*, and others fast on an elected day of the week often dedicated to a particular deity. The rigor of fasting intervals and type of food consumption vary. Fasts could comprise complete abstinence from food and water or simply consumption of vegetarian food. The *phalahar* category includes food grown naturally such as vegetables, fruits, roots and tubers, flowers or leaves, and excludes *anna*, such as wheat, barley, rice and lentils.<sup>9,35</sup>

Buddhism integrates fasting as a part of *Danjiki*, an ascetic traditional ritual that involves fasting (abstinence from solid food, drinking water, with limited carrot juice and miso soup for electrolyte replenishment), meditation and strenuous physical training. *Danjiki* can be short-termed (2–3 days) and longer lasting (a week or longer). Limited studies/case reports have shown that *Danjiki* was associated with decrease in body weight by 5 kg, lower level of LDL cholesterol and triglycerides levels but no effect on fasting glucose level and blood pressure.<sup>36</sup>

In Christianity, particularly Roman Catholicism and Eastern Orthodoxy, there are various types of fasting throughout the year particularly during *Advent*, a penitential period before Christmas and a 40-day fasting during *Lent*, a spring period of penitence before Easter. In 1962–65 the Second Vatican Council allowed greater individual choice with mandatory fasting only on *Ash Wednesday* and *Good Friday* during Lent. Fasting frequently involves removing animal protein, refined sugars and sweets from the diet. Coptic Christians fast for 210 days in a year ([www.culturalawareness.com](http://www.culturalawareness.com)). In the Indian state of *Kerala* many Catholics fast by avoiding meat including eggs for 25 days before Christmas. Protestant churches generally leave the decision to fast to individual followers.

In the Islamic lunar calendar, Muslims observe *Ramadan* during the ninth month, known as the month of *the Quran*. Fasting is one of the five pillars of *Islam* and it commemorates the revelation of the *Quran* to the *Prophet Muhammad*. During the month of Ramadan, Muslims abstain from any food and beverage (including water) during the daytime, between sunrise and sunset. Intermittent fast is integral part of worship and celebration of the Almighty and physical way to cleanse the body and soul. Exceptions from Islamic recommendations are those who are ill, elderly, children, pregnant or breastfeeding women or those traveling. Ramadan fasting most closely mimics form of intermittent fasting that has now gained

popularity as a non-pharmacological way to lose weight and improve cardiometabolic health. It has been shown that Ramadan fasting is associated with reduction in total and LDL cholesterol,<sup>30,37,38</sup> and there is a marked increase in HDL cholesterol.<sup>38,39,40</sup> In addition to the obligatory fasting of Ramadan, there is *Sunnah* fasting wherein individuals fast two days a week, typically Mondays and Thursdays throughout the year.

Jains fast during religious festivals such as *Siddha Chakra* and *Paryusanan*. *Siddha Chakra* occurs twice a year, wherein they drink only water and eat one boiled food each day. *Paryusanan*, is an 8- or 10-day period of austerity in August–September drinking only boiled water. Fasting is often conducted according to prescribed rules and meditation that lead to a dissociated transcendent state.<sup>41</sup> Devout Jains avoid onions, garlic, root vegetables, fruits, fermented seeds, eggs, fish and meat; they follow other ascetic practices including meditation and variable vows of silence. Zoroastrianism prohibits fasting because of its belief that frugality does not aid the faithful in combating evil. However, they are supposed to avoid meat during the eleventh month of the Parsi year. Sikhs celebrate major festivals of their native Indian state of Punjab such as *Holi*, *Lohri*, *Baisakhi* and *Sankranti*. They also celebrate the day of foundation of the Sikh community and also honor their religious masters – Guru Teg Bahadur and Guru Arjan, for the martyrdom, and birthdays of Guru Nanak and Guru Gobind. During these festivals vegetarian lunch or langar is served in the community kitchen. Judaism has several dietary laws and customs and they observe fast days several times in a calendar year particularly during mourning or periods of penitence such as *Yom Kippur* (the day of Atonement). Caloric restriction, therefore, has been advocated by most religions globally for over centuries.

## 2.2. Fasting promotes stem cell and endothelial progenitor cell function

With aging, stem cells lose the ability both to proliferate and differentiate, and these changes contribute to biological aging. Changes in hematopoiesis,<sup>42</sup> particularly after the age of 70 years, are associated with immune dysfunction,<sup>43</sup> reduced capacity for regeneration,<sup>44</sup> cytopenia<sup>45,46</sup> and increased risk of blood cancers.<sup>47,48</sup> At the cellular level there is a gradual but lifelong accumulation of molecular changes including oxidative and replicative stress, attrition of telomeres, somatic mutations and epigenetic changes.<sup>49–51</sup> With ageing, there is a collapse of clonal diversity which is abrupt after 70 years, with loss of physiological cellular renewal including esophagus,<sup>52</sup> bronchus,<sup>53</sup> endometrium<sup>54</sup> and skin<sup>55</sup>. Fasting has profound impact on bone marrow cellularity<sup>56–59</sup> including hematopoietic and mesenchymal stem and progenitor cells,<sup>60,61</sup> gut immune cells<sup>62</sup> and bone marrow adipose tissue.<sup>63,64</sup> Tissue renewal is essential to maintain homeostasis and for healing tissue damage. Fasting or caloric restriction has been shown to help restore stem cell function and health into old age.

Fasting promotes hematopoietic stem cell (HSC) function<sup>60</sup> and has been implicated in the regulation of their self-renewal; cycles of short-term fasting, especially a 48 h fast once per week enhances hematopoietic stem cell self-renewal in mice, at least in part through reduced activity of insulin-like growth factor (IGF) signaling pathways. These positive effects of prolonged fasting have been shown in aged animals, which typically exhibit a reduction in hematopoietic stem cell function and multi-lineage potential. The effects of prolonged fasting could be reproduced in mice lacking the growth hormone receptor, which also have low levels of IGF-1. Transplantation experiments showed that low levels of IGF-1 in mice led to a reduction in IGF-1-mediated PKA signaling, both in hematopoietic cells and in associated stromal cells. The

hematopoietic function could be restored by siRNA-induced reduction in the levels of either IGF-R1 or the PKA catalytic subunit; benefits were abolished if exogenous IGF-1 was added. Hematopoietic stem and progenitor cells residing in the adult bone marrow were part of the Lin<sup>−</sup> Sca1<sup>+</sup> c-Kit<sup>+</sup> (LSK) population, and these cells were responsible for adult hematopoietic regeneration. The LSK population includes the self-renewing long-term (CD48<sup>−</sup> CD150<sup>+</sup>) and short-term (CD48<sup>+</sup> CD150<sup>−</sup>) hematopoietic stem cells and the multipotent progenitors (CD48<sup>+</sup>).<sup>65</sup> In the heterogeneous hematopoietic stem cells, several HSC subtypes are identified as lymphoid (Ly-HSC), balanced (Bala-HSC), and myeloid (My-HSC) according to their distinct mature blood cell output. In both mice and humans, these HSC subtypes modulate hematopoietic lineage potential and play an important role in lineage-homeostasis during aging. The role of multiple prolonged fasting cycles, lasting 2 days or more, on age-dependent and chemotherapy-induced immunosuppression were investigated in HSC self-renewal, and hematopoietic reconstitution outcomes through Ly-, My-, and Bala-HSC subtypes<sup>60</sup>; there was also a reversal of the age-dependent decline in the lymphoid-to-myeloid ratio.<sup>61</sup> The number of total and BrdU<sup>+</sup> mesenchymal progenitor stem cells increased 5- and 45-fold in the fasting (469.8 ± 179.5 and 69.8 ± 34.0) compared with control (95.5 ± 16.7 and 1.5 ± 0.6) mice. It has been proposed that a class of NAD<sup>+</sup> dependent deacetylase enzymes, sirtuins (SIRT 1–7) mediate epigenetic<sup>66</sup> and metabolic<sup>67</sup> influences, including beneficial effects of caloric restriction<sup>68</sup> on progenitor cells. Circulating endothelial progenitor cells contributed to ongoing endothelial repair.<sup>69, 70</sup> It is, conceivable that the fasting-induced HSC could contribute to renewal of endothelial cells throughout the vasculature and contributes to vascular health.

## 2.3. Conclusions

Targeted studies are needed to determine how intermittent fasting in humans improves vascular health. Is it a simple replenishment of risk factor (hypercholesterolemia, smoking, hypertension, hyperglycemia)-mediated exfoliation of endothelial cells? And that could be the easiest explanation for immediate effect of fasting. Or, is it a complete endothelial progenitor cell-mediated adult vasculogenesis as a main pathway of vascular regeneration including partial reemergence of traditional angiogenesis program? Irrespective of the mechanism involved therein abundance of endothelial progenitor cell release consequent to various fasting regimens is sufficient evidence for scientific basis of fasting or intermittent fasting rather than sidelining it to be an unsubstantiated religious fad.

## Funding

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