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Caloric restriction reduces age-related and all-cause mortality in rhesus monkeys

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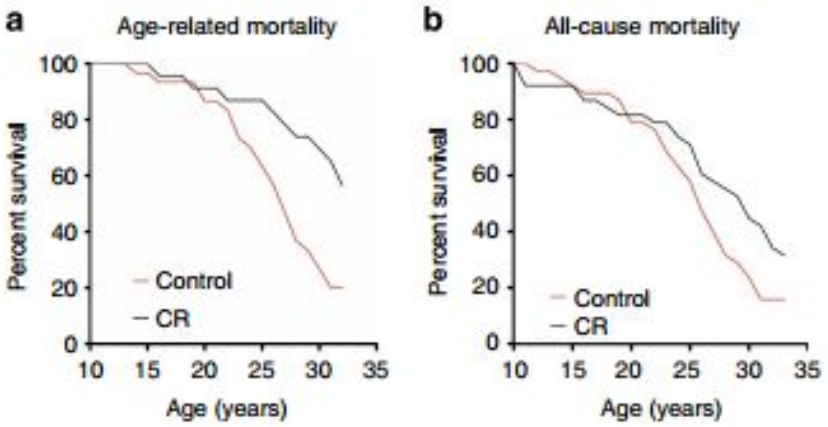
Caloric restriction (CR) without malnutrition increases longevity and delays the onset of age-associated disorders in short-lived species, from unicellular organisms to laboratory mice and rats. The value of CR as a tool to understand human ageing relies on translatability of CR's effects in primates. Here we show that CR significantly improves age-related and all-cause survival in monkeys on a long-term ~30% restricted diet since young adulthood. These data contrast with observations in the 2012 NIA intramural study report, where a difference in survival was not detected between control-fed and CR monkeys. A comparison of body weight of control animals from both studies with each other, and against data collected in a multi-centred relational database of primate ageing, suggests that the NIA control monkeys were effectively undergoing CR. Our data indicate that the benefits of CR on ageing are conserved in primates.



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Degradation of oxidized and glycoxidized collagen: Role of collagen cross-linking

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ABSTRACT

Skin aging is a multifactorial process leading to structural and physiological changes. Protein modifications are known to play here an important role. Since collagen is the most abundant protein in the extracellular matrix of the skin and due to its slow turnover rates it is a frequent target of modifications by reactive compounds. Using skin biopsies of young and old mice we demonstrated that advanced glycation end products (AGEs), such as argpyrimidine and pentosidine, accumulate in aged skin, whereas protein carbonylation is unchanged. To investigate whether this discrepancy in accumulation is the result of an increased formation or due to reduced degradation we used modified collagen type I in *in vitro* experiments and tested for proteolytic susceptibility. We were able to show that collagenase is able to degrade oxidized and AGE-modified collagen. However, if collagen is cross-linked heavily, collagenase is unable to degrade the modified collagen. Cross-linking of collagen is preferentially taking place in collagen fibers treated with glycoxidizing agents.

In summary, the low presence of oxidized collagen in aged skin seems to be the result of a sufficient degradation by collagenases, whereas the reason of the accumulation of AGE-modified collagen is at least partially an insufficient degradation.

Original Investigation

Glycated Hemoglobin Measurement and Prediction of Cardiovascular Disease

The Emerging Risk Factors Collaboration

Supplemental content at jama.com

IMPORTANCE The value of measuring levels of glycated hemoglobin (HbA_{1c}) for the prediction of first cardiovascular events is uncertain.

OBJECTIVE To determine whether adding information on HbA_{1c} values to conventional cardiovascular risk factors is associated with improvement in prediction of cardiovascular disease (CVD) risk.

DESIGN, SETTING, AND PARTICIPANTS Analysis of individual-participant data available from 73 prospective studies involving 294 998 participants without a known history of diabetes mellitus or CVD at the baseline assessment.

MAIN OUTCOMES AND MEASURES Measures of risk discrimination for CVD outcomes (eg, C-index) and reclassification (eg, net reclassification improvement) of participants across predicted 10-year risk categories of low (<5%), intermediate (5% to <7.5%), and high (≥7.5%) risk.

RESULTS During a median follow-up of 9.9 (interquartile range, 7.6-13.2) years, 20 840 incident fatal and nonfatal CVD outcomes (13 237 coronary heart disease and 7603 stroke outcomes) were recorded. In analyses adjusted for several conventional cardiovascular risk factors, there was an approximately J-shaped association between HbA_{1c} values and CVD risk. The association between HbA_{1c} values and CVD risk changed only slightly after adjustment for total cholesterol and triglyceride concentrations or estimated glomerular filtration rate, but this association attenuated somewhat after adjustment for concentrations of high-density lipoprotein cholesterol and C-reactive protein. The C-index for a CVD risk prediction model containing conventional cardiovascular risk factors alone was 0.7434 (95% CI, 0.7350 to 0.7517). The addition of information on HbA_{1c} was associated with a C-index change of 0.0018 (0.0003 to 0.0033) and a net reclassification improvement of 0.42 (−0.63 to 1.48) for the categories of predicted 10-year CVD risk. The improvement provided by HbA_{1c} assessment in prediction of CVD risk was equal to or better than estimated improvements for measurement of fasting, random, or postload plasma glucose levels.

CONCLUSIONS AND RELEVANCE In a study of individuals without known CVD or diabetes, additional assessment of HbA_{1c} values in the context of CVD risk assessment provided little incremental benefit for prediction of CVD risk.

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Skin Autofluorescence Is Associated With 5-Year Mortality and Cardiovascular Events in Patients With Peripheral Artery Disease

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Objective—Advanced glycation end products play a pivotal role in atherosclerosis. Recently, we showed that tissue advanced glycation end products deposition, noninvasively assessed by skin autofluorescence (SAF), is increased in patients with peripheral artery disease. The aim of the present study was to establish whether SAF is associated with all-cause mortality and with fatal or nonfatal major adverse cardiovascular events (MACE) in patients with peripheral artery disease.

Approach and Results—We performed a single-center prospective cohort study of 252 patients with peripheral artery disease (mean age, 66±11 years), recruited from the outpatient clinic (October 2007 to June 2008) who were followed until June 2013. SAF was measured with the AGE Reader. The primary end point was all-cause mortality, and the secondary end point was fatal or nonfatal MACE, defined as cardiovascular death and nonfatal myocardial infarction or stroke. During a median follow-up of 5.1 (interquartile range, 5.0–5.3) years, 62 (25%) patients died. Fatal or nonfatal MACE occurred in 62 (25%) patients. A higher SAF was associated with increased risk for all-cause mortality (hazard ratio per unit increase, 2.01; 95% confidence interval, 1.40–2.88; P=0.0002) and fatal or nonfatal MACE (hazard ratio, 1.82; 95% confidence interval, 1.28–2.60; P=0.001), also after adjustment for cardiovascular risk factors and the use of lipid-lowering drugs (hazard ratio, 1.63; 95% confidence interval, 1.13–2.34; P=0.009 and hazard ratio, 1.50; 95% confidence interval, 1.04–2.17; P=0.03, for all-cause mortality and fatal and nonfatal MACE, respectively).

Conclusions—SAF as a measure of advanced glycation end products deposition is independently associated with all-cause mortality and fatal or nonfatal MACE in patients with peripheral artery disease after a 5-year follow-up. (***Arterioscler Thromb Vasc Biol.* 2014;34:933-938.**)

NATURE NEWS BLOG

Call for acid-bath stem-cell paper to be retracted

10 Mar 2014 | 16:00 BST | Posted by David Cyranoski | Category: Biology & Biotechnology, Ethics, stem cells

Less than 40 days after a team led by Haruko Obokata of the RIKEN Center for Developmental Biology in Kobe, Japan, presented two stunning papers claiming a method of using a simple acid-bath method to reprogramme mature mammalian cells back to an embryonic state — so called STAP cells — researchers in Japan, including one of the paper's co-authors, are calling for them to be retracted.

Within weeks of their 30 January publication, the paper was criticized for irregularities and apparent duplicated images. Numerous scientists also had difficulty reproducing the supposedly simple method. The team responded with the promise of corrections and a list of tips to help other scientists to reproduce the results.

Over the weekend, however, two more serious problems surfaced. The *Nature* paper was found to contain two images apparently duplicated from Obokata's doctoral dissertation. Her thesis also reported experiments dealing with cells that were supposedly in an embryonic state, but the cells reported in the *Nature* paper were said to be derived from a different process in an altogether different experiment.

The revelation has led to a flurry of calls — including some from senior scientists in Japan — for the paper to be retracted.

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Long-Term Metformin Usage and Cognitive Function among Older Adults with Diabetes.

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Abstract

Evidence strongly supports the important role of insulin resistance in cognitive decline and dementia and suggests that insulin sensitizers may protect against cognitive decline in diabetic and pre-diabetic individuals. Inconclusive results have been reported in clinical trials of rosiglitazone, an insulin sensitizer that also increases cardiovascular mortality risks. No study has yet reported a protective cognitive effect of metformin, an insulin-sensitizing biguanide widely used in diabetic patients. We studied 365 older persons aged 55 and over in the population-based Singapore Longitudinal Aging Study with diabetes who were followed up over 4 years. The odds ratios (OR) of association of metformin use (n = 204) versus non-use (n = 161) with cognitive impairment (Mini-Mental State Exam ≤ 23), and by duration: up to 6 years (n = 114) and more than 6 years (n = 90) were evaluated in cross-sectional and longitudinal multivariate analyses. Controlling for age, education, diabetes duration, fasting blood glucose, vascular and non-vascular risk factors, metformin use showed a significant inverse association with cognitive impairment in longitudinal analysis (OR = 0.49, 95% CI 0.25-0.95). Metformin use showed significant linear trends of association across duration of use in cross-sectional and longitudinal analyses (p = 0.018 and p = 0.002, respectively), with use for more than 6 years significantly associated with lowest risk of cognitive impairment in both cross-sectional analysis (OR = 0.30, 95% CI 0.11-0.80) and in longitudinal analysis (OR = 0.27, 95% CI 0.12-0.60). No significant interactive effects of metformin use with APOE-ε4, depression, or fasting glucose level were observed. Among individuals with diabetes, long-term treatment with metformin may reduce the risk of cognitive decline. Further studies should establish the role of hyperglycemia and insulin resistance, and the protective role of metformin in the risk of cognitive decline and dementia.

REVIEWS

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Small molecule SIRT1 activators for the treatment of aging and age-related diseases

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Recent studies in mice have identified single molecules that can delay multiple diseases of aging and extend lifespan. In theory, such molecules could prevent dozens of diseases simultaneously, potentially extending healthy years of life. In this review, we discuss recent advances, controversies, opportunities, and challenges surrounding the development of SIRT1 activators, molecules with the potential to delay aging and age-related diseases. Sirtuins comprise a family of NAD^+-dependent deacylases that are central to the body's response to diet and exercise. New studies indicate that both natural and synthetic sirtuin activating compounds (STACs) work via a common allosteric mechanism to stimulate sirtuin activity, thereby conferring broad health benefits in rodents, primates, and possibly humans. The fact that two-thirds of people in the USA who consume multiple dietary supplements consume resveratrol, a SIRT1 activator, underscores the importance of understanding the biochemical mechanism, physiological effects, and safety of STACs.

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Chemical kinetics for drug discovery to combat protein aggregation diseases

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Protein misfolding diseases are becoming increasingly prevalent, yet there are very few effective pharmacological treatments. The onset and progression of these diseases is associated with the aberrant aggregation of normally soluble proteins and peptides into amyloid fibrils. Because genetic and physiological findings suggest that protein aggregation is a key event in pathogenesis, an attractive therapeutic strategy against this class of disorders is the search for compounds able to interfere with this process, in particular by suppressing the formation of soluble toxic oligomeric aggregates. In this review, we discuss how chemical kinetics can contribute to the fundamental understanding of the molecular mechanism of aggregation, and speculate on the implications for the development of therapeutic molecules that inhibit specific steps in the aggregation pathway that are crucial for preventing toxicity.

[1,2]. However, the power of this approach in the area of protein aggregation disorders largely remains unexploited. The purpose of this review is to highlight the opportunities and challenges that emerge from the application of chemical kinetics to the study of protein aggregation phenomena and their biological consequences. In particular, we discuss the key role that chemical kinetics can play in the search for measure of combatting neurodegenerative disorders, including Alzheimer's disease (AD) and Parkinson's disease (PD), which collectively represent one of the leading causes of death in the modern world [3].

With increasingly aging populations, the number of people affected by these diseases is predicted to grow further in the coming years. Currently, few effective disease modifying pharmacological therapies are available for these disorders, and indeed the commonly available therapies mainly focus on ameliorating symptoms [4]. The absence of effective drugs

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Role of advanced glycation end products in cellular signaling ☆

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ABSTRACT

Improvements in health care and lifestyle have led to an elevated lifespan and increased focus on age-associated diseases, such as neurodegeneration, cardiovascular disease, frailty and arteriosclerosis. In all these chronic diseases protein, lipid or nucleic acid modifications are involved, including cross-linked and non-degradable aggregates, such as advanced glycation end products (AGEs). Formation of endogenous or uptake of dietary AGEs can lead to further protein modifications and activation of several inflammatory signaling pathways. This review will give an overview of the most prominent AGE-mediated signaling cascades, AGE receptor interactions, prevention of AGE formation and the impact of AGEs during pathophysiological processes.