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A new anti-ageing strategy focused on prevention of arterial ageing in the middle-aged population

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ABSTRACT

Ageing is a progressive process that according to available knowledge cannot be effectively reversed, slowed or stopped. Here we propose a new anti-ageing approach that may lead to the design of effective therapeutic intervention. First, we hypothesize that the "organ system" oriented anti-ageing approach represents a better anti-ageing target than the "whole body" or "cellular ageing" concepts. The arterial system is the most suitable target, as it interconnects all the organs in the body, thus influencing them all. Second, we propose that an anti-ageing approach could be more successful in early than late ageing stages; middle-aged people seem to be the most appropriate candidates. Third, we believe that instead of searching for new medication, we should rely on already established medications with beneficial effects on the arterial wall. Renin-angiotensin system inhibitors and statins fulfill these criteria and are potential cornerstones of the new approach. The fourth hypothesis is based on the concept that in the early stages of arterial ageing only slight injury is present and therefore subtherapeutic, low-dose treatment would be effective. Fifth, we hypothesize that slight initial age-related arterial wall changes are reversible and could be corrected by a short-term (one month) treatment. Sixth, we hypothesize that the effects would be present for a certain period of time even after treatment termination. The listed assumptions combined represent the basis for a new, original anti-ageing approach – a subtherapeutic low-dose combination of a renin-angiotensin system inhibitor and a statin for one month (followed by approximately 6–12 months without treatment) could delay or even reverse the arterial ageing process and consequently decrease the incidence of cardiovascular disorders.

Introduction

Anti-ageing medicine, in scientific and non-scientific terms, is flourishing in recent years, being continuously fuelled by enormous interest and expectations. There is hardly any other field in medicine in which so much potential therapeutic effort (from simple substances to high-technology genetic and rejuvenation techniques) has been invested. Enormous interest has been put into research on molecules that could influence the ageing process, whether whole-body ageing [1,2] and/or cellular ageing [3,4]. However, it seems that the desired effect has not been yet reached [4–10]. The probable reason for this situation lies in the complexity of the ageing process itself. It is important to emphasize that the aim of anti-ageing medicine is not merely life prolongation, but also improvement in the quality of life.

According to epidemiological data, cardiovascular diseases (ischaemic heart disease, stroke, etc.) are still the leading causes of morbidity and mortality in the ageing population of developed countries [11,12]. Existing cardiovascular disease prevention strategies are based on life-style improvement and risk factor modification, including treatment of chronic non-infectious diseases (hypertension, hyperlipidemia, diabetes, etc.). An additional preventive or treatment strategy focusing more specifically on arterial ageing, according to our belief, should become the mainstream of cardiovascular anti-ageing medicine. Numerous studies have shown that ageing is one of the most important risk factors for age-related arterial wall changes and atherosclerosis, even in the absence of other risk factors [13–17]. With increasing age, arteries become stiffened and their pulsatility increases, thus leading to damage of the circulation in the target organs heart, brain, kidney, etc. [13,18–20]. The occurrence of age-related arterial wall changes is already present in middle-aged individuals and progresses with ageing, underlying the development of cardiovascular diseases [21,22].

Existing medications possessing beneficial effects on the arterial wall through improvement of its functional and structural characteristics are of great interest. Two groups of widely used medications, namely renin-angiotensin system inhibitors and statins, fulfill these criteria through their beneficial pleiotropic effects, which are independent of their basal effects (blood pressure lowering and plasma cholesterol reduction) [23,24]. These benefi-

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cial pleiotropic effects are manifested through a wide spectrum of mechanisms, most of them being similar in both groups of drugs. It is well known that angiotensin II signaling enhances production of pro-inflammatory cytokines and oxidative stress mediators, both leading to chronic pro-inflammatory state in the arterial wall [20]. We believe that renin-angiotensin system inhibitors and statins lead to slowing down arterial ageing process through reduction of angiotensin II effects. Overall, it can be summarized, that they possess anti-inflammatory and anti-oxidative activity, as well as the ability to improve endothelial function [20,24–27]. Previous studies confirmed the beneficial effects of renin-angiotensin system inhibitors and statins in therapeutic doses [28–31], while a few studies showed that these medications are also effective in low doses [32,33]. Although the listed medications exert pleiotropic beneficial effects separately, they were proven to be even more effective when given in combination, thanks to their additive or even synergistic action [34–37].

The hypothesis

Our main hypothesis is based on the following sub-hypotheses, using the steps in causal assumptions which are outlined below, and finally lead to introduction of a new anti-ageing approach. We hypothesize that:

(i) the arterial system represents a more logical target for anti-ageing intervention than the "whole body" or "cellular ageing" approach;
(ii) arterial anti-ageing efforts should start in the early stages of arterial ageing; preferably middle-aged people are appropriate candidates for intervention;
(iii) for the mentioned approach we propose the use of already established medications, particularly those that have beneficial pleiotropic effects on the arterial wall;
(iv) it appears probable that in the case of initial subtle age-related injury, a subtherapeutic low-dose combination of renin-angiotensin system inhibitor and statin would be the most effective;
(v) initial age-related changes are reversible and could be relatively rapidly (in a one month treatment period) corrected;
(vi) age-related changes reoccur after discontinuation of treatment (in the rest period), but this takes much longer than is needed for their removal.

To summarize, we hypothesize that short-term (one month) treatment with the subtherapeutic, low-dose combination of a renin-angiotensin system inhibitor and a statin would improve arterial wall characteristics in middle-aged populations. We propose the intervention be regularly repeated (once or twice per year) over long time periods (decades), resulting in slowing, delaying or even reversing arterial ageing.

Evaluation of the hypothesis

The definitive and complete confirmation or rejection of our hypothesis demands a long-term study of alternating "treatment" and non-treatment, so-called "rest" periods, probably lasting at least a decade or even more. However, some surrogate end-points, for example arterial functional and structural arterial wall characteristics improvement, could be measured and followed in intermediate studies (with one-month treatment periods which would be repeated every 6–12 months). The measured parameters should be followed for a few years (after several "treatment-rest" periods) to confirm the body's ability to repeatedly achieve beneficial effects after one-month treatment repetition on a continuous basis from year to year (Fig. 1). On the other hand, quality of life, the incidence of cardiovascular diseases in older age and longevity could only be monitored in longer-term studies.

The arterial system is of outmost importance in the whole body, as it interconnects all the various tissues and organs. Consequently, proper functional and structural arterial wall characteristics are required for normal organ functioning. The process of organ or tissue ageing occurs not only because of direct organ ageing, but also as a consequence of arterial system ageing [38,39]. Thus, the arterial system, having the main role in distributing oxygen and nutrients to all tissues, in our opinion is a more logical target for anti-ageing intervention than the "whole body" or "cellular ageing". Even more, the process of arterial ageing already starts in late childhood and progresses with increasing age [40,41]. The early stages of arterial ageing represent subtle changes which because of their small extent are more likely to be reversible. The early arterial wall changes are mostly functional, such as endothelial dysfunction that is later accompanied by arterial stiffness; both were shown to be reversible, at least in their early stages [41,42]. Considering all the above facts, our hypothesis covers the population of middle-aged people (defined as individuals aged between 30 and 55 years), who are still in the early stages of arterial ageing, consequently capturing them in their reversible phase. In such an approach, already established medications would be used that in clinical practice have proven their safety and to possess beneficial pleiotropic effects on the arterial wall. These criteria are fulfilled by renin-angiotensin system inhibitors basically used for blood pressure lowering, and statins basically used for cholesterol level reduction [24,26]. Based on the relatively subtle initial age-related arterial wall injury in the population considered, we believe that a subtherapeutic, low-dose combination of the mentioned medications would be effective. The effectiveness of low-doses was shown in several previous studies [32,33]. It was also shown that their combination is more effective than the separate medications due to occurrence of additive or even synergistic effects. The proposed mechanisms of action are the improvement of endothelial function on one side and anti-oxidative and anti-inflammatory activity in the arterial wall on the other [35–37]. We have partially shown in our previous pilot studies that the hypothesis explained in this paper might indeed work [43–45], but this issue should be further explored at a theoretical basis and proven in the long-term studies. The duration of the effect obtained after one-month treatment remains to be established, but we expect a prolonged beneficial effect, lasting for at least 6–12 months after therapy discontinuation, although declining continuously throughout that period. The time of the return of the situation to that before therapy would represent the suitable start point for cycle repetition.

As for the treatment approach, the subtherapeutic combination of a low-dose renin-angiotensin system inhibitor and a statin should be used for one month followed by 6–12 months of a no treatment, "rest" period. The proposed anti-ageing approach should be tested on an apparently healthy middle-aged population with functional and structural arterial wall changes already present. For exploration of the arterial wall characteristics, the brachial artery flow-mediated dilation (FMD), artery pulse wave velocity (PWV) and carotid artery intima-media thickness (IMT) would be measured at the beginning and at the end of every treatment and rest period. Regular monitoring of these arterial wall characteristics would enable determination of the most appropriate "rest" period duration.

Consequences of the hypothesis

The described hypothesis allows design of a new, original anti-ageing approach in the middle-aged population with a subtherapeutic, low-dose combination of a renin-angiotensin inhibitor and a statin for one month, followed by approximately 6–12 months without