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Turning Back the Clock on Aging? A Perspective on Selected Mechanisms and Therapeutic Avenues

Den Alterungsprozess verlangsamen? Eine Perspektive über ausgewählte Mechanismen und therapeutische Möglichkeiten

REVIEW

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Summary

› **Increasing life expectancy** has resulted in a growing number of individuals living with chronic, age-related conditions. This challenges healthcare systems worldwide and results in loss of quality of life in individuals living with chronic conditions. Strategies to promote healthy aging are thus gaining attention.

› **Lifestyle factors** such as caloric restriction, carbohydrate restriction and physical activity specifically modify a number of biological pathways associated with aging. One central shared mechanism seems to be the upregulating of maintenance pathways such as the AMPK signaling pathway, triggered by a low cellular energy status, as well as downregulation of anabolic pathways such as the insulin/IGF-1 signaling pathway. The transient energy deficit evoked by (intermittent) caloric restriction or vigorous physical activity – or the phenotypic imitation of this physiological state by dietary carbohydrate restriction – might offer some biologic plausibility for the observation of the benefits of these lifestyle factors. Largely independent of these mechanisms, physical activity directly impacts on downstream adaptive cellular responses via muscle-tissue crosstalk through myokines, i.e. hormone-like substances secreted by skeletal muscle in response to exercise. It is worth noting that distinct pharmaceuticals such as metformin, SGLT2-inhibitors and statins have the potential to complement lifestyle factors by directly modifying these longevity-associated pathways.

› **Lifestyle factors** are relevant determinants of health- and potentially of lifespan. Recent findings have significantly advanced our understanding of the mechanisms involved. This narrative review provides a perspective on selected modifiable determinants of healthspan and furthermore elucidates therapeutic avenues that have the potential to attenuate premature aging and to refine personalized preventive care.

KEY WORDS:
Caloric Restriction, Exercise, Ketosis, ß-Hydroxybutyrate, Nutrient Sensing Pathways, AMPK, Insulin, IGF-1, mTOR, Metformin, SGLT2i, Statins

Zusammenfassung

› **Mit der steigenden Lebenserwartung** nimmt der Anteil an Menschen mit chronischen, altersbedingten Krankheiten stetig zu. Dies geht einher mit einer Verlängerung der Krankheitsspanne, verbunden mit einer Zunahme der Kosten für das Gesundheitssystem. Strategien zur Verlängerung der Gesundheitsspanne gewinnen deswegen an Aufmerksamkeit.

› **Lebensstilfaktoren** wie bspw. Kalorien- und Kohlenhydratrestriktion sowie körperliche Aktivität beeinflussen eine Reihe von biologischen Signalwegen, welche im Alterungsprozess eine Rolle spielen, und können so direkt auf die Gesundheitsspanne und wahrscheinlich die Lebensspanne Einfluss nehmen. Ein zentraler Mechanismus hierbei scheint die verstärkte Expression von Instandhaltungssignalen (bspw. AMPK Signalweg) zu sein, angestoßen durch niedrige zelluläre Energiespiegel, sowie die verminderte Expression von Wachstumssignalen (bspw. Insulin/IGF-1 Signalweg). Das durch (intermittierende) Kalorienrestriktion und körperliche Aktivität hervorgerufene transiente Energiedefizit – bzw. die phänotypische Imitierung dieses physiologischen Zustandes durch eine alimentäre Kohlenhydratrestriktion – könnte eine biologisch plausible Erklärung für die bekannten protektiven Effekte dieser Lebensstilfaktoren sein. Unabhängig davon nehmen Myokine – durch den bewegten Muskel freigesetzte hormonähnliche Botenstoffe, direkten Einfluss auf mit Langlebigkeit assoziierte zelluläre Signalwege. Erwähnenswert ist zudem, dass pharmakologische Wirkstoffe wie Metformin, SGLT2-Inhibitoren und Statine durch Eingreifen in den AMPK Signalweg sehr direkt auf mit Alterungsprozessen assoziierte Vorgänge Einfluss nehmen und so als sinnvolle Ergänzung zu einem günstigen Lebensstil erwogen werden können.

› **Lebensstilfaktoren** haben einen relevanten Einfluss auf die Gesundheitsspanne. Das Verständnis der zugrundeliegenden Mechanismen hat sich in den letzten Jahren erheblich verbessert. Ziel dieser Arbeit ist es, eine Perspektive über ausgewählte Einflussfaktoren auf Alterungsprozesse sowie die zugrundeliegenden Mechanismen zu geben. Zudem werden therapeutische Strategien als Grundlage für personalisierte Präventionskonzepte aufgezeigt.

SCHLÜSSELWÖRTER:
Kalorienrestriktion, Bewegung, Ketose, ß-Hydroxybutyrat, Nährstofferkennungswege, AMPK, Insulin, IGF-1, mTOR, Metformin, SGLT2i, Statine

Introduction

Due to improved hygiene, technological, and pharmacological advances in medicine, life expectancy has been steadily increasing during the last decades (9). This is paralleled by a demographic shift with the number of people aged 60 years and older being projected to increase from 12% in 2015 (900 million) to 22% in 2050 (2 billion) worldwide (56). Of concern, years of life gained are often spent living with non-communicable, "age-related" chronic diseases such as type 2 diabetes mellitus (T2DM), ›

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atherosclerotic cardiovascular disease (ASCVD), cancers, neurodegenerative diseases (e.g. dementia), chronic kidney disease (CKD), osteoporosis and sarcopenia (18, 20). Therefore, strategies to prolong healthspan, i.e. the time that someone lives in full health, are gaining interest to prevent loss of quality of life and to mitigate the socioeconomic burden of the rising number of age-related and non-communicable diseases (NCDs). In this regard, it is worth noting that the World Health Organization (WHO), in addition to the metric life expectancy, has introduced the concept of healthy life expectancy (HALE) with the rationale of capturing both fatal and non-fatal health outcomes in a summary measure of average levels of population health. HALE is defined by the WHO as "the average number of years in full health a person (usually at age 60) can expect to live based on current rates of ill-health and mortality" (57).

A number of lifestyle factors and pharmacological interventions have been identified that modulate downstream regulatory pathways implicated in healthspan and/or longevity (18, 20, 33) (Figure 1).

The aims of this narrative review are to provide a perspective on selected biological pathways involved in longevity and to discuss therapeutic avenues that have the potential to attenuate premature aging and age-related diseases. Of note, this viewpoint is neither a systematic review nor an exhaustive presentation of the existing literature on longevity and associated pathways.

Selected Signaling Pathways Involved in Aging

Intracellular energy sensing pathways closely monitor cellular energy status to orchestrate anabolic and catabolic metabolism (24). Chronic positive energy balance results in upregulation of anabolic pathways such as the insulin/IGF-1 - and by extension, among others, the phosphatidylinositol-3-kinase (PI3K)/ protein kinase b (AKT/PKB)/ mechanistic target of rapamycin (mTOR) (PI3K/AKT/mTOR) signaling pathway and downregulation of maintenance pathways such as the AMPK signaling pathway (2, 43). This causes metabolic stress and has been linked to premature aging as well as numerous NCDs including cancer and atherosclerotic cardiovascular disease (21, 28, 30, 44). Conversely, (intermittent) exposure to low nutrient availability upregulates nutrient sensing pathways associated with health and longevity (AMPK signaling) and downregulates anabolic pathways (insulin/IGF1 signaling). AMPK/Sirtuin 1 (SIRT1) upregulation and insulin/IGF1 downregulation result in a number of physiologic adaptations such as a downregulation of mTOR signaling, fatty acid synthesis, glycogen synthesis, and inflammation and an upregulation of lipolysis/β-oxidation, ketogenesis, autophagy, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PPARα) and mitochondrial biogenesis. Collectively, lifestyle factors that evoke an energy deficit and/or dietary/pharmacologic concepts that mimic that state via activation of the master regulator AMPK (24) impact on surrogate markers for health- and longevity by reducing cumulative exposure to growth signals and by upregulating pathways involved in maintenance and healing. This "metabolic switching" seems to be important to restore cellular energy homeostasis (3, 24) (Figure 1).

Cellular Energy Status

Insulin Pathway

Insulin is a major anabolic hormone that regulates growth and that has an important role in glucose-, fat-, and protein metabolism (44). If chronically elevated, insulin, via the insulin/IGF-1 receptor, results in persisting activation of the PI3K/AKT/mTOR pathway resulting in chronic exposure to anabolic signals (28). This has been associated with an increased risk of premature aging, onset and progression of a variety of cancers and ASCVD and furthermore provides some biological plausibility for the observation of increased rates of cancer and ASCVD in those with obesity and T2DM, which may be attributable to hyperinsulinemia, elevated IGF-1, or potentially both factors (18, 21). Conversely, low insulin/IGF-1 levels are associated with reduced expression of anabolic signaling (PI3K/AKT/mTOR signaling pathway) and are thus associated with relative protection from cancer growth and progression (21, 25, 28).

Low levels of insulin and/or fasting lead to accelerated adipose tissue lipolysis and mobilization of free fatty acids (FFA)/ non-esterified fatty acids (NEFA) (48). NEFA are transported to the liver and metabolized by β-oxidation to produce (via Acetyl-CoA) the ketones ß-hydroxybutyrate (BHB), acetoacetate (AcAc) and acetone. BHB provides an alternative fuel source for different tissues and organs such as muscle, heart, kidneys and the brain and reduces muscle loss from proteolysis for gluconeogenesis (3). Furthermore, the regulatory kinase mTOR, which senses changes in the nutrient environment such as amino acids, fatty acids and growth factors such as insulin and IGF-1 is downregulated in the context of low insulin (44). Inhibition of mTOR induces autophagy, a maintenance process that is implicated in longevity and aging, and extends lifespan in model organisms like yeast, C. elegans, Drosophila, and mice (34, 44).

AMPK Pathway

On a cellular level, periods of prolonged fasting result in a depletion of cellular ATP levels which subsequently increases the [AMP]:[ATP] ratio. In turn, this intricately monitored balance activates several pathways that are associated with longevity and healthspan. These include the activation of AMPK and SIRT1 and the subsequent suppression of intermediary signaling pathways associated with growth (such as mTOR). This converges to a coordinated set of adaptations where metabolism switches from lipid synthesis and fat storage to mobilization of fat as free fatty acids and fatty acid-derived ketones. Increased AMPK activity is linked to β-oxidation, ketogenesis, improved mitochondrial function and autophagy by inhibiting the mTOR pathway (48).

Activation of AMPK during states of low cellular energy regulates energy balance by inhibition of anabolism to minimize ATP consumption and the stimulation of catabolism for ATP production. Accordingly, AMPK regulates processes associated with growth through modulation of the master regulator of growth mTOR leading to decreased cell growth, protein synthesis and activation of autophagy (23, 35, 44).

Collectively, low insulin signaling and/or low cellular energy status induce a coordinated set of adaptive cellular responses associated with health, maintenance and longevity by down- or up- regulation of cellular mediators such as mTOR or AMPK.

Aging and Lifestyle Factors

The adherence to low-risk lifestyle factors holds potential to increase healthspan, and potentially lifespan (33). The aim of this chapter is to discuss selected protective lifestyle factors and mechanisms that account for this observation based on the aforementioned pathways.

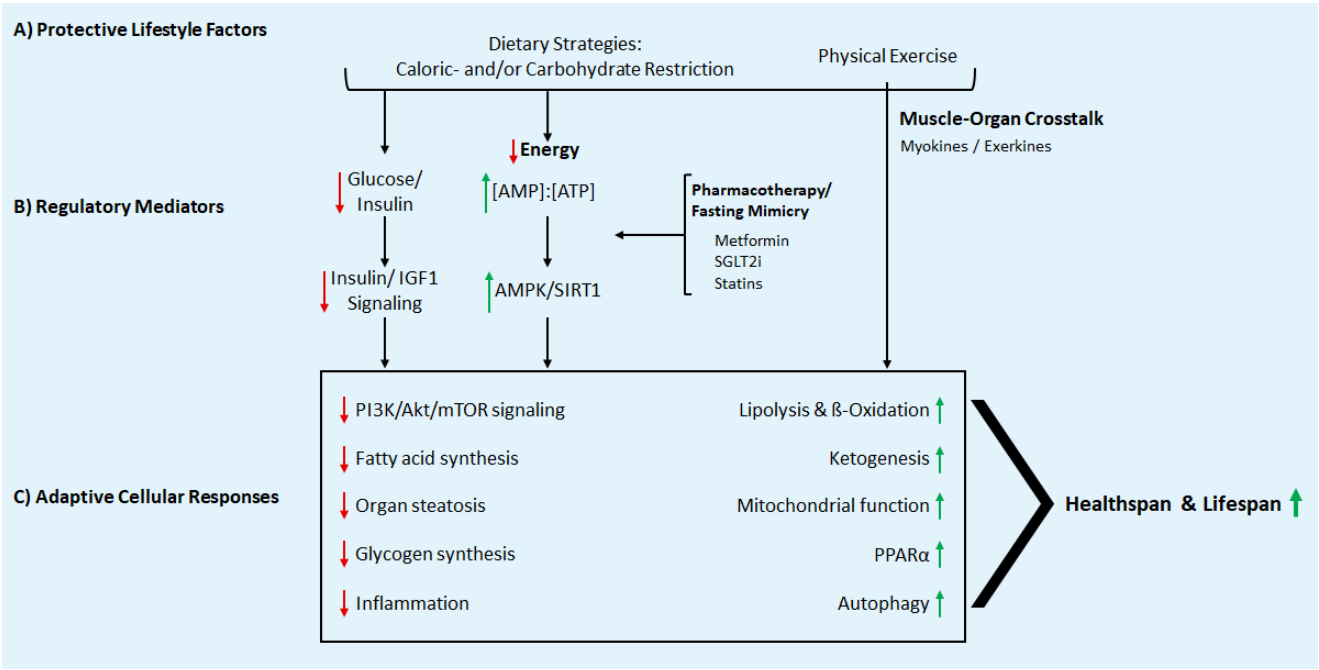

Figure 1

Selected modifiable determinants of the biological clock. A) Protective lifestyle factors; B) Regulatory mediators of (A) resulting in an up-/downregulation of cellular responses (C) associated with health and longevity; C) Adaptive cellular responses and downstream targets of (A) and (B) that link protective lifestyle factors with biochemical surrogate markers for health and longevity. A low cellular energy status, which can be achieved by (intermittent) caloric restriction (iCR) and vigorous physical activity (PA) is associated with an upregulation of the AMP-activated protein kinase (AMPK) pathway. Furthermore, iCR and PA are both associated with low blood glucose and insulin levels, leading to downregulation of insulin/insulin-like growth factor 1 (IGF1) signaling. Of note, very low carbohydrate diets that induce nutritional ketosis phenocopy many of the effects of iCR and vigorous PA even in the absence of an energy deficit. AMPK/Sirtuin 1 (SIRT1) upregulation and insulin/IGF1 downregulation by lifestyle- or pharmacologic concepts impact on various surrogate markers for health- and longevity by reducing cumulative exposure to growth signals and by upregulating pathways involved in maintenance and healing. Largely independent of these mechanisms, PA evokes distinct cellular responses via muscle-organ crosstalk through hormone-like substances secreted by skeletal muscle in response to exercise termed 'myokines'/'exerkines'.

Dietary Strategies

Caloric Restriction (CR)

The reduction of caloric intake (in the absence of malnutrition) has been shown to extend healthy lifespan in rodents and other model organisms (14). However, outcome evidence in humans is lacking. Short-term clinical trials suggest that daily caloric restriction (CR) reduces body weight and improves surrogate markers for cardiometabolic health such as dyslipidemia, blood pressure, insulin-sensitivity, and oxidative stress as measured by DNA damage (44). However, a major limitation of long-term caloric restriction in obesity intervention trials has been feasibility. For example, despite intensive dietary and behavioral counseling, participants in the two-year CALERIE 2 (Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy) trial managed to sustain only a 12%, instead of the targeted 25% daily decrease in caloric intake (1). For this reason, increasing focus has been directed to alternative approaches that might be easier to sustain over longer periods of time such as intermittent caloric restriction (iCR) or intermittent fasting (IF) regimens. In contrast to traditional caloric restriction (CR), periodically restricting caloric intake is a dietary approach that requires CR only for certain time periods, typically for 12-16 hours. Encouragingly, this approach has been shown to evoke similar cellular and metabolic adaptations as chronic CR (33). One of the mechanisms that is being discussed for underlying this observation is metabolic switching, i.e. the induction of a low cellular energy state with concomitant activation of AMPK (3, 14). Collectively there is data to suggest that IF evokes comparable weight loss as chronic daily CR, improves glucose regulation, increases cellular stress resistance, and lowers visceral fat mass and inflammation (14).

Low Carb/Ketogenic Diets

Carbohydrate restriction resulting in nutritional ketosis seems to phenocopy many of the effects of CR, a shared mediator of these effects being downregulation of the insulin/IGF-1 pathway and the induction of ketosis.

Ketosis is triggered by very low insulin levels, depletion of hepatic glycogen stores and increased lipolysis which flips the 'metabolic switch' from anabolic pathways such as glycogenesis/gluconeogenesis to maintenance pathways such as lipolysis/ketogenesis, typically 12 to 36 hours after the last meal (3, 49).

The ketone body BHB inhibits the assembly of the NLRP-3 inflammasome resulting in a reduction of its downstream mediators (i.e. the IL-1β/IL-6 axis). Its anti-inflammatory potential and its impact on causal inflammatory pathways for ASCVD makes BHB – and by extension lifestyle factors that result in its elevation – interesting therapeutic options for a variety of NCDs including ASCVD (5, 58, 59). BHB furthermore activates PPAR. This is associated with mitochondrial biogenesis and reduced oxidative stress. (58).

Utilization of ketones as a fuel source reduces glucose demand of the brain and other organs thereby reducing catabolism of structural proteins. A rise in free fatty acids and enhanced β-oxidation then leads to the generation of acetyl-CoA followed by a subsequent increase in circulating ketone bodies (10, 49).

In addition to their role as an alternative fuel source, ›

ketones, especially BHB, act as signaling molecules with major effects on metabolic functions and signaling pathways (40). For example, BHB can suppress class I histone deacetylases, thereby affecting epigenetic regulation (58).

Elevating BHB levels through exogenous administration of ketones improves surrogate markers for cardiometabolic health. In an animal model of hypertension with salt-sensistive rats, exogenous ketone administration resulted in decreased mitochondrial stress and improved blood pressure (12). In humans, exogenous intravenous administration of BHB increased myocardial, cerebral and renal blood flow (51, 59). Furthermore, ingestion of ketone salts and/or esters reduces blood glucose, FFA and triglycerides (59). Findings from an randomized controlled trial (RCT) in 20 patients with signs of early neurodegeneration show that elevated BHB levels improved cognitive function after oral administration of MCT (49). These findings support the notion that elevation of BHB levels, including through exogenous ketones, can be beneficial (51).

An on-going, two-year clinical study investigating the effects of a ketogenic/low-carbohydrate high-fat (LCHF) eating pattern involving nutritional ketosis in 262 patients living with T2DM, reports reductions in HbA1c, fasting glucose and insulin, body weight, systolic and diastolic blood pressure, triglycerides, and liver alanine transaminase while increasing HDL-C. A reversal of diabetes was observed in 53.5% and remission in 17.6 % of participants (6). Although higher levels of plasma LDL-C were observed due to increases in concentrations of larger LDL particles, there was no increase in total LDL particles (levels of small LDL particles decreased), ApoB or progression of CIMT which provides reassuring evidence that this dietary intervention did not adversely affect risk of CVD despite a diet high in dietary fat (7).

Overall, evidence from animal and human studies suggests that dietary interventions that evoke a physiologic starvation response have measurable effects on body weight and other surrogate markers indicative of cardiometabolic health. Time restricted feeding regimens are emerging as alternatives to long-term caloric restriction due to better long-term sustainability with evidence pointing to similar benefits to CR. Interestingly, ketogenic diets seem to largely phenocopy the biochemical signature of fasting, activating similar molecular pathways associated with healthspan and longevity. A common factor seems to be the ketone body BHB. Elevations in BHB can be achieved by nutritional strategies such as IF and carbohydrate restriction as in ketogenic diets. Nutritional ketosis has been linked to an inhibition of major signaling pathways that are associated with (unregulated) growth (insulin, IGF-1 and mTOR), the induction of antioxidant genes and the activation of AMPK. In this regard, BHB is likely a downstream regulatory mediator for many of the benefits observed with nutritional ketosis and (intermittent) CR. Very low carbohydrate dietary patterns resulting in nutritional ketosis reduce broad, systemic inflammation and most biomarkers of CVD risk. Thus, ketogenic / LCHF diets present a promising alternative to intermittent caloric restriction by mimicking the biochemical characteristics of fasting in a cellular starvation response through activation of AMPK.

Finally, a major limitation of dietary intervention studies has been the lack of adequate devices for real-time monitoring of the efficacy of these interventions. In this regard, the measurement of BHB in capillary blood obtained by finger-prick, as well as ketone breath sensors and ketone urine dipsticks are emerging biomarker-oriented strategies with tremendous potential for application. The measurement of BHB in capillary blood obtained by finger-prick correlated better with patient relevant outcomes (seizure reduction) than did ketones in urine (49). Contrarily, breath sensors seem to be in good agreement to capillary blood BHB measurements and thus may be a promising non-invasive and easily applicable tool to monitor and/or guide the implementation of dietary recommendations in clinical practice (23).

Physical Activity and Exercise

The terms 'physical activity' and 'physical exercise' are often used interchangeably but evoke distinct metabolic consequences. "Physical activity"' (PA) is any muscle-induced bodily movement which increases energy expenditure above ~ 1.0/1.5 metabolic equivalents of task (METs, 1 MET = 1 kcal (4,184 kJ) × kg-1 × h-1). "Physical exercise training" (ET) refers to a specific, planned and structured form of physical activity, mostly with a specific training goal (11).

Increased PA represents a low-cost intervention in primary and secondary prevention. It improves functionality, surrogate markers for cardiometabolic health and reduces the risk of all-cause mortality (4, 36). Lack of PA, i.e. sedentarism, promotes low-grade systemic chronic inflammation and obesity which increases the risk for numerous diseases including NAFLD, T2DM, ASCVD, osteoporosis, various types of cancer and neurodegenerative and mental disorders (18, 20).

Increased PA, in the form of a structured ET, mitigates sarcopenia and delays the age-related development of functional disability (36).

Overall, evidence from epidemiological studies underscores the association between PA and increased risk for age-related diseases. Switching from physical inactivity to meeting the weekly recommendations of 150 min of moderate-intensity aerobic activity lowers the risk of CVD mortality, CVD and T2DM incidence (53). Furthermore, increased leisure-time physical activity is associated with lower risks of many cancer types independent of body weight or smoking history (37).

Recommendations

The current WHO guidelines for healthy adults aged 18-64 recommend a minimum of 150 minutes moderate-intensity or 75 minutes vigorous-intensity aerobic activity (i.e. exercise) and muscle-strengthening activities at moderate or greater intensity that involve all major muscle groups on two or more days a week. In addition, older adults even with disabilities or chronic conditions are advised to do varied multicomponent (chronic) physical exercise that emphasizes functional balance and strength training at moderate or greater intensity, on three or more days a week, to enhance functional capacity and to prevent falls (55). Observational evidence suggests that it might be advisable to particularly encourage PA on days with plenty of leisure time but less work-related physical activity such as sundays (26).

Physical Exercise – Chronic Effects

PE, even if started at an older age, improves functional independence and reduces mortality (36). Mechanistically, PE increases autonomic balance, improves nutrient sensing and downregulates pathways related to growth signaling and inflammation. In ASCVD, PE improves endothelial function, and preserves a stable plaque phenotype of pre-existing atherosclerotic lesions. In addition, it exerts a mild anti-depressant effect (19, 30, 31).

ET leads to improved body composition in overweight/obese individuals by decreasing ectopic adipose tissue mass, i.e. visceral and visceral organ fat mass including intrahepatic, intrapancreatic and pericardial adipose tissue depots (31, 47).

Improved body composition, besides other factors, promotes an overall anti-inflammatory and anti-atherogenic milieu (18, 19).

In a systematic review of 20 studies, Gordon et al. described profound effects of supervised resistance exercise training on glycemic control and insulin sensitivity implying similar effects as caloric restriction or ketogenic diets (22). However, results are heterogenous and in patients with pre-existing metabolic dysregulation, a combined approach of PA and nutritional intervention might be necessary to improve metabolic dysregulation (52). Furthermore, studies of chronic physical exercise demonstrate a decrease in the risk of a multitude of age-related and lifestyle-related disorders (47) despite the different exercise protocols being tested.

Physical exercise impacts similar molecular pathways as CR or ketogenic / LCHF diets, such as activation of AMPK, thereby mimicking a low-energy status leading to improved body composition and decreases in inflammation. This commonality points to synergistic benefits of low-risk lifestyle interventions for overall health and healthspan by improving body composition, glycemic control and inflammation.

Physical Exercise – Acute Effects of a Single Bout

Not all observed benefits of PA/PE are attributable to its effects on energy balance or improvements in traditional risk factors. Skeletal muscle also acts as an endocrine organ capable of producing myokines ("exerkines") and metabolites in response to exercise, enhancing muscle-organ crosstalk with direct effects on lipid and glucose metabolism, cognition, adipose tissue phenotype (i.e. browning of white adipose tissue), bone formation, endothelial cell function, hypertrophy, skin structure, and tumor growth (47).

While chronic exercise shows overall anti-inflammatory effects via several mechanisms including reduction in ectopic adipose tissue, a single bout of exercise ensues an acute inflammatory response raising clinical inflammation markers such as IL-6 or CRP (47).

Exercise-induced acute increases in IL-6 ensue the production of anti-inflammatory cytokines such as IL-1 receptor antagonist (IL-1ra) and IL-10. In turn, IL-1rα inhibits IL-1β signal transduction and IL-10 inhibits TNF-α synthesis (47).

During exercise, muscle also works as an immunoregulatory organ which is reflected by shifting numbers of leukocyte subsets (46). In turn, these may be easily evaluated by clinical measures such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and systemic immune-inflammation index (SII = NLR × platelets) (54).

During an acute exercise bout, both neutrophil and lymphocyte counts increase (by mobilization from liver, spleen and other reserves). Neutrophilia persists post-exercise while lymphocyte count decreases (lymphocytopenia) (54).

The dynamics in changes of the cellular compartment of the immune system reflect exercise intensity with higher NLR values occurring after acute high intensity interval training compared to moderate continuous training in persons suffering from multiple sclerosis (54).

In addition to effects on the cellular compartment of the immune system, Morville et al. found a host of metabolites (833 in total) following acute exercise intervention. Of note, lactate and BHB were among the highest induced metabolites following resistance or endurance exercise, respectively. Induction of BHB after endurance exercise reflects ketogenesis after liver glycogen depletion (38).

Furthermore, lactate has been implicated in rodent studies to mediate some of the benefits of exercise on learning and memory by inducing neuronal brain-derived neurotrophic factor (BDNF) expression. This is further supported by the observation that exogenous lactate administration increases peripheral and central BDNF levels (17, 45).

Apart from its anti-inflammatory-effects, BHB may strengthen neuronal connectivity through increased hippocampal and cortical BDNF expression (14).

BDNF has a dominant role in mediating the effects of exercise on the hippocampus. It acts as a growth factor and is involved in, for example, cell survival, synaptic plasticity and learning. Furthermore, the myokines cathepsin-B and irisin may pass the blood–brain barrier and provoke an increase in BDNF in the hippocampus and stimulate neurogenesis. In addition, the myokine irisin is also implicated in the facilitation of white adipose tissue browning which is secreted upon muscular PGC1-α expression (38, 46, 47).

The muscle-brain connection is further highlighted by pre-clinical studies in rodents that report activation of PGC-1α1-PPARα/δ after acute exercise training, which enhances kynurenine conversion to kynurenic acid thereby reducing plasma levels of kynurenine. In turn, reduced plasma levels of kynurenine protect the mouse brain from stress-induced depression (2).

These observations are consistent with the contention that physical exercise is considered to have neuroprotective effects and even a single bout of exercise can benefit cognitive performance (39, 46).

Taken together, physical activity is an effective, low-cost and easily accessible approach to improve health metrics. Even a single bout of exercise elicits broad systemic effects on inflammatory markers, metabolism and cognition through tissue and organ crosstalk with 'myokines' ('exerkines') and 'adipokines'. These metabolites from skeletal muscle activity may be useful biomarkers for monitoring exercise prescriptions in people with cancer, diabetes, or neurodegenerative diseases (47).

It should however be noted that there are still limitations with regard to monitoring the efficacy of exercise treatment and with regard to individualization of exercise prescriptions. In line, results from randomized controlled trials report a wide inter-individual variability in response to a given exercise regimen. This heterogeneity may originate from the fact that there are "responders" and "non-responders" with respect to the impact of physical exercise on physiological outcome parameters (i.e., VO_2 peak). Another layer of complexity is added by the possibility that patient-specific factors determine outcome but these patient-specific factors are rarely accounted for in clinical trials. In this regard, further studies are needed to investigate causes and consequences of inter-individual response variability. Especially, monitoring of internal and external load and of cellular adaptations could thereby enhance personalized exercise prescriptions.

The combination of different training modalities such as resistance training and endurance training may result in greater cumulative benefit as they evoke different training adaptations and are thus complementary. Strategies to increase physical activity and to improve the quality of movement are warranted to prevent loss of quality of life and to reduce socioeconomic burden. The implementation of 'Lifestyle Research Centers' in universities will further advance our mechanistic understanding of the health benefits of exercise and will at the same time offer quality exercise training programs at no cost for individuals. ›

Pharmacotherapy with Senolytic Potential: Physical Activity, Caloric Restriction, and Dietary Carbohydrate Restriction – one Pill to Rule them All?

Pharmacotherapy is no substitute for a healthy lifestyle. It is however encouraging to note that selected pharmaceuticals seem to phenocopy some of the effects of caloric restriction, physical activity, and dietary carbohydrate restriction. In this regard, metformin, SGLT2 inihibitors (SGLT2i) and statins interfere with the energy-sensing AMPK pathway (15, 40, 42) - thus mimicking a state of low cellular energy status even in the absence of dietary intervention and/or vigorous physical activity.

Metformin is an approved treatment of T2DM. Its glucose lowering effects are mediated by suppression/inhibition of hepatic gluconeogenesis, however, the exact cellular mechanism of action remains incompletely understood. Specifically, two pathways are discussed that may account for the inhibition of hepatocellular gluconeogenesis: (1) Complex I inhibition and subsequent AMPK activation and (2) modulation of the cellular redox state by inhibiting glycerol-3-phosphate dehydrogenase 2 (GDP2) and thereby increasing the intracellular [NADH]:[NAD+] ratio. In turn, this may inhibit the conversion of glycerol (from white adipose tissue lipolysis) to glucose (28). In addition, the increased redox state prevents the conversion of lactate to pyruvate by the enzyme lactate dehydrogenase (LDH). This results in metformin inhibiting gluconeogenesis only from gluconeogenic substrates, which may be one explanation for its low risk of inducing hypogylcemia. Either of the aforementioned hypotheses may additionally explain the pleiotropic health benefits of metformin beyond its effects on hepatic glucose production. Its potential to upregulate the AMKP signaling pathway, among other effects, makes metformin an interesting pharmacologic compound to attenuate aging. Indeed, Metformin is being investigated in the Targeting Aging with Metformin (TAME) trial for life extension in healthy individuals (8, 42).

SGLT2i are a class of new, initially anti-diabetic drugs, with prognostic benefit for treatment of diabetes mellitus, heart failure and kidney failure. Mechanistically, similar to Metformin, SGLT2i induce a state of low cellular energy status (high [AMP]:[ATP] ratio), thus mimicking a fasted state, which consequently upregulates the (low-) energy sensor AMPK. In addition, SGLT2i activate SIRT1, another low-energy sensor that mediates favorable adaptions to low-nutrient conditions (reviewed in detail in 9). Collectively, SGLT2i have pleiotropic benefits on health, and promote effects far beyond their antidiabetic potential including cardio- and renal-protective properties with prognostic implications (40).

Statins (3-hydroxy-3-methylglutaryl-coenzym-A-reductase [HMG-CoA] inhibitors), are a safe and efficacious strategy to lower ASCVD risk in patients with dyslipidemia at risk for adverse cardiovascular events (13). Interestingly, beyond their lipid modulating properties, statins have been found to activate the cellular low energy sensor AMPK, which is discussed as one of the mechanisms underlying their anti-inflammatory, antineoplastic and antithrombotic effects (15).

Collectively, Metformin, SGLT2i and Statins impact on longevity pathways by mimicking a cellular low-energy status, implying potential as complementary strategies to lifestyle interventions for increasing healthspan in individuals not meeting the criteria for disease. In this regard, studies are warranted to test the hypothesis that these drugs are safe and provide a meaningful impact on health- and lifespan in this subgroup. Meanwhile, therapy with these agents in "healthy individuals" is off-label. Treatment decisions must involve a shared decision-making process and physicians with expertise in this field must comprehensively address open questions and discuss risk-benefit considerations with patients.

Conclusions and Future Directions

Aging is a multifactorial, systemic process that progresses at various rates depending on genetic predisposition (34), acquired exposures such as environmental stressors (30) and their interplay as genome-exposome interactions (i.e. epigenetics).

The phenomic signature of accelerated aging – i.e. chronic upregulation of anabolic signals such as the insulin/IGF-1 pathway and downregulation of maintenance signals such as the AMPK pathway – may be regarded as a coordinated response to metabolic stress. This may be caused for example by chronic positive energy balance due to overnutrition and/or sedentary behavior (43). In that regard, it is worth noting that dietary carbohydrates per se, due to their strong impact on glucose/insulin levels, are being discussed as key regulators of healthspan (27, 42).

Conversely, the adherence to protective lifestyle factors shifts hormonal cross-talk from a growth promoting, proinflammatory milieu conducive for accelerated aging to a milieu that promotes maintenance and healing. Caloric restriction, vigorous physical exercise and dietary carbohydrate restriction resulting in nutritional ketosis all are associated with low insulin levels and/or low cellular energy status. This evokes a set of phenotypic adaptations characterized by downregulation of pathways involved in growth regulation (i.e. PI3K/Akt/mTOR signaling pathway) and upregulation of the AMPK signaling pathway involved in maintenance and healing (28).

Collectively, lifestyle factors associated with intermittent states of low cellular energy status and/or dietary and pharmacological strategies that mimic that state modulate signaling pathways associated with longevity, cancer growth and atherosclerotic cardiovascular disease risk. Consistent with the lifetime exposure model, the largest absolute benefits likely accrue if protective factors are adapted early in life and maintained over a lifetime. Furthermore, the greatest cumulative benefit is likely to be achieved by combining various approaches. In conclusion, comprehensive information about strategies to slow biological aging and attenuate disease risk - if brought to attention of individuals early in life - may guide lifestyle choices and may help to address the increasing burden of NCDs.

Conflict of Interest

Stiebler M, Müller P, Bock M, and Lechner B declare no conflict of interest. Lechner K has received speaker's honoraria from Goerlich Pharma, Novo Nordisk, Sanofi, and Amgen.

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