Review

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Review

A Biochemical View on Intermittent Fasting Effects on Human Physiology—Not Always a Beneficial Strategy

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Simple Summary: Intermittent fasting (IF) has gained popularity both as a dietary practice and as a potential therapeutic approach in clinical settings. While widely used for health benefits such as weight management and improved insulin sensitivity, its effects on various diseases remain complex. Studies suggest IF could influence metabolic processes, alleviate obesity-related conditions like type 2 diabetes, and improve mental health, but responses vary significantly across individuals. Recent research highlights its potential in treating diseases like non-alcoholic fatty liver disease, cardiovascular conditions, and cancer, though long-term effects are still under investigation. The mechanisms behind IF, including activation of metabolic pathways like AMPK, may offer insights into how it can be more effectively applied in specific patient groups. However, the evidence supporting IF as a universal disease-modifying strategy is limited, and many proposed trials may lead to disappointing results. This review argues that the therapeutic potential of IF should be carefully considered, with future research focusing on optimizing protocols for individual needs and specific pathologies.

Abstract: Intermittent fasting (IF) has emerged as a widely practiced dietary regimen, increasingly utilized in both clinical and non-clinical settings for its potential health benefits. Evidence suggests that IF can improve metabolic health by enhancing insulin sensitivity, reducing inflammation, and aiding weight management. Recent studies have also explored its role in mitigating obesity-related diseases, such as type 2 diabetes and non-alcoholic fatty liver disease, and its ability to support cardiovascular health and mental function. However, the effects of IF are not universally beneficial, with a significant portion of patients showing no clinical improvement or even worsened outcomes. The mechanisms underlying IF, including metabolic switching and activation of adenosine monophosphate-activated protein kinase (AMPK), suggest that the benefits of IF may be context-dependent, varying with individual pathologies and metabolic states. While preclinical data indicate potential therapeutic effects in diseases like cancer, rheumatoid arthritis, and neurodegenerative conditions, these findings are not yet sufficiently supported by human studies. Moreover, while IF's impact on fat metabolism and lipolysis is well-documented, its effects on muscle function and long-term metabolic health, particularly in athletes or those with advanced disease, require further investigation. This review argues that while IF holds promise as a disease-modifying strategy, its application must be tailored to individual patient profiles, and future clinical trials should focus on optimizing fasting protocols to enhance therapeutic outcomes.

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1. Intermittent Fasting Is Increasingly Used in a Medical/Clinical Context

Intermittent fasting constitutes a voluntary temporal abstinence or reduction in food consumption, usually according to a (semi-)circadian or pattern. Being a popular form of dieting, intermittent fasting is widely practiced for a variety of societal or religious reasons (e.g., Ramadan), but also increasingly for its perceived health benefits [1,2]. With respect to the latter, a substantial body of research has shown that intermittent fasting exerts a wide spectrum of impacts on improving indicators of health, especially with regard to weight management [3] while recent meta-analyses support its effects on insulin sensitivity [4] and inflammation [5], even as a recent study failed to replicate an effect of time restricted eating over calorie restriction *per se* on metabolic health in obese individuals [6]. Intriguingly, preclinical work in experimental rodents [7] supports that intermittent fasting is associated with a prolonged life expectancy, although there is a paucity of data that corroborate that for humans similar effects exist as well [8]. A recent study in elderly human subject, however, showed improved mental faculties following intermittent fasting [9]. Thus the body of evidence that supports intermittent fasting as a healthy life choice appears compelling.

Not surprisingly, the notion that intermittent fasting supports health has led to studies investigating the potential use of intermittent fasting as a disease-modifying strategy. While short-term studies certainly support improved clinical behaviour of obesity-related diseases like type 2 diabetes [10] and non-alcoholic steatotic liver disease [6], beneficial responses to intermittent fasting are certainly not universal, with a substantial fraction of patients actually showing worse clinical course when submitting themselves to intermittent fasting [11], while a recent meta-analysis showed that apart from increases in high-density lipoproteins, intermittent fasting had no significant long-term effects on insulin, haemoglobin A1c%, total cholesterol, low-density lipoprotein, or systolic blood pressure in obesity [12]. In oncological medicine, intermittent fasting has been linked to improved responses to advanced chemotherapeutic regimens like FOLFOX [13] while trials investigating its potential for improving quality of life when subjected to such therapy are currently conducted as well [14]. Also in rheumatoid arthritis and asthma, positive effects of intermittent fasting have been reported [15,16] and further trials have been initiated [17]. Similarly, trials in autoimmune disease like Inflammatory Bowel Disease [18,19] and lupus [20] are contemplated as well. Prompted by encouraging results in mice, such studies are proposed in Parkinson's disease [21] and stroke [22,23] as well. In animal studies, the improvements in cardiovascular health indicators show up at 2–4 weeks after the start of intermittent fasting [24] and a clinical trial in myocardial infection has been initiated [25]. Hence, it is fair to say that a broad variety of pathologies will be investigated in the near future for its potential to be clinically targeted through intermittent fasting.

Here, however, we shall argue through exploring the biochemical effects of intermittent fasting, that its effects are likely restricted to specific patients and pathologies. As insight into the mechanisms mediating the effects of intermittent fasting, beyond calorie restriction slowly emerge it should become possible to identify specific individuals like to benefit from intermittent fasting and also to develop more effective fasting protocols. Overall, we shall argue that many of the currently proposed trials are likely to yield disappointing results.

2. Intermittent Fasting and Reset of Metabolic Physiology

Intermittent fasting *per se* is associated with reduced calorie intake both in experimental animals [26] as well as in human subjects [27], although over time this decrease in energy intake diminishes as compensatory behaviour develops and compliance diminishes [28]. Although in general, the degree of weight loss achieved with intermittent fasting is on a par with that achieved with traditional dieting approaches (daily calorie restriction) [27], vocal intermittent fasting advocates maintain that periodic fasting helps resetting metabolic processes (so-called metabolic switching [29]) in turn supporting fat utilization and insulin sensitivity. This idea is supported by pointing out an evolutionary perspective. It is maintained, originally based on the Kalahari Research Project data that primitive Dobe !Kung hunter-gatherers often consume meals twice a week while maintaining a

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vigorous physiology, even as more recent research has discredited this notion [31]. In addition, it can be argued that as great apes spend most of the day foraging and eating [32], constant food intake has been the evolutionary norm for our species. Regular meals mitigate glucose spikes [33] and has thus been proposed to protect pancreatic beta cells from overstimulation in diabetes [34], a key aspect in long-term metabolic health in these patients. In apparent agreement, in obese subjects, ingestion of meals in a low-frequency pattern increases postprandial insulin responses [35]. Thus beneficial effects of intermittent fasting beyond the effects of calorie restriction do not intuitively emerge from our current insights in the workings of human physiology.

3. Intermittent Fasting, Activation of AMPK and Human Disease

Having said that, depletion of (hepatic) glycogen stores will activate Adenosine Monophosphate Kinase (AMPK) in metabolically relevant cells [36], an event associated with improved course of diabetes type 2 [37]. Studies in patients with metabolic syndrome suggests that following consumption of 70 grams of glucose after an overnight fast, lipolysis commences already four hours after the onset of fasting [38] and thus even moderate temporal abstinence of calorie intake results in reduced size of the lipid droplet compartment [39], an event beneficial in individuals with for instance metabolic dysfunction–associated fatty liver disease/non-alcoholic fatty liver disease [40,41], mainly because of the resulting reduction in steatosis relieves hepatic endoplasmatic cell stress [42]. Likewise, especially in combination with moderate exercise, moderate temporal restriction may aid losing fat in athletes competing in sports with weight categories [43], like e.g., Judo, boxing or weight lifting. From 12 hours of fasting, onwards, however, in healthy controls blood ketone starts to increase [44] and thus body protein starts to be converted to energy, potentially negatively effecting muscle strength through increased muscle ketone flux [45], while concomitantly provoking deep quiescence in muscle stem cells through ketone body signalling [46], hampering muscle repair following (exercise-induced) damage. Hence, intermittent fasting regimes aimed at improving athlete anthropomorphic characteristics probably require careful design (fasting periods should probably be shorter as 12 hours) and monitoring (for ß-hydroxybutyrate and acetoacetate, the main primary products of hepatic ketogenesis [47]), as to avoid ketone flux.

Intermittent fasting-provoked ketogenesis may have additional benefits for specific groups as well: ketogenesis appears beneficial in steatotic liver disease (although the mechanisms involved remain obscure, potentially immune modulation plays a role) [48,49], supporting a role of intermittent fasting in managing such patients through repeated temporary ketogenesis that might be uncoupled from the effects on calorie intake *per se*. In addition, ketogenesis improves vascular wall condition through post-translational upregulation of endothelial Oct4 expression and hence the cyclic ketogenesis associated with intermittent fasting might be beneficial for subjects with poor vessel condition, e.g., (former smokers) and indeed a body of preclinical evidence supporting the usefulness of intermittent fasting for counteracting vascular dementia exists (e.g., [50]), although such effects may have a ketosis-independent but AMPK-dependent component as well [51]. In intensive care medicine, inducing ketosis by delaying parenteral calorie intake is associated with improved outcomes, both in adults [52] as well as children [53], even as not all studies did not fully recapitulate this result [54] and results remain mixed. Thus the potential benefits of intermittent fasting and in ketosis in general for such patients remain uncertain and future work is needed to establish whether such a benefit exists [55]. Generally speaking, although the capacity of intermittent fasting to repeatedly activate AMPK may be exploited for improving human health in specific situations, but it remains very difficult to translate this notion into specific protocol recommendations.

5. Potential Effects of Intermittent Fasting via AMPK-Mediated mTOR Inhibition on Cancer and Immunity

Apart effects on metabolic state, activation of AMPK can influence processes relevant for oncological medicine. As activation of AMPK slows down mitotic processes in pre-cancerous tissue

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[56], the potential for malignant transformation arising from such tissue isP diminished. In addition, through reduced activity of signalling through the Mammalian Target of Rapamycin (mTOR), AMPK stimulates cellular autophagy and some cancer cells appear specifically sensitive to increased autophagy, counteracting the oncological process and thus submitting themselves to intermittent fasting might constitute rational life style advice in patients at risk for oncological disease [57], although in the absence of further proof, e.g., by submitting tumour-prone to intermittent fasting and correlating effects on AMPK or mTOR activation to those tumour formation (which was used to objectify chemopreventive effects of statin treatment through mTOR inhibition in colorectal cancer [58]), such statements remain premature. Intriguingly, however, Every-other-day feeding extends lifespan in mice by delays in life-limiting neoplastic disorder and thus this possibility deserves urgent attention [59]. In this context it should also be noted that an AMPK-mediated inhibition of mTOR may negatively influence human immunity. Adequate activation of mTOR has emerged as critical for defending the body against a variety of potentially dangerous viruses, including e.g., Rotavirus [60] and Hepatitis E [61]. The potential effects of intermittent fasting on the capacity of the body to defend itself against pathogens has not been well-investigated, but in experimental tuberculosis immune response against the mycobacterium were critically impaired [62], whereas many immune parameters indicate reduced activity of the immune system in mice subjected to every-other-day feeding [59], and AMPK-activation in fasting causes monocytes to reenter the bone-marrow hampering peripheral immune responses [63]. Overall, intermittent fasting can be expected to counteract effective immunity and should not be recommended to patients at high risk of being exposed to infectious agents, e.g., vulnerable individuals commuting using public transport [64].

Reduced functionality of the immune system through AMPK-mediated inhibition of mTOR signalling in intermittent fasting, however, may be exploited for counteracting auto-immune conditions or other pathology associated with immune system activation. It has, for instance, been reported that intermittent fasting improve factors that are associated with the onset and progression of multiple sclerosis, especially brain-derived neurotropic factor through the activation of AMPK [65,66]. A recent feasibility study of intermittent fasting in patients with this disease yielded some positive signals, even as these did not reach statistical significance, maybe because the study appears underpowered [67]. It is important to note, however, that despite AMPK and mTOR being a highly drugable master regulators of human immunity [68–70], the relationship between pathogenesis of autoimmune disease and AMPK-dependent mTOR inactivation is certainly not clear cut and not many examples of successfully targeting human autoimmune disease through the pharmacological targeting of either AMPK or mTOR exist in body of contemporary biomedical literature [71,72]. In apparent agreement, although in preclinical models intermittent fasting has been used successfully to attenuate experimental autoimmune disease, successful human trails are scarce. An important characteristic of AMPK-dependent inhibition of mTOR is the induction of autophagy and defects in autophagy are certainly an important causative factors for many forms of intermittent fasting [73]. Genetic polymorphisms predisposing to autoimmune disease, however, tend to negatively influence autophagy downstream of mTOR, the *ATG16L1* and *IRGM* polymorphisms predisposing to Crohn's disease being a good example of this [74]. Overall, employing intermittent fasting to improve the natural history of autoimmune diseases may very well require the definition of very specific patient groups.

6. Intermittent Fasting May Drive Acquisition of Oncogenic Mutations or Confer Protective Effects Depending on the Individual Context

The most frequently mutated oncogene in cancer is *KRAS* [75], for instance being mutated in for practical purposes all cases of pancreatic ductal adenocarcinoma [76]. Oncogenic KRAS alters the metabolism of tumour cells resulting in increased glucose uptake and enhanced glycolysis, even in the presence of abundant oxygen (the so-called Warburg effect or aerobic glycolysis) [77]. These metabolic effects of oncogenic KRAS have been explained by transcriptional upregulation of glucose transporters *GLUT1* and *GLUT3* and by stimulating the activity of glycolytic enzymes through

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transcriptional and other mechanisms [78–80]. Importantly, low extracellular sugar drives expansion of cellular compartments that are more proficient in glucose uptake and mobilisation for ATP production [81] and thus provide positive selection pressure in the body for cells harbouring oncogenic *KRAS* mutations, increasing the risk for full malignant transformation. In healthy volunteers, even moderate intermittent fasting (9 hours *per diem* in a so-called early time-restricted feeding design involving fasting between 6:00 h to 15:00 h) lowered blood glucose levels by approximately 10 % to 25 % [82]. Prolonged exposure of cells in the body to such low glucose levels may foster acquisition of Ras mutations. Especially in the context of other potentially premalignant mutations, Ras mutation may be sufficient for the progression towards an aggressive cancerous phenotype. For instance, the potential of *KRAS* mutations to confer a metastasis-prone phenotype in the context of colon cancer has been well-described and is non-controversial [83]. Other studies document that lower extracellular nutrient availability can drive selection of clones that are potentially more carcinogenic, like acquiring alterations in open chromatin upon adaptation to lower external glucose in pancreatic ductal cells [84,85]. One can thus envision that in patients who exhibit relative large compartments of *KRAS* mutation-negative premalignant cells, e.g., patients with an extended Barrett's segment in the oesophagus [86,87] or substantial intestinal metaplasia in the stomach [88,89], intermittent fasting does not constitute a rational strategy in the management of such individuals. Indeed, whereas in general weight loss associated with intermittent fasting would be expected to confer protection from gastric cancer development [90], in a large prospective multicentre cohort study body weight loss did not associate to reduced propensity to progress from intestinal metaplasia to full-blown gastric cancer [91].

Having pointed out that intermittent is not necessarily indicated in the management of individuals having potentially pre-cancerous conditions, the weight loss associated with intermittent fasting *per se* should have a preventive effect with regard to oncological disease in general. Overweight or obesity is a strong risk factor of cancer incidence at several cancer sites [92]. Especially in colon cancer a relation between obesity and fat mass is evident [93], potentially because the fat-derived hormone Leptin is potent growth factor for precancerous cells in the colon [94]. Importantly, intermittent fasting reduces leptin levels substantially, especially when combined with physical activity, [95], although there is a notable trend that this effect is weaker in more recent studies [96] as compared to older studies [97]. Furthermore, there is uncertainty on the capacity of intermittent fasting to maintain reduced size of the adipose compartment -and *per extenso* leptin production-, a recent systematic review highlighting the possibility that weight loss efficacy of time-restricted eating without calorie counting may peak around 3 months [98], which is probably not enough to significantly dent the life time risk for developing adiposity-related cancer. Also, the efficacy of intermittent fasting over calorie-restriction *per se* for controlling adiposity remains uncertain, although an effect may be present [99]. Thus while controlling adiposity is important goal for improving health in general and also in the context of oncological disease, the specific additive value of intermittent fasting for controlling cancer development though effects on fat mass is for now far from obvious and requires further research at best.

Effects of Time-Restricted Eating Through Modulation of the Microbiome

It remains controversial whether intermittent fasting confers specific health benefits or potentially deleterious effects beyond calorie restriction *per se* [100]. Cochrane systematic reviews and meta-analyses are regarded as the gold standard for high-quality information [101,102]. A Cochrane review on the potential role of intermittent fasting for the prevention of cardiovascular disease found that while intermittent fasting was seen to be superior to ad libitum feeding in reducing weight, this was not clinically significant [103]. A long-term clinical trial on intermittent energy restriction in patients with type 2 diabetes did not evidence in the superiority of time-restricted eating over conventional calorie restriction [104]. As compared to conventional calorie restriction, however, intermittent fasting poses risks due to dehydration, hypotension, and safety issues related to hypoglycaemia and of glycemic variability. Although not investigated in a systematic fashion, case

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reports suggest that for instance Ramadan intermittent fasting can provoke severe hypoglycaemia that poses risks to car drivers or those using potentially dangerous apparatus [105]. Hence, intermittent fasting advocates are challenged to come up with mechanistic hypotheses that support time-restricted eating beyond calorie restriction.

Advocates generally provide two answers to such challenges [106]. One involves the circadian rhythm. Feeding/fasting paradigms influence the circadian cycle, with time-restricted feeding aligning circadian cycle-related gene expression, and thus altering physiological processes, at least in experimental animals [107–109]. Intermittent fasting regimes are widely divergent with respect to the timing of fasting and it is certainly possible that because meta-analyses pool studies with contrarian timing food restriction [110], obscuring potential effects. Indeed, an epidemiological study shows divergent effects of breakfast and lunch skipping to dinner skipping with respect cardiovascular health [111], but it is fair to say that human studies systematically comparing and contrasting the effects of divergent timing of intermittent fasting in humans are required before statements in this respect can be confidently made.

The second plausible explanation comes from effects time-restricted eating may have on the microbiome. It is becoming clear that the community of organisms living on the human body is intimately related with health and disease. The major reservoir for such organisms is the human gastrointestinal tract, different elements of gut being colonized by other microflora [112], and especially the colon dominates the human microbiome [113]. The microbiome is an important determinant of many aspects of physiology, e.g., colonization of gut by bacteria following birth and milk consumption drives the transition from fetal intestinal epithelium to more mature forms. For instance following the partus the murine intestine does not yet contain crypts but following colonization with bacteria . Instead, proliferative cells are restricted to the epithelium between the villi, the intervillus epithelium reshapes to form crypts and the associated cell types [114]. This process, potentially mediated through induction of the transcription factor *Blimp1* [115], is mediated by the colonization of the gut by butyrate producing bacteria [116], the latter being an usually bioactive short chain fatty acid with capacity to profoundly steer intestinal morphogenetic coding [117]. Many relations between microbiome composition, physiology and pathophysiology have been established, e.g., during pregnancy microbiome composition changes and may alter clinical course of inflammatory bowel disease or even modulate maternal immunity [118] to help the expecting coping with the challenge of maintaining maternal pathogen responses in face of the relentless fetal uptake of immunoglobulins from the maternal circulation [119]. The importance of controlling bacterial biofilm colonization of the buccal cavity through oral hygiene for maintaining dental health is well recognized but may even also be related to preventing right-sided colon cancer [120,121]. Thus the relation between microbiome composition and human health is not in doubt.

Importantly, the microbiome is highly dynamic and intermittent fasting has a pronounced effect on its composition. Short-chain fatty acids producing bacteria are as compared to other bacterial species relatively proficient in mucus degradation [122] and in the context of food withdrawal such bacteria quickly obtain a competitive advantage when other intestinal nutrient sources have been depleted. Many potentially beneficial effects have been linked to short-chain fatty acids and for instance improved liver enzymes in healthy volunteers following temporally-restricted eating has been tentatively linked to increased numbers of butyrate producing bacteria [2]. Such claims, however, await confirmation in studies involving more relevant groups of the population (e.g., patients with steatotic liver disease) and better definition of the mechanistic details by which butyric acid or other short chain fatty acids potentially active in this respect (e.g., propionic acid [123,124]) counteract hepatocyte damage. Intriguingly, however, evidence has been presented that processes like adipocyte browning (obesity may be caused by lowered brown adiose tissue activity [125]) in response to cold challenge may require butyrate-producing flora [126]. Thus it is possible that calorie restriction-independent effects of intermittent fasting may require combining with other interventions/conditions, obscuring potential effects in epidemiological studies.

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Conclusion

Overall it is clear that intermittent fasting is evidently active at a physiological level and can have profound effects on the natural history of disease. Whether such effects are beneficial, however, is clearly context dependent and also the benefit of time-restricted eating over calorie restriction *per se* is for now not evident. Better mechanistic understanding of the effects involved is necessary for making rational recommendations as to which individuals are likely to benefit from the practice and which individuals are more likely to benefit from alternative approaches.

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