Xu D, et al., J Gerontol Geriatr Med 2020, 6: 058
DOI: 10.24966/GGM-8662/100058

HSOA Journal of Gerontology & Geriatric Medicine

Review Article

Metformin Use beyond Diabetes: Reducing Cardiovascular Events in the Healthy Elderly

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Abstract

As the global ageing population rises, there is increasing interest and demand for research evaluating anti-ageing strategies. One such strategy involves investigating a drug that may have additional mechanisms and pathways of action to combat ageing - metformin. This common glucose-lowering agent for diabetes has been safe, effective and globally affordable for over 60 years. Research into the use of metformin and its beneficial influence on healthy ageing is currently emerging. Although metformin's effect on clinical ageing outcomes may be speculative, findings from studies into cellular and animal models and from observational and pilot human studies support its potential beneficial effects on ageing. Ageing has a significant impact on the cardiovascular system and is the leading non-modifiable risk factor for Cardiovascular Disease (CVD). The incidence and prevalence of CVD increases with advancing age, and CVD is the leading cause of death for populations over 65 years of age. However, most CVD prevention research has focused on development of interventions that target "traditional" CV risk factors such as hypertension, hypercholesterolaemia and diabetes. Metformin has been proposed to be an "anti-ageing" drug, based on preclinical experiments with lower-order organisms and numerous retrospective data on beneficial health outcomes for patients with type 2 diabetes. At present, randomised clinical trials to evaluate metformin's clinical impact on healthy ageing are limited. Here, we review the role of metformin and its potential to reduce cardiovascular events in the healthy elderly.

Keywords: Cardiovascular risk factors; Healthy ageing; metformin

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Citation: Xu D, Affandi JS, Yap T, Reid CM (2020) Metformin Use beyond Diabetes: Reducing Cardiovascular Events in the Healthy Elderly. J Gerontol Geriatr Med 6: 058.

Received: June 18, 2020; **Accepted:** June 23, 2020; **Published:** June 30, 2020

Introduction

Australia's ageing population continues to rise from 3.8 million aged over 65 years in 2017, to a projected 8.8 million by 2057 [1]. The combination of a growing ageing population, longer life expectancy and greater prevalence of multiple chronic diseases such as Cardiovascular Disease (CVD), is increasing and contributes significantly to the disease burden in Australia [2]. In 2017-2018, the prevalence of heart, stroke and vascular disease among adults increased with age, affecting more than 1 in 4 of those aged 75 years and over [3]. People with Type 2 Diabetes (T2DM) and pre-diabetes (impaired glucose tolerance and fasting glucose but insufficient for T2DM diagnosis) have also been shown to have an elevated risk of CVD [4]. CVD is the leading cause of death worldwide representing 31% of all deaths, of which 85% are due to heart attack and stroke [5]. In 2014, Americans between 60-79 years of age and over 80 years of age have over 70% prevalence and 80% prevalence rate of CVD respectively [6]. In Australia, CVD continues to be the most expensive disease burden, costing the government almost $8,8 billion in 2017-2018, with hospital admissions constituting more than half of that cost [7]. As the main risk factor for CVD is age, there is increasing interest and demand for research evaluating strategies that address the global burden of ageing. One such strategy involves investigating a drug that may have additional mechanisms and pathways of action to combat ageing - metformin.

The aim of this review is to outline the potential benefits of metformin, beyond glycaemic-control to reduce the burden of ageing and to promote healthy ageing in healthy people without diabetes. Current clinical trials involving metformin will be reviewed, and the feasibility of a large Randomized Clinical Trial (RCT) to examine the role of metformin in primary prevention to reduce cardiovascular events in the healthy elderly will be discussed.

Metformin Use and its Safety

Metformin has been successfully used for long-term treatment in older adults as both the first-line therapy and prevention for T2DM [8,9]. Metformin can be safely started at 500 mg per day and titrated towards the target dose of 1000 mg twice daily with eGFR is above 45 ml/min/ 1.73m^{-2}. Kidney function needs to be monitored in patients with cessation of metformin when Estimated Glomerular Filtration Rate (eGFR) is below 30 ml/min/ 1.73m^{-2} and lowering the dose to a maximum of 1000 mg per day if GFR stays above 30 but below 45 ml/min/ 1.73m^{-2} [10,11]. In terms of serious adverse events, there is ongoing literature debate whether or not metformin is associated with lactic acidosis [12,13]. Nonetheless, the current consensus in clinical practice preventive guideline is to temporarily withhold metformin in

the setting of hospitalisation, acute kidney injury, and use of iodinated-contrast procedures and in the setting of acute severe illness with hypoxia following which metformin therapy is re-implemented [14].

Metformin and CVD

Recently, metformin has been proposed as an anti-ageing drug [15]. Research into metformin's clinical benefits beyond diabetes originated from the observed cardiovascular risk reduction in individuals with diabetes treated with metformin [16]. Since then, there is growing interest and reports regarding its potential clinical benefits beyond glycaemic control. Metformin has a long history of successful use of as the primary drug for the prevention and treatment of T2DM in Australia and globally [17]. Beyond improving glycaemic control, metformin's effects on clinical ageing outcomes may still be considered speculative, although findings from cellular and animal models, observational and pilot human studies support the existence of beneficial effects on ageing [18]. At present, progress for human research, using randomised clinical trials to evaluate metformin's clinical impact are underway. Its use has been associated with a significantly decreased risk of Myocardial Infarction (MI), and CVD in populations with T2DM taking metformin, independent of its effects on blood glucose level, and all-cause mortality [19]. Compared with other medications prescribed for T2DM treatment, metformin does not cause weight gain, and is generally associated with a low risk of hypoglycaemia [20]. People living with diabetes and pre-diabetes have both been shown to have an elevated risk of CVD [4], but the effects of metformin on CVD risk in populations without diabetes are unclear.

Investigation of metformin's mechanisms of action has gained traction due to the protective effects seen in both human and animal studies. As well as the anti-atherogenic effects of metformin [21,22], it has been shown to prevent diabetes-induced oxidative stress [23,24]. The role of metformin in preventing oxidative stress may account for the preventative CVD effects seen in populations with diabetes due to the role of diabetes-related oxidative stress in vascular tissue damage [25]. Metformin has been implicated in the inhibition of the Mechanistic Target of Rapamycin (mTOR) signaling in monocytes pathway [26], reducing cardiac remodeling [27]. Metformin reduces cardiovascular mortality, all-cause mortality and cardiovascular events in Coronary Arterial Disease (CAD) patients [28]. In MI and CAD patients without T2DM, metformin has no significant effect of reducing the incidence of cardiovascular events, although metformin was more effective than sulfonylureas. Clinical evidence shown in patients with diabetes clearly demonstrated the therapeutic benefit of metformin in reducing cardiovascular mortality and morbidity in T2DM patients. However, there is a paucity in research investigating metformin's beneficial effects in healthy older individuals without diabetes. Except in the Diabetes Prevention Program, participants with higher baseline fasting glucose or glycosylated Haemoglobin (HbA1c) and women with a history of Gestational Diabetes Mellitus (GDM) benefitted the most from a 15-year metformin intervention [29].

A recent cohort study of older veterans with T2DM in the US showed that metformin reduced CVD events among individuals with T2DM [30]. There were CVD risk reductions 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 cardio-metabolic effects of metformin in adults with type 1 diabetes (for ≥ 5 years) and high CVD risk, showing 88% of overweight or obesity with an average age of 55.2 ± 8.5 years [31]. After 3 years, there was no difference in the primary outcome of carotid artery Intima-Media Thickness (cIMT), however there were reductions in body weight, LDL-cholesterol, and in atherosclerosis progression, based on maximal cIMT analysis. These findings highlight the potential of metformin for decreasing CVD risk. In a meta-analysis by Han et al., in MI patients and CAD patients without T2DM, metformin had no significant effect of reducing the incidence of cardiovascular events, however metformin was more effective in reducing the incidence of cardiovascular events than sulfonylureas [28,32,33].

Positive effects were seen in dyslipidemia and obese patients when prescribed atorvastatin combined with metformin compared with atorvastatin monotherapy in lowering the rate of obesity and subclinical inflammation [34]. Metformin use also showed positive cardiovascular effects in female patients with symptomatic myocardial ischemia [35], in women with polycystic ovary syndrome [36], and in patients with peripheral arterial disease [37]. Mohan et al., also showed that metformin reduced Left Ventricular (LV) mass indexed to height, improved Systolic Blood Pressure (SBP), reduced oxidative stress and reduced measures of obesity in patients with CAD [38]. Conversely, a more recent study showed no effects on several markers of CVD for patients without diabetes but with high cardiovascular risk [39]. Despite these findings, studies trialing metformin in populations with established CVD have little relevance to primary prevention of CVD due to the cumulative effect of lifestyle factors from a young age that impact on CVD risk in adulthood [40-42] and the comparatively short duration of the trial. The 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 [35]. These findings stressed the importance of metformin use as an additional therapy to reduce cardiovascular risk factors [43]. Further research is required to establish the impact of metformin on CVD risk in those without diabetes [39].

Definition of Ageing in General Practice

There are different personal, cultural and societal perspectives on parameters constituting 'ageing' and elderly. Chronological age for older adults in the USA is age ≥ 65 years, whereas in Europe and other parts of the world, it is 60 years and older. Generally accepted biological definitions of ageing include 'the reduced capacity to regenerate damaged tissue' [44] and 'a deficit in maintaining homeostatic processes over time, leading to functional decline and increased risk for disease and death' [45]. Ageing, insulin resistance and inflammation are associated with the pathogenesis of non-communicable diseases including T2DM [46], CVD [47], cancer [48], depression [49], dementia [50] and frailty [51], a condition of increased vulnerability and adverse health outcomes. The prognosis of an elderly with multiple comorbidity is poor due to functional, psychological and social issues. As our society has a rising elderly population, there is growing interest for research addressing interventions beyond healthy lifestyle to extend the number of functional years.

Age-dependent (physiological ageing) and age-related diseases (pathological ageing) in healthy ageing

In order to better understand the healthy ageing process and how to

invest in it, it is important to highlight the difference between age-dependent and age-related diseases. Age-dependent diseases include CAD, cerebrovascular disease, T2DM, osteoporosis and Alzheimer's disease. Its pathogenesis appears to involve physiological ageing processes, chronic damage from inflammation [52] and metabolic syndrome [53]. Mortality and morbidity in these diseases increase exponentially with advanced age. In contrast, age-related diseases have a temporal relationship with age and are not necessarily related to the physiological ageing process. A recent review [54] raised the debate on whether ageing is a disease in itself, suggesting that physiological ageing is indistinguishable from pathology [55] whereas other studies argue that ageing differs from age-related diseases and other pathologies [56,57]. The answer to this question will have important theoretical and practical consequences with various interventions capable of decelerating the ageing process [58,59]. If ageing is treated as a disease, treatment and intervention including lifestyle modifications, drugs and medical treatments that counteract the mechanisms of ageing may delay frailty for decades, ideally until the apparent inevitable limit of human lifespan is reached [60]. The more radical approach is to rejuvenate human tissues, organs, and whole body in order to overtake the above-mentioned limits of human lifespan [60].

Mechanism of ageing

The process of ageing is complex and multifactorial. Indeed, physiological and evolutionary theories have been suggested in order to deduce the mechanisms of ageing [61]. DNA damage is one such mechanism that has received the most attention in order to identify pathways that can be contained or modified to halt or delay ageing itself. Endogenous sources for DNA damage include Reactive Oxygen Species (ROS), alkylation and hydrolysis, whereas exogenous sources include chemicals, Ultraviolet (UV) and other forms of radiation [62]. Oxidative stress, a process where free radicals cause DNA damage and impairment in proteins and lipids translation, provides another mechanism of ageing via genetic damage [63]. Most ageing research comes from animal experiments attempting to expand lifespan. Indeed, a novel CRISPR/Cas9 genome-editing therapy that can suppress the accelerated ageing observed in mice with Hutchison-Gilford progeria syndrome, a rare genetic disorder that also afflicts humans, has been put forward. This treatment provides important insight into new molecular pathways involved in accelerated ageing, as well as how to reduce toxins via gene therapy [64].

The evolutionary theory of ageing assumes a linear increase in mutations over time whilst ageing and death are initially circumvented by cellular redundancy mechanisms [65], as mutations overwhelm the system with ineffective protein translation resulting in ageing. From the cellular level, this leads to organ dysfunction, causing diabetes, cardiovascular diseases, neurodegenerative diseases, chronic inflammatory diseases leading to early frailty, delirium and falls, indicated that ageing and pathologies share the same common mechanism [54].

The impact of metformin on mechanisms related to the ageing process

The mechanisms by which metformin impact on glucose homeostasis 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 [66], altering mechanisms related to ageing. Furthermore, it has been well documented that metformin mildly reduces levels of High-Sensitivity C-Reactive Protein (hsCRP) [67], and improves endothelial function [68,69], enhancing the benefits against the ageing process. Anti-diabetic activity of metformin may be potentiated via action on the enterocytes and enteroendocrine cells [70]. Metformin has been implicated as the antagonist of the gut hormone Glucagon-Like with Peptide-1 (GLP-1) in patients with T2DM [71]. In addition to GLP-1, two other hormones including Peptide YY (PYY) and Growth/Differentiation Factor 15 (GDF15) are increased significantly on metformin therapy, GDF15 being produced mainly in the intestine via the "integrated stress response" [72]. GDF15 was positively associated with the incidence of diabetes mellitus in the longitudinal Malmo Diet and Cancer-Cardiovascular cohort [73]. Metformin exerts its anti-diabetic effects by increasing the activity of Adenosine Monophosphate-Activated Protein Kinase (AMPK) and mediating the mitochondrial complex I receptor for the anti-diabetic action of metformin [74].

Psychological health including depression and anxiety

A placebo-controlled Chinese study by Guo et al., with participants with T2DM and mild to moderate depression, showed metformin improved depressive symptoms, possibly related to better glycemic control [75]. The outcome of this study is clinically relevant for clinician to be proactive in view of high prevalence of depression in the elderly with or without diabetes. Another case-control study in China examining elderly patients with diabetes using geriatric depression scale concluded that overweight status, poor physical capabilities and low activity level, and the presence of more than two additional illnesses were risk factors for depression, and metformin was a protective factor against depression in elderly patients with diabetes [76]. In light of the anti-depressive effects of metformin in the Chinese population, it will be prudent to examine whether metformin will have similar effects in the western population or different cultural groups.

There is no direct evidence in human regarding the effects of metformin on anxiety. An interesting mice study suggest that metformin may act by decreasing circulating Branched-Chain Amino Acids (BCAAs) levels to favour serotonergic neurotransmission in the hippocampus and promote anti-anxiety effects in mice fed a High-Fat Diet (HFD) [77]. These findings can potentially translate into clinical practice that a diet poor in BCAAs with metformin use or as add-on therapy to conventional anti-anxiety drugs could help to relieve anxiety symptoms in patients with metabolic comorbidities. It will be interesting to explore whether there is any role of metformin in relieving anxiety symptoms in the elderly as part of healthy ageing coping strategies.

Mild cognitive impairment and dementia

Metformin has been shown in many observational studies to lead to reductions in Mild Cognitive Impairment (MCI) [78] and dementia [79,80] among participants with diabetes taking metformin when compared with no medication or other glucose-lowering agents. A study in Taiwanese individuals aged ≥ 50 years showed that metformin use significantly decreased the risk of dementia compared with no medication (Hazard Ratio [HR] 0.76 [95% Confidence Interval {CI} 0.58-0.98]) [75]. Another evaluation study examined data from 365 individuals from the Singapore Longitudinal Ageing Study (aged ≥ 55 years) to demonstrate that metformin use was associated with lower risk of MCI (Odds Ratio [OR] 0.49 [CI 0.25, 0.95]) [79].

Another study from Taiwan used an insurance database from 67,731 individuals and found that dementia risk was lower in those taking metformin compared with other glucose-lowering medications [80]. It is essential to be aware of the limitations of confounding factors influencing the outcome interpretation of these studies. Despite of the limitations in these studies, a recent clinical trial substantiated the above evidence by showing that metformin improved cognition in individuals without Diabetes [81]. Eighty amnestic MCI participants (aged 55 to 90 years) without treated diabetes were randomly assigned to metformin or placebo for 12 months' follow-up. Participants on the metformin arm 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. A recent retrospective cohort study suggested that metformin use in T2DM patients was associated with a significantly lower risk of dementia, especially after use for more than two years [82]. The risk reduction showed a dose-response pattern, was consistent in sensitivity analyses and was not affected by the year of enrollment.

In contrast, an Australian clinical study showed that participants with diabetes (n=126, including 35 metformin users and 91 non-users) displayed worse cognitive performance in the metformin group (OR 2.23, 95% CI 1.05-4.75) [83]. The finding was in consistent with later evidence that metformin may be associated with deleterious effects on cognitive function in the elderly [84]. Researchers in mouse models of ageing reported worsening tau aggregation (causing neurofibrillary degeneration and neurotoxicity associated with the development of Alzheimer's disease) and abnormal behavior [85] or impaired spatial memory and visual acuity [86]. Furthermore, a recent analysis of patients' cognitive function 8-10 years after metformin use did not support any benefit of metformin use [87]. The most recent study showed that metformin is associated with a higher risk of vitamin B12 and vitamin B6 deficiency, leading to an increased risk of cognitive dysfunction [88]. Thus, vitamin supplementation is strongly recommended to metformin users.

In summary, although there have been extensive research and clinical trials involving metformin in patients with diabetes, inconsistent dementia risk and cognitive function results warrant more in-depth research. Metformin is relatively safe and would not cause hypoglycemia when used as monotherapy. However, its clinical impact on the prevention of dementia in individuals with and without diabetes warrants a large RCT as part of the healthy ageing strategies.

Future Developments in Metformin Research

One of the priorities to reduce healthcare costs in an ageing society is to delay the onset of frailty by identifying risk factors such as cardiovascular and musculoskeletal diseases in the pre-frailty stage. It is well documented that lifestyle modifications including diverse exercise interventions have several advantages with the challenge of adherence over time [89]. Metformin offers a cost-effective alternative besides controlling diabetes or reducing its risk, improving mood and cognitive and physical function. Metformin's "off-label" use alone or in combination with other anti-diabetics gains popularity for effective prevention of diabetes [90] as well as for management of metabolic syndrome, obesity and polycystic ovarian disease [91,92]. The TAME trial primary endpoints comprise the incidence of MI, congestive heart failure, stroke, most cancers, dementia, and death, but not diabetes and frailty. A clinical trial by Espinoza et al. provides arguments that frailty may be an important endpoint [93]. TAME plans to randomize 3,000 older persons aged between 65-79 years without diabetes including persons with chronic diseases [94] and most likely only persons with impaired glucose tolerance/fasting hyperglycemia. In addition, the TAME biomarker sub-study includes blood-based biomarkers including interleukin- 6, C-reactive protein, insulin-like growth factor 1, insulin, cystatin C, N-terminal prohormone of brain natriuretic peptide, HbA1c, and GDF15, but not GLP-1 [95]. The biomarker workgroup raised important mechanism questions from basic science points of view for TAME and other trials including cancer or neurological diseases impacted by metformin use, in which metformin increases the activity of AMPK and may stimulate autophagy [96-98] or modulate it in leukocytes of T2DM patients [99]. Similar to the pharmaceutical system in the United States, metformin can be listed on our Australian Pharmaceutical Benefits Scheme (PBS) system for the novel indications if the research proves its efficacy. There is also plan from the TAME researchers to "repurpose" metformin for increasing lists of disease indications in mice and humans with advancing age [100,101]. The TAME trial has been listed in ClinicalTrials.gov as of November 2019 and the study protocol is now in the public domain.

Another large clinical trial sponsored by the Veterans Administration (NCT02915198; VA-IMPACT) started on February 19, 2019. This trial plans to study 7,868 subjects with prediabetes and established atherosclerotic disease for 4.5 years in a double-blind placebo control trial with metformin extended release versus placebo for a combined primary endpoints. The primary endpoints include the time to death from any cause, MI, stroke, hospitalization for unstable angina, or symptom-driven coronary revascularization, while time-to-events for oncology-related diseases and diabetes are secondary endpoints.

A recent double blind, randomized Glucose Lowering in Non-Diabetic Hyperglycaemia Trial (GLINT) testing the feasibility of metformin reducing the risk of cancer in elderly obese patients with a high risk of CVD and non-diabetic hyperglycemia concluded that 20,000 subjects are required to obtain significant results for only CVD [102]. Metformin in Longevity Study (MILES) was a small, double-blind, placebo-controlled crossover trial in which they investigated differentially expressed genes in muscular and adipose tissue biopsies after 6-week administration of placebo or 1.5 g per day of metformin [103]. The study reported biomarkers (such as interleukin-6, C-reactive protein, tumour necrosis factor α, insulin-like growth factor 1, cystatin C, N-terminal B-type natriuretic peptides and haemoglobin A1c) selected by the TAME working group except GDF15 [95]. Early Prevention of Diabetes Complications in Europe (ePREDICE) is another large multicenter RCT and currently 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 [104].

Taken together, metformin has been identified as a potential agent for primary prevention of cardiovascular diseases and reduction in Major Adverse Cardiovascular Events (MACE) and mortality in low cardiovascular risk and healthy individual (Table 1).

Author and Year	Design	Target population and size	Outcomes measured	Follow up time	Summary of findings
Orio et al., [36]	Prospective, baseline-controlled trial	N=30 Young women with PCOS without additional metabolic or CV disease	Complete hormone profile, serum insulin, glucose, lipid and endothelin-1. Brachial artery diameter and cIMT	6 months	6-month course of metformin improves endothelial structure and function in young, normal-weight women with PCOS.
Khan et al., [37]	Retrospective cohort study	N=1204 Patients who underwent revascularization for chronic limb ischemia	Primary patency, secondary patency, limb salvage, major adverse limb events, major adverse cardiac events and survival rates	Mean of 48 months	Metformin is associated with improved survival and decreased incidence of adverse cardiac events in PAD patients. It did not have an impact on patency or limb salvage rates.
Preiss et al., [39]	Double-blind, placebo-controlled trial	N=173 Patients taking statins, without T2DM with coronary heart disease and large WC	Mean distal cIMT, carotid plaque score, glucose, lipids, C-reactive protein and tissue plasminogen activator	18 months	Metformin had no effect on cIMT and little or no effect on several surrogate markers of cardiovascular disease in non-diabetic patients with high cardiovascular risk, taking statins.
Mohan et al., [38]	Double-blind, placebo-controlled trial	N=63 Patients without diabetes who have CAD with insulin resistance and/or prediabetes	LV mass indexed to height, LV ejection fraction, mass, and volume; abdominal obesity, glycaemic parameters, endothelial function, and blood biomarkers	12 months	Metformin treatment significantly reduced LV mass indexed to height and LV mass compared with placebo in patients with CAD without T2DM. It also improved SBP, reduced oxidative stress and reduced measures of obesity.
Lexis et al., [32]	Double-blind, placebo-controlled trial	N=379 Patients who underwent primary percutaneous coronary intervention for STEMI	LV ejection fraction, NT-proBNP, major adverse cardiac events	4 months	Metformin compared with placebo did not result in improved LV ejection fraction or NT-proBNP levels. As LV function is an important predictor of morbidity and mortality after STEMI, it is unlikely that metformin will have a significant effect on long-term outcomes.
Hartman et al., (2 year follow up of Lexis et al.,) [33]	Double-blind, placebo-controlled trial	N=379 Patients who underwent primary percutaneous coronary intervention for STEMI	Major adverse cardiac events, NT-proBNP, death, reinfarction, recurrent coronary intervention, stroke, heart failure, ICD implantation, and new-onset diabetes mellitus	24 months	Four months metformin treatment initiated at the time of hospitalization in STEMI patients without diabetes did not exert beneficial long-term effects
Knowler et al., [9]	Randomized clinical trial	N=3234 Non-diabetic persons with elevated fasting and post-load plasma glucose concentrations	Diabetes (glucose), adverse effects	Mean of 34 months	Lifestyle changes and treatment with metformin both reduced the incidence of diabetes in persons at high risk. The lifestyle intervention was more effective than metformin.
Kulkarni et al., [103]	Double-blind, placebo-controlled, Crossover trial	N=14 Older patients with impaired glucose tolerance but no diabetes.	Skeletal muscle and subcutaneous adipose tissue for number of expressed genes. Serum glucose, insulin,	3 months	6 weeks of metformin can improve age-associated metabolic derangements in glucose intolerant older adults. Metformin has metabolic and nonmetabolic effects linked to aging
Luchsinger et al., [81]	Double-blind placebo-controlled randomized pilot trial	N=80 Patients with aMCI, overweight or obese, without treated diabetes	Bushcke SRT, ADAS-cog, plasma Aβ42, relative glucose uptake in the posterior cingulate-precuneus measured by brain FDG PET and MRI	12 months	Preliminary evidence of efficacy to improve SRT but not ADASCog. A larger trial seems warranted to evaluate the efficacy and cognitive safety of metformin in prodromal Alzheimer's disease

Table 1: Summary of clinical trials with metformin in non-diabetic population.

PCOS, Polycystic Ovary Syndrome; CV, Cardiovascular; cIMT, Carotid Intima-Media Thickness; PAD, Peripheral Arterial Disease; T2DM, Type 2 Diabetes Mellitus; WC, Waist Circumference; CAD, Coronary Arterial Disease; LV, Left Ventricular; SBP, Systolic Blood Pressure; STEMI, ST-Elevation Myocardial Infarction; NT-proBNP, N-Terminal Pro-Brain Natriuretic Peptide; ICD, Implantable Cardioverter-Defibrillator; aMCI, Amnestic Mild Cognitive Impairment; SRT, Selective Reminding Test; ADAS-cog, Alzheimer's Disease Assessment Scale Cognitive Subscale; Aβ42, Amyloid Beta 42; FDG, F-labelled 2-Deoxy-2-fluoro-D-Glucose; PET, Positron Emission Tomography; MRI, Magnetic Resonance Imaging.

Conclusion and Clinical Perspectives

The rationale for the ongoing or planned metformin trials is almost exclusively based on observations of potential benefits in a population with diabetes (or prediabetes). Beyond its impact on diabetic control, metformin has diverse ranges of effects targeting multiple age-related mechanisms. Cellular and animal studies have found that metformin reduces insulin resistance and decreases inflammatory markers, NF-κB, ROS and mTOR pathways, thus decreasing DNA damage. Human observational studies have shown that metformin decreases the risk of CVD, cancer, depression and other age-related conditions. A few studies found that metformin may reduce MCI and dementia. Ongoing randomized 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 multi-morbidity, frailty and ageing in individuals with or without diabetes, especially in people with low cardiovascular risks or healthy elderly in the primary prevention trial. In terms of primary prevention trial, the Aspirin in Reducing Events in the Elderly (ASPREE) was a primary prevention trial that was established to investigate whether the daily use of 100 mg of enteric-coated aspirin would prolong the healthy life span of older adults conducted in Australia and the United States, recruiting 19,114 relatively healthy older persons from community settings. The primary end point was disability-free survival, which was defined as survival free from dementia or persistent physical disability. The primary composite end point was derived from the first end-point events of death, dementia and persistent physical disability. The use of low-dose aspirin did not differ significantly from placebo in influencing the rate of the primary end point after a median of 4.7 years of follow-up [105]. Taking together, metformin will have great potential to play an important healthy ageing role in combating cardiovascular risks and prolonging disability-free survival. Hence, a properly designed clinical trial similar to the ASPREE trial involving metformin use in the healthy population will most likely answer the challenges of healthy ageing in our modern society.

Funding

No external funding.

Acknowledgments

School of Public Health provided Ms Jacinta Chapman-Williams vocational scholarship to help collect the references of the literature review for the manuscript. Dr Natalie Ward provided some helpful comments in constructing the initial manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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