European Association of Urology - Press release

Researchers discover experimental obesity drug prevents development of kidney stones

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Copenhagen: Scientists have found that a drug connected with fat regulation prevents the formation of kidney stones in mice. This early work opens the possibility of developing drugs which may help prevent kidney stones in at-risk individuals. The work is presented at the European Association of Urology Conference in Copenhagen.

Passing a kidney stone in the urine can be extremely painful – it has been described as possibly the worst pain which someone can experience. The developed world is experiencing something of an epidemic of kidney stones. The EAU estimates that around 50 to 60million Europeans suffer from stones – that's roughly one European in 11, and is equivalent to the population of a large European country, such as the UK, France or Italy. The USA has a similar number of sufferers. Stone incidence has almost doubled over the last 20 years[1]. Doctors think that this increase is due to increasing obesity, and diet and lifestyle changes.

Now a group of Japanese scientists have discovered that an experimental drug leads to a significantly reduced number of kidney stones in mice. They gave 20 mice 1mg/kg of the β3- agonist CL316243 for 12 days. Then the mice, plus 20 controls, were then injected with glyoxylate, which causes the formation of kidney stones. At various time points, the mice were then checked to see if they had formed stones: the formation of stones decreased to 17.0% in the experimental group, compared with the controls.

"This is experimental work for now" said lead researcher Dr Teruaki Sugino (Nagoya City University Graduate School of Medical Sciences, Japan). *"But I believe that this may open the way to the development of the new drugs which can stop the development of kidney stones in at-risk people. So far we have only tested this on mice, but in mice it seems to work.*

We were able to analyse the biochemical differences between the control and experimental group, and discovered that the β3-agonist reduced the expression of adipocytokine molecules, which are associated with inflammation."

The researchers believe that free fatty acids cause inflammation and cytotoxic effects in kidneys, which promotes stones. β3-agonists are known to cause *white* fat cells (which are found in excess in overweight and obese persons) into *beige* fat cells, which burn extra calories, which is why these molecules are also being considered for anti-obesity uses. The researchers suspect that beige cells consume free fatty acids, which may be the cause of inflammation in the kidneys leading to kidney stones. This means that β3-agonists have the potential to prevent not only obesity but also kidney stones.

Commenting, Professor Thomas Knoll (Universität Tübingen, Germany) said:

"Renal stones affect many people, and have a high economic impact, so it's a pity that we still have an only rudimentary understanding on why stones form. Metabolic factors definitely play an important role and this work, contributes to unravelling the pathogenesis. We've had decades of urine crystallization studies, which have not really advanced the field. I hope that this work leads to more researchers doing work on the topic."

Professor Knoll was not involved in this work, this is an independent comment.

Currently, potassium-sodium citrate drugs are used to restrict the development of kidney stones, but some people can't use these drugs because they need to limit their potassium or sodium intake.

The authors note the limitations of the study. It is animal work, so cannot yet be directly applied to humans. The molecule has not been tested for tolerability, efficacy, or cost. It is also an initial 'proof-of-concept' study, so needs to be repeated with a larger sample size.

1. Selected kidney stone prevalence information: **Prevalence of Kidney Stones in the United States** Charles D. Scales, Jr.,[a,] Eur Urol. 2012 Jul; 62(1): 160–165. See also https://www.ndm.ox.ac.uk/osg/epidemiology for England data.

Note also EAU Patient info: http://patients.uroweb.org/i-am-a-urology-patient/kidney-ureteral-stones/

There was no external funding for this research

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Notes for editors

PLEASE MENTION THE EUROPEAN ASSOCIATION OF UROLOGY CONGRESS IN ANY STORY RESULTING FROM THIS PRESS RELEASE

The 33rd European Association of Urology conference takes place in Copenhagen from 16th to 20th March. This is the largest and most important urology congress in Europe, with up to 14,000 expected to attend. Conference website http://eau18.uroweb.org/

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Abstract 319: β3-adrenergic receptor agonist prevents kidney stone formation by suppressing inflammatory adipocytokine expression and improving antioxidant action EAU18 16-03-2018

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Session: Poster Session 24 Leave no stone unturned - research on stone formation

Location: Saturday, 17 March 2018, 16:00 - 17:30, Green Area, Room 1 (Level 0)

Introduction & Objectives
Our recent studies have revealed that adipocytokine secreted by adipocytes are important for the formation of kidney stones. β3-adrenergic receptor agonist is reported to suppress inflammatory adipocytokine expression. In this study, we investigated the effect of β3-agonist on kidney stone formation.

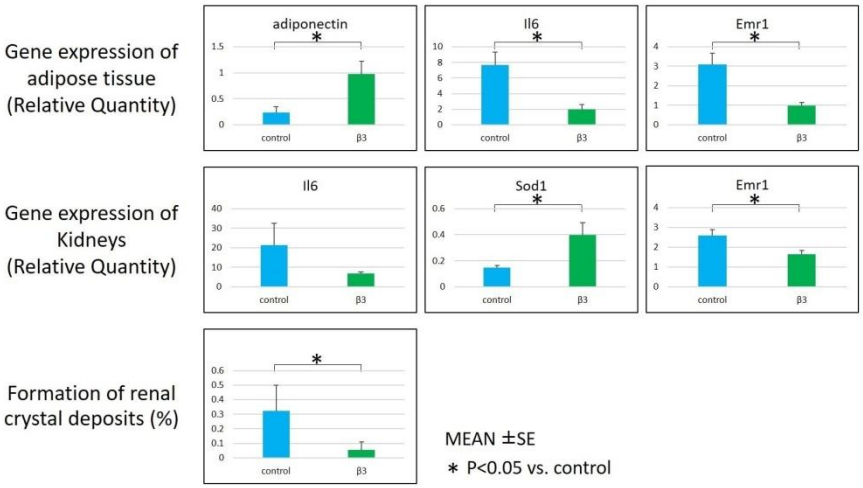
Materials & Methods

Mice were administered daily intra-abdominal injection of saline (control group) or 1.0 mg/kg β3- agonist CL316243 (β3 group) for 12 days. From days 6 to 12, we induced renal crystal deposits by daily intra-abdominal injection of 80 mg/kg glyoxylate. Adipose tissue and kidneys were extracted at days 0, 6, and 12, then evaluated their morphology as well as histology. Total RNA of these tissue were isolated and reverse-transcribed into double-stranded cDNA. Then, the expression of adipocytokine, and stone-related genes was assessed using quantitative real-time polymerase chain reaction (PCR). 24 hour urine was also collected and examined its biochemical parameters at days 0, 6, and 12. The formation of renal crystal deposits was observed using polarized light microscopy, and percentages of the depots as the total tissue area of the renal cross-section were expressed using the Image Pro software.

Results

There were no significant differences in the urine biochemistry between the two groups. In the adipose tissue, the expression levels of adiponectin in the β3 group increased by 4.2-fold compared with those in the control group at day 12 ($p = 0.01$). The expression levels of Il6 and Emr1 decreased by 0.3-fold and 0.2-fold ($p = 0.03$, $p = 0.01$). In the kidneys, the expression levels of Ccl2, Tnfα, and Il6 decreased by 0.2-fold, 0.6-fold and 0.3-fold ($p = 0.16$, $p = 0.19$, and $p = 0.18$). The expression levels of Sod1 increased by 2.3-fold ($p = 0.04$), and Emr1 decreased by 0.4-fold ($p = 0.04$). The formation of renal crystal deposits decreased to 17% in the β3 group ($p = 0.03$).

Figure 1 : Gene expression and Formation of renal crystal deposits (%)



Conclusions

Our results showed that β3-agonist reduced pro-inflammatory adipocytokine expression and improved antioxidant action, which resulted in prevention for renal crystal formation. This is the first report on the therapeutic role of β3-adrenergic receptor agonist for kidney stone formation.