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New theory of diabetic complications' origin suggests need for new therapeutic approach

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Use of anti-oxidants may be ineffective or even contribute to kidney disease and other complications of diabetes, rather than helping to treat such health problems. That conclusion, based on growing unexpected findings that stimulating mitochondrial function and superoxide production results in improved markers of renal, cardiovascular and nerve dysfunction, was presented this week in a "State-of-the-Art Lecture" at the 74th Scientific Sessions of the American Diabetes Association.

"Scientists have long hypothesized that oxidative stress underlies diabetic complications and is driven by mitochondrial superoxide production and subsequent free radical damage to proteins and DNA," said Kumar Sharma, M.D., F.A.H.A, U.C. San Diego professor, Director of the Center for Renal Translational Medicine, Division of Nephrology-Hypertension and the Institute of Metabolomic Medicine, and ClinMet scientific founder. "However, clinical trials to date have failed to demonstrate a benefit for anti-oxidant approaches and in some cases, such anti-oxidants have even increased mortality.

"Data from multiple independent investigations, including clinical metabolomics studies, now suggest that in response to excess calories, mitochondrial activity is actually reduced in target tissues for diabetes complications, and such persistent reduction may lead to the release of pro-inflammatory and pro-fibrotic cytokines and subsequent organ dysfunction. Moreover, approaches that restore mitochondrial function and mitochondrial superoxide production via exercise, caloric restriction

and medications should help promote tissue healing."

Dr. Sharma said that new research measuring real-time superoxide production demonstrated that stimulating such production was linked to improvement in diabetic kidney disease. Additionally he noted that in independent studies in humans, pretreatment of subjects with anti-oxidants (vitamin C and vitamin E) prior to exercise led to a loss in exercise's protective benefits for insulin resistance.

"The new insights relating to the benefits of mitochondrial superoxide production, termed 'mitochondrial hormesis,' has raised many new exciting questions on the mechanisms linking mitochondrial superoxide production to beneficial effects," Dr. Sharma said. "One potential link is that mitochondrial superoxide stimulates the master energy sensor AMPK, which when activated can suppress inflammation and fibrosis. The new theory is also a major boost for drugs that target and support mitochondrial function as potential treatments for diabetic complications and perhaps many other chronic diseases."

Provided by ClinMet

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