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Association of Initial and Longitudinal Changes in C-reactive Protein With the Risk of Cardiovascular Disease, Cancer, and Mortality

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Abstract

Objective: To evaluate the value of serial C-reactive protein (CRP) measurements in predicting the risk of cardiovascular disease (CVD), cancer, and mortality.

Methods: The analysis was performed using data from two prospective, population-based observational cohorts: the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study and the Framingham Heart Study (FHS). A total of 9253 participants had CRP measurements available at two examinations (PREVEND: 1997-1998 and 2001-2002; FHS Offspring cohort: 1995-1998 and 1998-2001). All CRP measurements were natural log-transformed before analyses. Cardiovascular disease included fatal and nonfatal cardiovascular, cerebrovascular and peripheral vascular events, and heart failure. Cancer included all malignancies except nonmelanoma skin cancers.

Results: The mean age of the study population at baseline was 52.4±12.1 years and 51.2% (n=4733) were women. Advanced age, female sex, smoking, body mass index, and total cholesterol were associated with greater increases in CRP levels over time ($P_{all}<.001$ in the multivariable model). Baseline CRP, as well as increase in CRP over time (ΔCRP), were associated with incident CVD (hazard ratio [HR]: 1.29 per 1-SD increase; 95% confidence interval [CI]: 1.29 to 1.47, and HR per 1-SD increase: 1.19; 95% CI: 1.09 to 1.29 respectively). Similar findings were observed for incident cancer (baseline CRP, HR: 1.17; 95% CI: 1.09 to 1.26; ΔCRP, HR: 1.08; 95% CI: 1.01 to 1.15) and mortality (baseline CRP, HR: 1.29; 95% CI: 1.21 to 1.37; ΔCRP, HR: 1.10; 95% CI: 1.05 to 1.16).

Conclusion: Initial as well as subsequent increases in CRP levels predict future CVD, cancer, and mortality in the general population.

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Cardiovascular disease (CVD) and cancer are the two major causes of addressing the "common soil" hypothesis indicate that besides aging and male sex,

TABLE 2. Correlates of Longitudinal Change in C-reactive Protein Levels

	Age, sex, baseline CRP adjusted		Multivariable adjusted	
	Sβ	*P*	Sβ	*P*
Age, y	0.107 (0.010)	<.001	0.093 (0.010)	<.001
Female sex	0.053 (0.019)	.004	0.079 (0.019)	<.001
Smoking	0.110 (0.021)	<.001	0.147 (0.021)	<.001
Body-mass index, kg/m^2	0.145 (0.010)	<.001	0.151 (0.010)	<.001
Total cholesterol, mmol/L	0.062 (0.010)	<.001	0.047 (0.010)	<.001
Antilipid medication	-0.022 (0.035)	.53	—	—
Glucose, mmol/L	-0.001 (0.011)	.95	—	—
Antidiabetic medication	-0.079 (0.060)	.19	—	—
Systolic blood pressure, mm Hg	0.046 (0.011)	<.001	—	—
Antihypertensive medication	0.062 (0.026)	.02	—	—
Prevalent cancer	0.008 (0.047)	.86	—	—
Prevalent cardiovascular disease	0.028 (0.041)	.50	—	—

Multivariable model included age, sex, and baseline C-reactive protein (CRP) levels along with variables with $P<.1$ in the age, sex, and baseline CRP-adjusted model. Stepwise selection was then performed, yielding the final model where all variables had a $P<.05$. Results are displayed as standardized β coefficient (Sβ), which represents the SD change in dependent variable for 1 SD change in the independent (continuous) variable or for 1 unit change in the independent (categorical) variable.

Atherosclerosis and arteriosclerosis

Tomoaki Murakami[1]

Keywords Aging · Arterial stiffness · Child · Dyslipidemia · Glucose intolerance

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Dyslipidemia is an important problem, even in children, because of the risk of future cardiovascular disease. However, evaluating the influence of dyslipidemia on vessels is difficult. In children, the short exposure time to various risk factors is challenging. Cruz's paper nicely demonstrates the clinical problems of dyslipidemia in children [1]. In this paper, the authors evaluated the carotid-femoral pulse wave velocity (cfPWV), one of the standard tools for evaluating arterial stiffness. The term arterial stiffness usually means arteriosclerosis; however, it can be sometimes used for atherosclerosis. They are different conditions but can overlap and are frequently confused.

Atherosclerosis is the result of a pathological process that starts with a local lesion in the intima of middle to large arteries. Lipid is then deposited in the intima, causing inflammation. Atherosclerosis results in occlusive disease. For example, atherosclerosis of the coronary artery causes coronary artery stenosis, which can induce angina. Rupture of the coronary atheroma plaque leads to myocardial infarction.

Arteriosclerosis is more of an aging process. One of the important features of arteriosclerosis is the increase in the stiffness of elastic arteries, including the aorta. The pathological characteristics of arteriosclerosis include elastin fracture, an increase in collagen fibers, and calcium deposition. In contrast to atherosclerosis, one of the morphological features of arteriosclerosis is dilation. It is well-known that the aorta gradually dilates with age. Elastin fracture depends on strain and the number of cardiac cycles experienced, hence, the strong impact of age on elastin fracture. Practically, Ohmori et al. reported no significant

et al. reported a close relationship between blood sugar level and baPWV [11].

It has been suggested that there is a nonenzymatic reaction between blood sugar and collagen in the arterial wall. The formation of advanced glycation endproducts on the vascular wall causes crosslinking of collagen molecules, thereby increasing arterial stiffness. The high glucose concentration and chronic exposure promote the glycation. Therefore, besides blood sugar and hemoglobin A1c levels, triglyceride levels can also be determinants of PWV, although some papers have reported no significant association [12].

Regarding the influence of therapeutic interventions for dyslipidemia on arterial stiffness, it was reported that treatment with statins was associated with a reduced PWV [13, 14]. However, the reduction was not necessarily caused by the change in lipid profile [13]. The effect may be one of the so-called pleiotropic effects of statins.

The relationship between dyslipidemia, which can cause atherosclerosis, and arterial stiffness is complicated, especially in the elderly [15] (Fig. 1). Arteriosclerosis and atherosclerosis are just concepts, and both conditions are common and frequently coincide in aged people. High blood pressure accelerates PWV, which is one of the most used biomarkers for arteriosclerosis, and wide pulse pressure, which is one of the features of arteriosclerosis, accelerates atherosclerosis. The relationship probably involves glucose metabolism, and time may also play a large role. Data regarding atherosclerosis, arteriosclerosis, dyslipidemia, and glucose intolerance in children can play an important role in elucidating the relationship of these factors. I hope that research into vascular biology, especially in the young, will continue to progress.

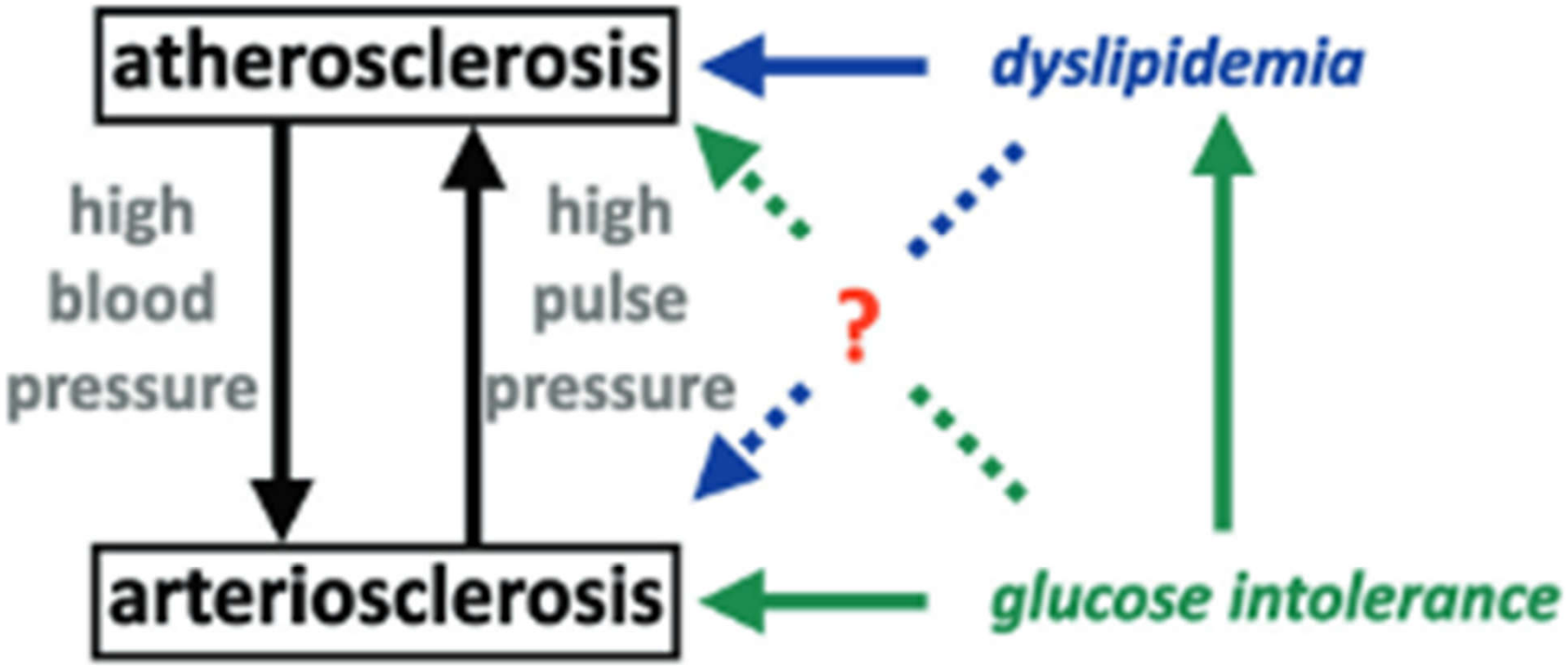

Fig. 1 Relationship between atherosclerosis and arteriosclerosis

et al. reported a close relationship between blood sugar level

NEWS RELEASE 20-APR-2023

Sugar rush: scientists discover key role of glucose in brain activity

New details on how healthy neurons metabolize glucose have implications for understanding neurodegenerative diseases

SAN FRANCISCO, CA—April 18, 2023—The human brain has a sweet tooth, burning through nearly one quarter of the body's sugar energy, or glucose, each day. Now, researchers at Gladstone Institutes and UC San Francisco (UCSF) have shed new light on exactly how neurons—the cells that send electrical signals through the brain—consume and metabolize glucose, as well as how these cells adapt to glucose shortages.

IMAGE: SCIENTISTS FROM GLADSTONE AND UCSF HAVE SHED LIGHT ON EXACTLY HOW NEURONS CONSUME AND METABOLIZE GLUCOSE, WHICH COULD HAVE IMPLICATIONS FOR UNDERSTANDING NEURODEGENERATIVE DISEASES. SEEN HERE ARE KEN NAKAMURA (LEFT), YOSHI SEI (CENTER), AND MYRIAM CHAUMEIL (RIGHT). view more ›

CREDIT: PHOTO: MICHAEL SHORT/GLADSTONE INSTITUTES

Previously, scientists had suspected that much of the glucose used by the brain was metabolized by other brain cells called glia, which support the activity of neurons.

"We already knew that the brain requires a lot of glucose, but it had been unclear how much neurons themselves rely on glucose and what methods they use to break the sugar down," says Ken Nakamura, MD, PhD, associate investigator at Gladstone and senior author of the new study published in the journal *Cell Reports*. "Now, we have a much better understanding of the basic fuel that makes neurons run."

Past studies have established that the brain's uptake of glucose is decreased in the early stages of neurodegenerative diseases like Alzheimer's and Parkinson's. The new findings could lead to the discovery of new therapeutic approaches for those diseases and contribute to a better understanding of how to keep the brain healthy as it ages.

Simple Sugar

Many foods we eat are broken down into glucose, which is stored in the liver and muscles, shuttled throughout the body, and metabolized by cells to power the chemical reactions that keep us alive.

Scientists have long debated what happens to glucose in the brain, and many have suggested that neurons themselves don't metabolize the sugar. They instead proposed that glial cells consume most of the glucose and then fuel neurons indirectly by passing them a metabolic

Nakamura's group next turned to mice to study the importance of neuronal glucose metabolism in living animals. They engineered the animals' neurons— but not other brain cell types—to lack the proteins required for glucose import and glycolysis. As a result, the mice developed severe learning and memory problems as they aged.

This suggests that neurons are not only capable of metabolizing glucose, but also rely on glycolysis for normal functioning, Nakamura explains.

"Interestingly, some of the deficits we saw in mice with impaired glycolysis varied between males and females," he adds. "More research is needed to understand exactly why that is."

Myriam M. Chaumeil, PhD, associate professor at UCSF and co-corresponding author of the new work, has been developing specialized neuroimaging approaches, based on a new technology called hyperpolarized carbon-13, that reveal the levels of certain molecular products. Her group's imaging showed how the metabolism of the mice's brains changed when glycolysis was blocked in neurons.

"Such neuroimaging methods provide unprecedented information on brain metabolism," says Chaumeil. "The promise of metabolic imaging to inform fundamental biology and improve clinical care is immense; a lot remains to be explored."

The imaging results helped prove that neurons metabolize glucose through glycolysis in living animals. They also showed the potential of Chaumeil's imaging approach for studying how glucose metabolism changes in humans with diseases like Alzheimer's and Parkinson's.

Finally, Nakamura and his collaborators probed how neurons adapt when they are not able to get energy through glycolysis—as might be the case in certain brain diseases.

It turned out neurons use other energy sources, such as the related sugar molecule galactose. However, the researchers found that galactose was not as efficient a source of energy as glucose and that it could not fully compensate for the loss of glucose metabolism.

"The studies we have carried out set the stage for better understanding how glucose metabolism changes and contributes to disease," says Nakamura.

His lab is planning future studies on how neuronal glucose metabolism changes with neurodegenerative diseases in collaboration with Chaumeil's team, and how energy-based therapies could target the brain to boost neuronal function.

editorials

Immunotherapy in Localized Microsatellite Instability–High/Mismatch Repair Deficient Solid Tumors: Are We Ready for a New Standard of Care?

Kristen K. Ciombor, MD, MSCI[1] and Cathy Eng, MD[1]

as yet uncertain long-term outcome.

In addition to longer follow-up and results that are pending from ongoing studies, translational efforts will be key to personalizing an immunotherapy approach for patients with dMMR/MSI-H solid tumors. Ludford et al[20] provided select examples in an exploratory analysis of immune profiling in their study—namely that more CD15+ granulocytic cells within the tumor microenvironment with proximity to cytotoxic CD8+ T cells, as well as T-cell exhaustion, may predict for lack of (or loss of) treatment response. Results from

Will neoadjuvant immunotherapy become the new standard of care for patients with localized dMMR/MSI-H solid tumors? Only more time will tell—but the collection of additional data from well-designed, prospective, multicenter studies will be essential to help answer these critical questions and guide our best treatment of patients with tumors that harbor this unique genomic signature.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

AuntMinnie.com

ARRS: What's the state of LDCT lung cancer screening today?

By Kate Madden Yee, AuntMinnie.com staff writer

April 21, 2023 -- Low-dose CT (LDCT) for lung cancer screening has been shown to be effective in reducing mortality rates. But despite a recent broadening of the eligibility pool, uptake of this preventive service has been low, according to a presentation at the American Roentgen Ray Society (ARRS) meeting in Honolulu.

Lung cancer is the number one cause of death in men and women in the U.S., but only a small percentage of eligible individuals are undergoing screening, said presenter Dr. Debra Dyer of National Jewish Health in Denver, CO.

"Only about 5.8% of individuals eligible for lung cancer screening are receiving it," she said. "Some states are doing better than that, some not so much."

Dyer began her talk with some sobering statistics:

- In 2021, there were almost 236,000 new cases and almost 132,000 deaths -- "more than breast, colon, and prostate cancer combined," she said

Number of stage 1A and stage IV lung cancers detected with and without LDCT screening

Stage	National Lung Cancer Screening Trial	NELSON trial
1A		
Screen detected	52%	47%
Non-screen detected	23%	7%
IV		
Screen detected	13%	6%
Non-screen detected	36%	52%

(Data from a study conducted by a team led by Dr. Jacob Sands of Dana Farber Institute in Boston and published in the Journal of