Metformin and ageing: improving ageing outcomes beyond glycaemic control

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Abstract

In a world where the population is ageing, there is growing interest and demand for research evaluating strategies that address the ageing process. After 60 years of successful use of metformin in our pharmaceutical armamentarium, we are learning that, beyond improving glycaemic control, metformin may have additional mechanisms and pathways of action that need further study. Although, metformin's effect on clinical ageing outcomes may still be considered speculative, the findings from studies into cellular and animal models and from observational and pilot human studies support the existence of beneficial effects on ageing. At present, progress for human research, using randomised clinical trials to evaluate metformin's clinical impact, has just started. Here, we present a review on the ageing process and the mechanisms involved, and the role that metformin may have to counter these. We go on to discuss the upcoming large randomised clinical trials that may provide insight on the use of metformin for ageing outcomes beyond glycaemic control.

Keywords

Ageing; Mechanisms of ageing; Metformin; Older adults; Review

Introduction

The combination of a growing ageing population, longer life expectancy and greater prevalence of multiple chronic diseases is increasingly leading to social, economic and healthcare challenges for those in developed and developing countries. By 2050, the world's population aged 60 years and older is expected to reach 2 billion, increasing from 900

million in 2015. Of these, 125 million individuals are 80 years or older, a number that will rise to 434 million by 2050, and 80% of them will live in low- and middle-income countries [1].

Ageing, insulin resistance and inflammation are associated with noncommunicable diseases (NCD), such as type 2 diabetes [2], cardiovascular diseases (CVD) [3], cancer [4], depression [5] and dementia [6], as well as frailty, a condition of increased vulnerability and poor health outcomes [7]. The prognosis and clinical outlook of an older adult with multimorbidity (a combination of several conditions within the medical domain) is further impaired by issues in the functional and psychological/mental domains (physical and cognitive dysfunction). Altogether, the ageing older person endures poor quality of life with increased vulnerability to losing independence, becoming hospitalised or dying. As our society is ageing, there is growing interest for research addressing interventions beyond healthy lifestyle to expand the number of functional years. Here, pharmacological therapy with safe and known agents, such as metformin, is of great interest.

Metformin has proven its efficacy for diabetes prevention and management. In the Diabetes Prevention Program (DPP), the efficacy of metformin in those aged 60 or older was not evident in the initial phase (using fasting and 2-h post-challenge glucose criteria) [8]. Nevertheless, long-term follow-up data, using HbA1c level for diabetes diagnosis, showed that metformin was effective in all age categories, including in participants age 60 or older at baseline, in whom a 21% diabetes risk reduction was observed [9]. Ageing outcomes in the Diabetes Prevention Program Outcomes Study (DPPOS) included frailty and physical and cognitive function (ClinicalTrials.gov registration no. NCT00038727); preliminary analysis of these factors did not show any benefits of metformin or lifestyle interventions in this cohort (unpublished results, H. Florez). Notwithstanding, our knowledge of potential mechanisms leading to metformin benefits beyond glycaemic control is increasing, while efforts are being made to reduce the impact of conditions commonly associated with the ageing process. This year, 2017, there are plans to commence two major, large randomised clinical trials aiming to evaluate these additional benefits of metformin for individuals without diabetes. Here, we outline the relevant pathways and mechanisms underlying the potential ability of metformin to reduce the burden of ageing and its related NCDs. We also discuss the available evidence on clinical benefits from observational studies, and details of the upcoming clinical trials that aim to shed light on the impact of metformin on ageing outcomes beyond glycaemic control.

Ageing and its associated diseases

There are different personal, cultural and societal perspectives on what constitutes 'ageing' and who are considered older adults. Using chronological age, the criteria for older adults in the USA is age 65, whereas in Europe and other parts of the world, it is 60 years and older. Generally accepted biological definitions of ageing include 'the declining ability to regenerate damaged tissue' [10] and 'a deterioration in the maintenance of homeostatic processes over time, leading to functional decline and increased risk for disease and death' [11]. These definitions, however, do not necessarily take into account the normal ageing process or even healthy ageing.

Age-dependent and age-related diseases

In order to understand the ageing process and how to intervene in it, it is important to highlight the difference between age-dependent and age-related diseases. In age-dependent diseases, such as coronary artery disease, cerebrovascular disease, type 2 diabetes, osteoporosis and Alzheimer's Disease, the pathogenesis appears to involve basic ageing processes, chronic damage from inflammation [12] and dysregulated cellular metabolism [13]. Mortality and morbidity in these diseases increase exponentially with advanced age. In contrast, age-related diseases have a temporal relationship with the age of the host but are not necessarily related to the ageing process. These diseases occur at a specific age, but with a further increase in age, they either decline in frequency or increase at a less than exponential rate. Examples are gout, multiple sclerosis and many (but not all) cancers.

Mechanisms of ageing

The process of ageing is complex and multifactorial. Nonetheless, physiological and evolutionary theories can be used to deduce the mechanisms of ageing [14]. Among these mechanisms of ageing, DNA damage receives the most attention, with hopes to identify pathways that can be contained or modified to halt or delay aging itself. Endogenous sources for DNA damage include reactive oxygen species (ROS), alkylation and hydrolysis, whereas exogenous sources include chemicals and ultraviolet (UV) and other radiation [15]. Further, oxidative stress, a process where free radicals cause DNA damage, affecting protein translation, provides another mechanism of ageing via genetic damage [16]. Most of the data evidencing the process of ageing comes from animal experiments attempting to expand lifespan; blocking oxidative stress in older gerbils (aged 15–18 months) restored levels of function (assessed via the maze test for temporal and spatial memory) similar to that seen at younger stages of life, when the animals were aged 3 months [17].

The evolutionary theory of ageing assumes a linear increase in mutations over time and, whilst ageing and death are initially circumvented by cellular redundancy mechanisms [18], as mutations overwhelm the system, ineffective protein translation eventually occurs, resulting in ageing. From the cellular level, this leads to organ malfunction, causing decreased elasticity in skin, propensity to neoplasms, decreased strength and endurance, osteoporosis and many other conditions. In turn, this can lead to geriatric syndromes, in which frailty, delirium and falls are increased.

Table 1 highlights some of the physiological changes associated with ageing, their pathophysiological consequences and associated diseases [14,19,20].

The impact of metformin on mechanisms related to the ageing process

Our current understanding of the mechanisms by which metformin improves glycaemic control includes the non-competitive inhibition of the mitochondrial glycerophosphate dehydrogenase enzyme, which alters hepatocellular redox state, thus reducing the conversion of lactate and glycerol to glucose, decreasing hepatic gluconeogenesis [21]. As already mentioned, beyond the impact of metformin on glycaemic control, this drug is also proposed to alter mechanisms related to ageing (Fig. 1). For example, inflammatory

markers, such as interleukins and TNF, can activate a variety of cellular processes that lead to cellular and tissue damage. IL-6 can induce fibroblast proliferation and collagen production, leading to cardiac remodelling. It can also promote myocyte hypertrophy, depressed contractility and apoptosis [22]. Metformin has been shown to alter inflammatory responses through suppression of NF-kB via AMP-activated protein kinase (AMPK)-dependent pathways [23–25]. In addition, metformin reduces the production of ROS through reverse electron flux [26] and via the mechanistic target of rapamycin (mTOR), leading to a reduction in superoxide, which may otherwise lead to DNA damage and mutations [27,28].

High concentrations of ceramides in the skeletal muscle are also proposed to be involved in the ageing process. This can lead to reduced myoblast proliferation, aberrant cell cycle regulation and a senescent myoblast phenotype. Cell studies showed that treatment with metformin can limit the negative effects of ceramides, thus potentially preventing myoblast senescence [29]. This may potentially be helpful for the growing population of older adults with sarcopenic obesity, while possibly improving tissue health and function.

Similarly, other experimental models indicate that metformin may increase lifespan and delay the ageing process [30–32], as well as offer protection for specific tissues. A report indicated a potential cardioprotective role of metformin, since it stimulates ischaemia-induced revascularisation through an endothelial nitric oxide synthase -dependent pathway [33].

Other cell studies have shown that metformin may have a neuroprotective role, reducing neuronal injury and improving oxygen/glucose deprivation, resulting in better neuronal survival [34] and preventing etoposide-induced apoptosis in primary neurons [35]. In a mouse model of neuroblastoma, metformin normalised the diabetes-induced reduction of cell proliferation and neuroblast differentiation in the hippocampus [36]. Moreover, an in vitro model of insulin resistance using the Neuro-2a neuronal cell line demonstrated that metformin prevented the appearance of molecular and pathological characteristics associated with Alzheimer's Disease [37].

Clinical impact of metformin beyond glycaemic control

Research into metformin's clinical effects beyond glucose management originated from the observed reduction in cardiovascular risk in individuals with diabetes treated with metformin [38]. Since then, there is growing interest and reports suggesting clinical benefits beyond diabetes. Fig. 2 summarises the potential clinical benefits of metformin in the ageing person.

Cardiovascular health

A recent cohort study of US older veterans with type 2 diabetes showed that metformin reduced CVD events among individuals with type 2 diabetes, according to the baseline risk [39]. The likelihood of CVD was reduced by 6 % among otherwise healthy individuals, by 18 % among those at risk of frailty and by 48 % among those at high cardiovascular risk. Another recent large double-blind randomised, placebo-controlled trial evaluated the cardiometabolic effects of metformin in adults with type 1 diabetes (for 5 years) and high CVD risk [40]. Participants had an average age of 55.2 ± 8.5 years and 88 % had overweight

or obesity. After 3 years, there was no difference in the primary outcome of carotid artery intima-media thickness (a surrogate marker of CVD). Still, there were reductions in body weight, LDL-cholesterol, and also in atherosclerosis progression, based on maximal carotid artery intima-media thickness analysis. These findings highlight the potential of metformin for decreasing CVD risk.

Weight loss

Several studies have shown a small but beneficial level of weight loss with metformin therapy in individuals without diabetes [41], at risk [42], or with type 2 diabetes [43]. Metformin is not approved as an anti-obesity medication, but practitioners often incorporate off-label use for individuals with obesity at high risk for diabetes.

Inflammation, endothelial function and angiogenesis

Furthermore, metformin mildly reduces levels of high-sensitivity C-reactive protein [44], and improves endothelial function [45,46]. While this may be partially related to weight loss, the additional impact of metformin on inflammation, endothelial function and angiogenesis, enhances the benefits of this drug against the ageing process. Notably, a pilot placebo-controlled study of women without diabetes showed that, besides improving variables of vascular function, metformin also improved measures taken during an exercise tolerance test: maximal ST-segment depression, Duke score and chest-pain incidence [47]. These findings provide further evidence that metformin may reduce CVD, supporting its use as an additional therapy to reduce cardiovascular risk factors [48] and complications, including death [49,50]. Importantly, however, since this effect has been most widely reported in individuals with diabetes, further research is required to fully establish the impact of metformin on CVD risk in those without diabetes [41].

Psychological health

Depression—Regarding the psychological health, in a placebo-controlled Chinese study in participants with type 2 diabetes and mild to moderate depression, metformin improved depressive symptoms [51], possibly because of better glycaemic control. Considering the established relationship and high prevalence of depression in older individuals with or without diabetes, this outcome is highly relevant.

Cognitive function

There is also evidence that metformin alters cognition. Observational studies show reductions in mild cognitive impairment (MCI) [52] and dementia [53,54] among participants with diabetes taking metformin when compared with no medication or other glucose-lowering agents. For example, a Taiwanese study in individuals aged 50 years found that metformin use significantly decreased the risk of dementia compared with no medication (HR 0.76 [95% CI 0.58, 0.98]) [51]. In another study, researchers evaluated data from 365 individuals from the Singapore Longitudinal Aging Study, aged 55 years; they found that metformin use was associated with lower risk of MCI (OR 0.49 [CI 0.25, 0.95]) [53]. In another study in Taiwan, researchers analysed data from 67,731 individuals using an insurance database and found that dementia risk was lower in those taking metformin

compared with other glucose-lowering medications [54]. It must be noted that, because of their observational design, and despite adjusting models for confounders, such as age, education, diabetes duration, CVD and other risk factors, the possibility of residual confounding in these studies persists. Nonetheless, while these studies have limitations, a recent pilot clinical trial substantiated their findings by showing that metformin improved cognition in individuals without diabetes [55]. Specifically, eighty individuals, aged 55 to 90 years, with amnestic MCI and without treated diabetes were randomly assigned to metformin or placebo and followed for 12 months. The participants treated with metformin showed improvements in the selective reminding test, even after adjusting for baseline values for the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) score.

On the other hand, concerns were recently raised that metformin may be associated with deleterious effects on cognitive function in older individuals [56]. Researchers reported worsening tau aggregation and abnormal behaviour [57] or impaired spatial memory and visual acuity [58] in mouse models of ageing. Nevertheless, investigators from the DPPOS have just published an analysis of cognitive function, measured 8–10 years after therapy with metformin [59]. While the results did not support benefit, they did not show negative impact from long-term metformin use.

Physical function

In regard to the functional medical domain, as mentioned previously, the potential impact of metformin on skeletal muscle may be particularly helpful in sarcopenic obesity. It is yet to be established whether metformin enhances physical function and mobility, or prevents their decline in older adults. However, in an observational study metformin seemed to decrease the likelihood of frailty and other age-related comorbidities [39].

Metformin can be used safely in older adults

Metformin has been successfully used for long-term treatment in older adults and it is the first-line therapy for type 2 diabetes [60]. It has also been used long-term to prevent diabetes [61]. For individuals who have never previously used metformin, metformin can be safely started at 500 mg per day and slowly titrate (to ensure tolerance) towards the target dose of 1000 mg twice daily, as long as GFR is above 45 ml min^{-1} [1.73m]$^{-2}$ [62]. Kidney function needs to be monitored in patients and there may be a need to stop metformin in those with signs of kidney disease (for example if there is an acute increase in serum creatinine). After the situation is resolved, metformin can be resumed with caution, as long as GFR remains above 30 ml min^{-1} [1.73m]$^{-2}$ [62,63], lowering the dose to a maximum of 1000 mg per day if GFR stays above 30 but below 45 ml min^{-1} [1.73m]$^{-2}$ [62].

Regarding adverse events, there is ongoing debate whether or not metformin is associated with lactic acidosis [64,65]. Nonetheless, the event frequency is so small that, in most clinical practices, the preventive approach is to temporally place metformin on hold in the setting of hospitalisation, acute kidney injury, use of iodinated-contrast procedures, or in the setting of acute severe illness with hypoxia (all of which increase the risk of lactic acidosis), following which metformin therapy is reimplemented and use is continued [66].

Future developments in metformin research

We are facing increased healthcare costs in an ageing society, for which interventions to reduce the burden of NCDs and to promote healthy ageing are needed. Lifestyle modifications, including exercise interventions, have several advantages, but are difficult to adhere to and maintain over time [67]. Metformin offers a cost-effective alternative that, besides controlling diabetes or reducing its risk, may improve mood and cognitive and physical functions. Two large metformin clinical trials in individuals without diabetes will soon start to evaluate the benefit of metformin treatment on these outcomes. The Veterans Affairs' Investigation of Metformin in Pre-Diabetes on Atherosclerotic Cardiovascular OuTcomes (VA-IMPACT; ClinicalTrials.gov registration no. NCT02915198) is a placebo-control study in individuals with CVD and intermediate hyperglycaemia, the latter defined as: one measure of glycated HbA_{1c} 5.7–6.4% (38.8–46.4 mmol/mol); two measurements of fasting blood glucose (on separate days) between 5.6mmol/l and 6.9 mmol/l; or a 2-h blood glucose level between 7.8mmol/l and 11.1 mmol/l following a 75 g glucose load OGTT; all in the absence of known diabetes or use of a glucose-lowering agent. The primary outcomes include the time to death from any cause, myocardial infarction, stroke, hospitalisation for unstable angina, or symptom-driven coronary revascularisation. The Targeting Ageing with Metformin (TAME) study is another major placebo-controlled trial in older adults without diabetes but at increased risk of functional decline [68]. TAME will evaluate the potential ability of metformin to slow down the development of age-dependent and age-related diseases, including cancer, CVD and dementia. In addition, TAME will include outcomes of physical function and mobility. Both VA-IMPACT and TAME are in the final stages of approval and implementation, and aiming to begin recruitment this year, in 2017. Finally, the Early Prevention of Diabetes Complications in Europe (ePREDICE) is another large multicenter randomised clinical trial, already recruiting participants mostly in Europe, evaluating the impact of metformin (compared with a dipeptidyl peptidase-4 inhibitor) on microvascular complications and cognitive function in individuals with non-diabetic intermediate hyperglycaemia (impaired glucose tolerance, impaired fasting glucose, or both) [69].

Conclusion

Beyond its impact on glycaemic control and diabetes-related outcomes, metformin has pleotropic effects targeting multiple age-related mechanisms. Cellular and animal studies have found that metformin decreases inflammatory markers, NF-κB, ROS and mTOR pathways, thus decreasing DNA damage. In addition, metformin reduces ceramide-dependent damage in myoblasts. Human observational studies have shown that metformin decreases the risk of CVD, cancer, depression and frailty. A pilot study found that metformin may reduce MCI. Upcoming randomised clinical trials will evaluate whether metformin can decrease death from any cause, CVD, stroke, prevent or delay the development of age-dependent diseases, and improve physical and cognitive function. Given its known safety and long-term use in humans, metformin could become a pharmacological intervention against multimorbidity and ageing in individuals with or without diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

CVD	Cardiovascular disease
DPPOS	Diabetes Prevention Program Outcomes Study
ePREDICE	Early Prevention of Diabetes Complications in Europe
MCI	Mild cognitive impairment
mTOR	Mechanistic target of rapamycin
NCD	Noncommunicable diseases

ROS   Reactive oxygen species

TAME   Targeting Ageing with Metformin

VA-IMPACT Veterans Affairs' Investigation of Metformin in Pre-Diabetes on Atherosclerotic Cardiovascular OuTcomes

Learning points

Age-dependent diseases

Pathogenesis involves mechanisms related to the ageing process, chronic inflammation and dysregulated cellular metabolism.

Age-related diseases

Temporal relationship with age of host but are not necessarily associated with the ageing process.

Metformin might inhibit the ageing process

Metformin reduces inflammation and ameliorates DNA and cellular damage. Data from definitive large randomised clinical trials in humans are lacking, but observational and pilot data show that metformin may improve clinical outcomes beyond diabetes, including cognition, depression and other ageing outcomes.

Upcoming clinical trials of metformin

1. VA-IMPACT: Participants with heart disease, without diabetes. Outcomes include time to death from any cause, myocardial infarction, stroke, hospitalisation for unstable angina, or symptom-driven coronary revascularisation.

2. TAME: Participants without diabetes. Outcomes include time to development of age-dependent diseases (e.g. cancer), CVD, dementia and type 2 diabetes.

3. ePREDICE: Participants with prediabetes. Outcomes include microvascular complications and cognitive function.
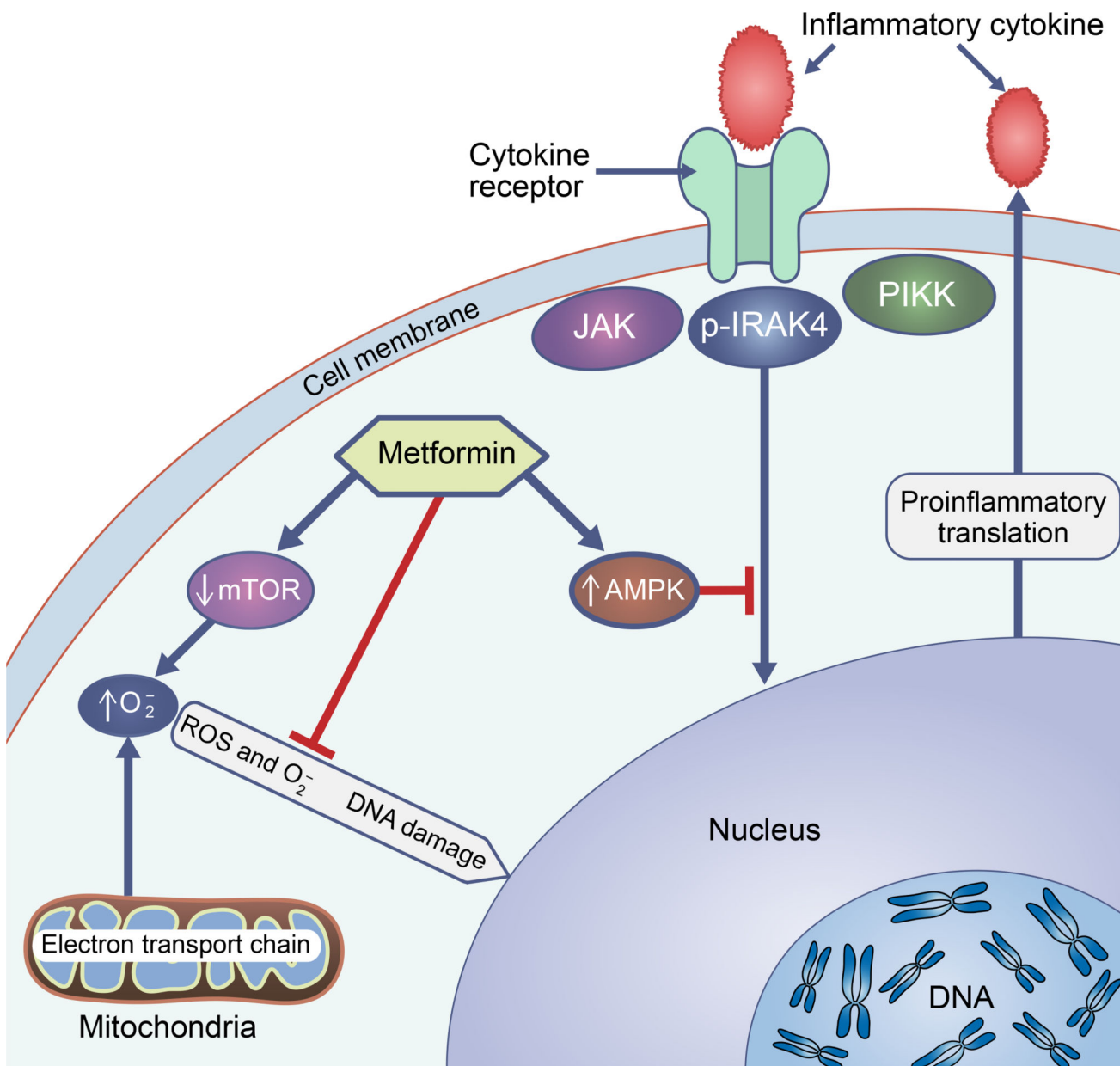
Fig. 1.
Anti-ageing mechanisms of metformin. Metformin impacts on mechanisms of ageing, preventing DNA damage and inflammation; it activates the AMP-activated protein kinase (AMPK) signalling pathway, blocking inflammatory-cytokine mediated DNA translation. It also prevents DNA damage from excess production of superoxide by directly decreasing ROS synthesis via reverse electron flux, and by inhibiting mTOR signalling pathways that result in superoxide production. IRAK4, IL-1 receptor-associated kinase 4; JAK, Janus kinase signalling pathway; O_2^-, superoxide; PIKK, phosphatidylinositol 3-kinase
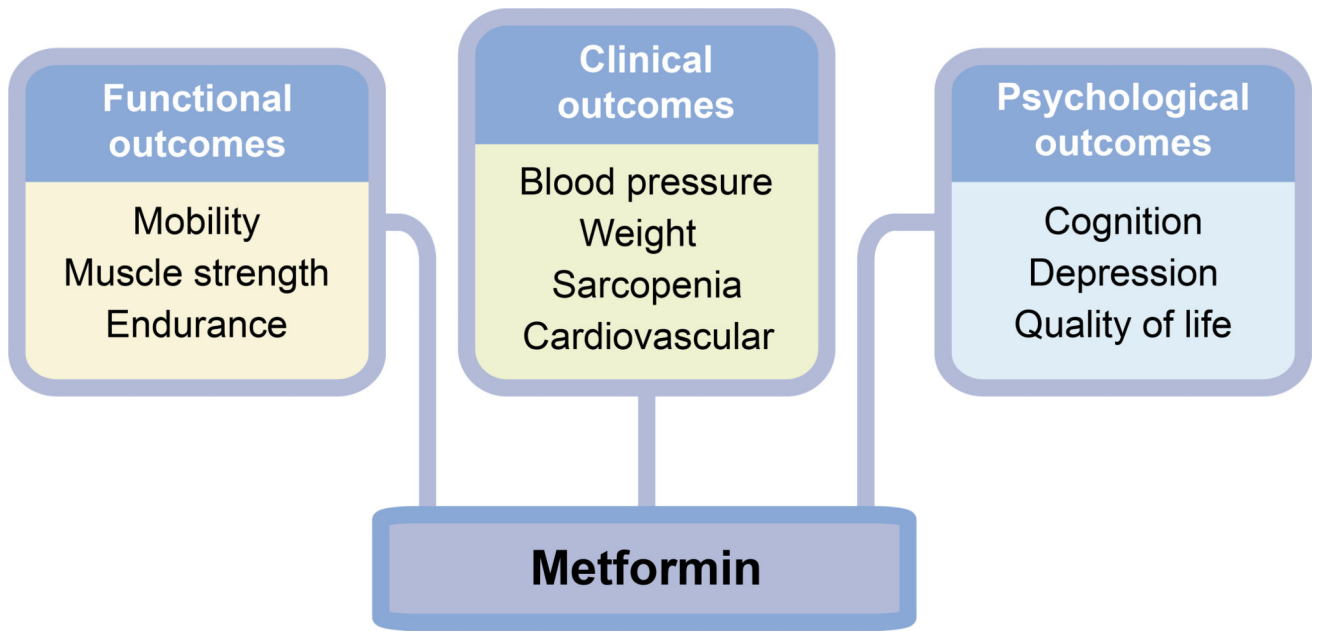
Fig. 2.
Potential clinical targets for metformin, beyond glycaemic control. In the ageing individuals, metformin may provide many benefits other than glycaemic control. These benefits may improve physical function (e.g. mobility, muscle strength and endurance), clinical outcomes (e.g. blood pressure, weight and cardiovascular health), and psychological health (e.g. cognition, depression and quality of life)

Table 1

The ageing process: physiological changes, pathophysiological consequences and associated diseases

System	Ageing-related change	Consequence	Age-dependent and older age-related disease/outcomes
Endocrine	Fat deposition in pancreas; ↓ in insulin signalling Thyroid atrophies, ↑ fibrosis, ↑ nodule formation ↑ Parathyroid fat deposition but no atrophy Atrophy of ovaries; ↓ testosterone levels, with asynchronous feedback to Luteinizing hormone	↓ Response to glucose-lowering medications aimed at pancreatic function Changes in body composition Menopause Late-onset male hypogonadism	Type 2 diabetes Thyroid disorders Orthostatic hypotension Osteoporosis
Cardiovascular	↑ Left ventricular wall thickness with ↓ cavity size ↑ Fat deposits; ↑ vascular stiffness with ↓ responsiveness to drugs	↑ Systolic BP, ↑ pulse wave velocity, ↓ peak ventricular filling rate, ↓ maximal heart rate and variability, ↓ $\dot{V}O_{2max}$	CVD Heart failure Hypertension ↓ Endurance
Neurological	↓ Neurons, ↓ axon potential, ↓ dendrite branches	Memory loss	Cognitive impairment and dementia Self-care deficit Risk of delirium
Muscular	↓ Peak strength of contraction, slower contraction and relaxation, ↓ muscle tone and contractility	↓ Muscle strength, ↓ endurance	Sarcopenia Impaired mobility/gait Functional decline and disability
Optical	↑ Lipid infiltrates/deposits, ↑ thickening of the lens, ↓ pupil diameter	Vision impairment, presbyopia, cataracts	Macular degeneration, increased risk of falls and loss of independence
Auditory	↑ Tympanic membrane thickens, loss of both elasticity and efficiency of ossicular articulation	Conductive hearing loss	Presbycusis
Skeletal	↓ Bone density, stiffer joints, thinner intervertebral discs, flattening of foot arches	↓ Height, scoliosis, kyphosis, slower and unsteady gait	Osteoporosis and osteoarthritis Greater risk for falls and fractures
Gastrointestinal	Abnormal peristalsis, ↓ gastric acid, mucosal cell atrophy	Dysphagia, malabsorption (iron, vitamin B12, calcium), increased risk for malnutrition	Unintentional weight loss Constipation
Renal	↓ Kidney size and weight, ↓ functional glomeruli, ↓ length/function of renal tubules	↓ Reabsorption capacity, impaired renal function	Chronic kidney disease
Immune	↓ Memory cells, ↑ autoimmune antibodies ↓ T lymphocytes, ↓ natural killer cells, ↓ cytokines	↓ Immune function (requires more stimulus and more time to become activated), ↓ response	Greater risk for infections and less effective response to control them Some types of cancer
Dermal	↓ Skin thickness, ↑ collagen cross-links	↓ Elasticity, ↑ fungal infections, neoplasms	Pressure ulcers

Table adapted from [14,19,20]