# Reducing age-related vascular dysfunction

Cardiovascular diseases (CVD) remain the leading cause of death, with ageing being the primary risk factor due in part to age-related changes within arteries that contribute to vascular dysfunction. **Dr Amy L Sindler**, Assistant Professor of Health and Human Physiology at the University of Iowa, is investigating how ageing and other age-related disorders worsen vascular function. In addition, her laboratory is interested in how pharmacological interventions and/or exercise training may be useful in combatting CVD risk in older individuals.

Ageing is the primary risk factor of cardiovascular diseases (CVD) with nearly 90% of all CVD occurring in individuals over the age of 40. Complicating this burden is the fact that the global population of older individuals (aged 65 years and over) is expected to double by 2050. Ageing causes multiple changes to arteries that increase the risk of CVD, and two key contributors are stiffening of the large elastic arteries (aorta and carotids) and the development of vascular endothelial dysfunction due to loss of the vascular protective molecule nitric oxide (NO). To make matters even worse, other common age-associated disorders such as obesity, type II diabetes and chronic kidney disease (CKD) affect millions of people worldwide. As well as being debilitating in their own right, these disorders also contribute to the progression of vascular dysfunction and increase the risk of dying of CVD. For example, between just one and two percent of individuals with kidney disease actually die of renal failure – instead, they die of CVD. Arterial stiffness and endothelial dysfunction are thought to be primarily to blame.

Dr Sindler's group investigates the underlying mechanisms which contribute to vascular dysfunction, as well as testing natural compounds for their capacity to reduce or reverse the CVD risk. Using preclinical models of ageing, kidney disease, and obesity, the group are able to probe how these factors affect vascular dysfunction using both *in vivo* (whole animal) and *in vitro* (isolated tissue) techniques. Dr Sindler's work has the potential to change clinical practice by identifying the therapeutic potential of natural compounds to treat vascular dysfunction in individuals who have multiple co-morbidities (multiple conditions at the same time) such as ageing, CKD, obesity and type II diabetes.

**Common age-related disorders such as kidney disease, type II diabetes and obesity affect millions of people worldwide. These diseases are debilitating in their own right. However, most people with other age-related pathologies will die of CVD**

## MAKING THE MOLECULES AVAILABLE

Recent work by the group has identified how improving the bioavailability of important signalling molecules such as the vascular protective molecule nitric oxide (NO) can improve vascular function. NO is a powerful vasodilator (blood vessel dilator), with a short half-life of only a few seconds in the blood, that is produced by the vascular endothelium (monolayer of endothelial cells lining the blood vessels). If NO is in short supply, the blood vessels are not able to respond appropriately, an effect which is known to contribute to vascular dysfunction.

Dr Sindler's group, including colleagues at the University of Colorado Boulder, have shown that by providing precursors such as sodium nitrite in the form of dietary supplements, they can restore physiological responses to control levels and improve vascular (blood vessel) health in mouse models of ageing and diabetes. Importantly, the other metabolic markers were unaffected, demonstrating that the effects on the vasculature were independent of metabolic aspects of the disease and tying the results to increased availability of NO in the blood vessels.

Taking this one step further, they showed that this effect is also seen in older adult humans. Sodium nitrite supplementation was well tolerated and increased available NO without altering blood pressure, an important consideration in the treatment of CVD.

The mechanisms responsible for these beneficial effects are still not well understood, but are actively being studied by many scientists and may relate to multiple metabolic or cellular pathways. The group have therefore been identifying other disorders where nitrite

**Determining novel pathways by which age and age-related diseases contribute to vascular dysfunction is key to developing natural therapeutic strategies that can lower the risk of CVD and have the potential to improve the quality of life in older individuals**

supplementation may be effective in treating vascular dysfunction and reducing overall CVD risk, as well as continuing their work investigating the underlying molecular pathways involved using preclinical models of ageing and disease.

**DAMAGE HERE, DAMAGE THERE**

One example of this is the close link between kidney disease and vascular dysfunction. Acute kidney damage can result in the initiation and progression of the decline in kidney and vascular function. These changes contribute to the increased risk of CVD, though the association is poorly understood. Similarly, even when managed appropriately, other risk factors such as obesity and type II diabetes can cause artery and kidney damage, which are also associated with increased risk of CVD.

The stiffening of the aorta plays a key role in disease progression and is a predictor of future CVD events and death. Dr Sindler believes this is due to oxidative stress which reduces NO and also modifies structural proteins in arteries making them stiffer and less compliant. One new and exciting area currently being studied by Dr Sindler's lab is whether increased oxidative stress may be caused by impaired nicotinamide adenine dinucleotide (NAD) and sirtuin function, which are NAD dependent enzymes that have anti-ageing properties. Dr Sindler's lab is very interested in understanding the role of SIRT3 (one of the sirtuin proteins that are found in mitochondria and regulate metabolism and mitochondrial-derived oxidative stress). Normal biological processes create reactive oxygen species (ROS, highly reactive molecules), which have the potential to damage cells in a number of ways. For this reason, cells contain a range of protective measures which either attempt to 'mop up' the ROS or repair the damage they produce. This is one protective function of NAD and SIRT3; if these are not functioning correctly, the cells will sustain significant damage, leading to detrimental changes in arteries.

**SENDING IN THE SUPPLIES**

Dr Sindler aims to counteract the deficits in NAD by providing supplements of a B3 vitamin precursor called nicotinamide riboside (NR). This was identified as a bacterial growth promoter as early as 1944, but only identified as a precursor of NAD in 2004, in her collaborator Dr Charles Brenner's lab, and as a sirtuin activating compound in 2007. It is hoped that NR will increase the bioavailability of NAD and consequently improve SIRT3 activity, thus reducing ROS, oxidative stress and improving the bioavailability of NO. The net effect has the potential to reduce the subsequent vascular and renal complications contributing to the overall CVD risk.

In order to achieve this her group must first elucidate the mechanisms by which ageing and other age-related disorders contribute to physiological dysfunction. This will then help to determine how reduced NAD availability mediates vascular and renal dysfunction. Once this is better understood, the therapeutic potential of NR in this field will be determined more fully.

**A RICH HISTORY, A BRIGHT FUTURE**

A similar study with colleagues at the University of Colorado Boulder and Washington University School of Medicine in St Louis tested a related compound that increases NAD levels which was able to reverse age-related arterial dysfunction by decreasing oxidative stress.

Dr Sindler's current studies will continue to examine the implications of improving NO and NAD bioavailability on vascular and renal function in individuals who are at the highest risk. Understanding the pathways by which ageing and age-related co-morbidities contribute to increased risk of CVD and death, particularly in older individuals, is a vital step in developing therapeutic strategies which have the potential to save lives and improve overall human health. With such past success in testing novel mechanisms to treating these disorders with natural interventions, such as supplements and/or exercise, and understanding the body's own processes and systems to reverse the damage, Dr Sindler is ideally placed to complete this work.

## Q&A

***Why is age-related cardiovascular disease (CVD) of such concern at the moment?***

CVD is the leading cause of death. Ageing is the primary risk factor contributing to increased CVD and nearly 90% of all CVD occurs in middle-aged and older adults. By 2050 the number of older individuals (65 years and older) is expected to double, further contributing to this massive biomedical and economical burden.

***How do other diseases contribute to the progression of CVD?***

In additional to the traditional risk factors that are associated with CVD, such as advancing age, male sex, high blood pressure, smoking, sedentary lifestyle, and dyslipidaemia (high cholesterol, triglycerides), individuals with other disease pathologies have additional risk factors to consider. These include, but are not limited to, oxidative stress, inflammation, endothelial dysfunction, vascular calcification, insulin resistance, anaemia, adipokine imbalance, and epigenetic modification. Very few treatment options exist to lower CVD risk in individuals with multiple co-morbidities.

***What successes have you had so far in addressing these issues?***

Previous work mostly focused on the healthy ageing process and attempting to slow down the arterial ageing by increasing physical activity, replenishing the vascular protective molecule NO with inorganic nitrate/nitrite supplementation or other novel strategies that reduce oxidative stress and chronic low-grade inflammation. We know that exercise is one of the best ways to reduce and/or prevent age-related impairments in vascular function and reduce overall CVD risk.

***What is the next stage in your investigations of age and disease-related CVD?***

Investigating novel pathways that become altered and contribute to arterial ageing which can be slowed down and/or prevented with naturally occurring therapeutic compounds. Our overall goal is to translate our findings into clinical trials determining the efficacy on improving CV health and quality of life of people at the highest risk.

***What, if anything, can individuals do to reduce their risk of developing CVD?***

Exercise; eat more healthy, whole food; maintain a healthy weight; minimise processed foods, salt, a sedentary lifestyle and excess stress.

**Ageing is the primary risk factor contributing to increased CVD**

## Detail

**RESEARCH OBJECTIVES**

Dr Sindler investigates how ageing and other age-related disorders such as kidney disease, diabetes, and obesity worsen cardiovascular (endothelial function and arterial stiffness) and renal function.

**FUNDING**

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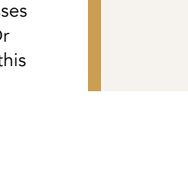
**COLLABORATORS**

Drs Diana Zepeda-Orozco, Darren Casey, Marie Migaud, Charles Brenner, and Melissa Bates



**BIO**

Dr Amy Sindler completed a BS and MS in Exercise Physiology and PhD in Cellular and Integrative Physiology with Dr Judy Muller-Delp at West Virginia University. She completed post-doctoral training at the University of Colorado Boulder with Dr Douglas Seals. She is currently an Assistant Professor in the Department of Health and Human Physiology at the University of Iowa. Dr Sindler's laboratory aims to provide new insight into novel pathways involved in vascular dysfunction, including the role of impaired nitric oxide (NO) and/or nicotinamide adenine dinucleotide (NAD) bioavailability with ageing, kidney disease, and obesity.

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