Press Release

Keio University

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Keio University School of Medicine

Crocetin May Have Suppressive Effect on Myopia Progression in Children
－A New Approach as Prevalence of Myopia Increases－

In a joint research study with Osaka University and Rohto Pharmaceutical Co., Ltd., a research team at the Keio University School of Medicine has confirmed that crocetin[1] can significantly suppress myopia by slowing axial length (AL) [2] elongation in children. The study was a multicenter, randomized, double-blind, placebo-controlled clinical trial where 69 elementary school students were treated with crocetin, a natural carotenoid derived from gardenia. The Keio University team included Professor Kazuo Tsubota, Project Associate Professor Toshihide Kurihara, Instructor Hidemasa Torii, and Instructor Kiwako Mori of the Department of Ophthalmology. The Osaka University team included Professor Kohji Nishida, Endowed Associate Professor Shizuka Koh, and fourth-year doctoral candidate Satoko Fujimoto of the Department of Ophthalmology, Graduate School of Medicine.

These new findings show that crocetin can inhibit myopia progression in humans and follow previous studies that showed the same effect in mice. The study confirmed the treatment's effectiveness when used during childhood, the time when AL increases the most. This shows that the administration of crocetin can prevent childhood myopia, which could greatly reduce the number of cases that progress to high myopia in the future.

The results of this study were published on August 7 in the multidisciplinary online journal *Journal of Clinical Medicine*.

1. Research Background

In recent years, the prevalence of myopia has increased worldwide, and one-third of the global population is said to be myopic (Holden BA et al. *Ophthalmology*. 2016). Myopia is particularly prevalent in Asian countries. In China, more than 90% of adults are reported to be myopic, making it the country's second leading cause of blindness.

Myopia is also on the rise in Japan and the prevalence of high myopia, a severe level of nearsightedness, is estimated to be around five percent for those 40 years of age and older. When myopia progresses to high myopia, there is a dramatic increase in the risk of pathological myopia, which can lead to blindness. Pathological myopia was reported to be the fourth leading cause of blindness in a national survey conducted in 2005 by the Ministry of Health, Labor and Welfare's Research Committee on Chorioretinal Degenerations and Optic Atrophy.

These reports show that myopia is not just an inconvenience for individuals but a serious social problem that can lead to visual impairment, which is why there is a need for new approaches that can prevent high myopia, and in particular childhood myopia, when progression most easily occurs.

2. Research Significance and Future Development

The main cause of myopia is thought to be the elongation of the eye (axial length: AL), which renders it unable to focus images on the retina. According to an earlier study by this team, the natural carotenoid crocetin, which is derived from gardenia, has an ability to increase the expression of EGR-1[3], one of the genes proven to suppress myopia progression in mice. Further, they have proven, for the first time in the world, that when crocetin is administered to a myopia-induced mouse model, axial elongation and refractive shift are significantly suppressed (Mori K et al. *Scientific Reports*. 2019). See 4. Related Press Release below.

In the human eye, growth of the AL normally ceases with physical growth around puberty, with excessive increase in AL leading to the progression of myopia. The research group studied the effects of crocetin on myopia progression in children between the ages of 6 and 12, a time when myopia can easily progress.

This study was a double-blind, placebo-controlled clinical trial, where 69 children with mild myopia who obtained guardian consent to participate were randomly divided into a crocetin group and a placebo group and observed for 24 weeks to compare changes in refractive power and AL (see Fig. 1).

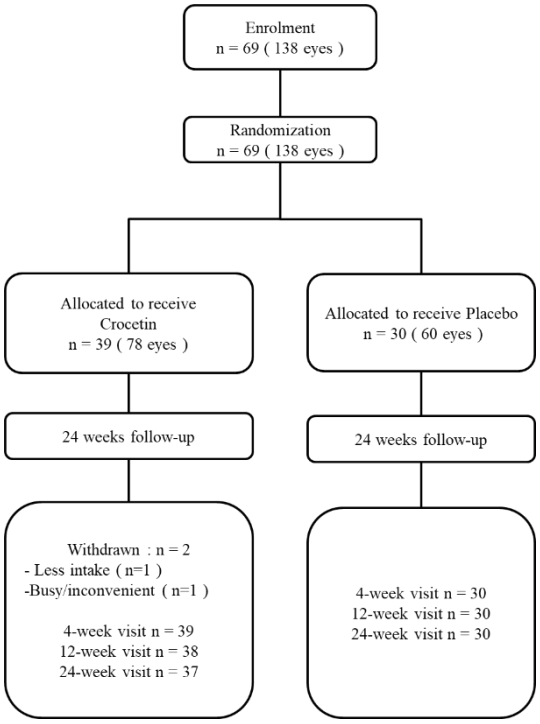

Fig. 1: The 69 participants were divided into a crocetin group and a placebo group.

Both groups were administered one capsule daily, the crocetin group's capsule containing 7.5 mg of crocetin, while the placebo group's did not. After administration of crocetin, participants were evaluated for AL elongation after 4, 12, and 24 weeks, as well as changes in spherical equivalent refraction (SER)[4] after 4 and 24 weeks.

Results showed that, compared to the placebo group, myopic progression was significantly suppressed in the crocetin group ($P < 0.05$), with a 14% suppression of axial elongation and a 20% suppression of reduction in refractive power (see Fig. 2).

The research team also examined the effects of crocetin on the choroid[5]. It is known that in myopia-induced mouse models, when there is axial elongation and myopia increases, it is accompanied not only by a change in visual acuity (refraction), but also by thinning of the choroid that surrounds the retina (Mori K et al. *Scientific Reports*. 2019). See 4. Related Press Release below for details. For children in this study, choroidal thinning was observed in the placebo group, while such choroidal changes were significantly suppressed in the crocetin group ($P < 0.001$), indicating that this protective effect on the choroid may be one of the mechanisms by which crocetin suppresses myopia (see Fig. 3).

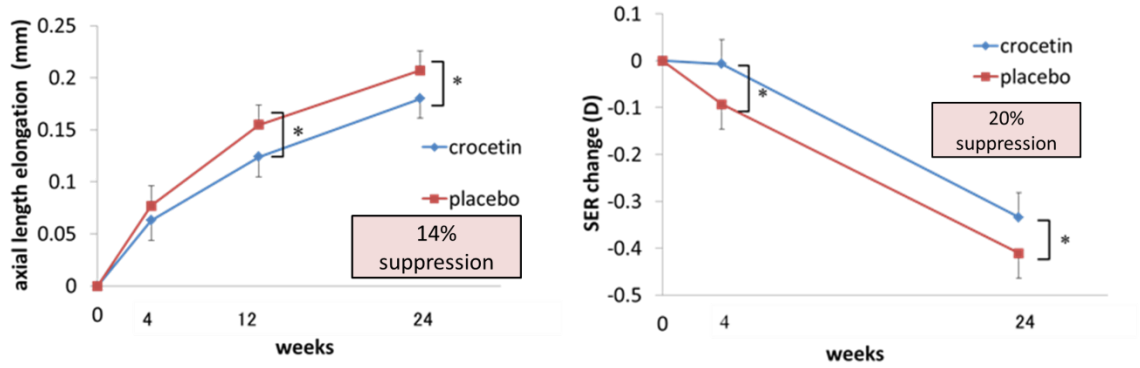

Fig. 2: After receiving either a placebo or crocetin, participants were evaluated for axial length (AL) elongation after 4, 12, and 24 weeks, as well as changes in spherical equivalent refraction (SER) after 4 and 24 weeks. (*p<0.05: statistically significant)

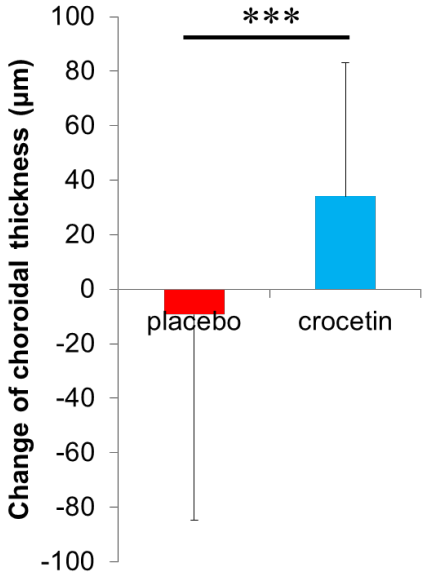

Fig. 3: Change in choroidal thickness. Choroidal thinning was observed in the placebo group, while the choroidal thickness significantly increased in the crocetin group. (***p<0.001: statistically significant)

These results confirm the effectiveness of crocetin on myopia suppression during childhood, the time when AL increases most. They also show that beyond the prevention of childhood myopia, crocetin may be able to play a significant role in reducing the number of cases that progress to high myopia in the future.

3. Research Paper

Tile: The Effect of Dietary Supplementation of Crocetin for Myopia Control in Children:
A Randomized Clinical Trial

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Publication: Journal of Clinical Medicine (online release)

4. Related Press Release (Japanese)
New Discovery May Lead to New Myopia Treatment as Prevalence Increases: Development of Myopia Prevention Using Crocetin Expected
https://www.keio.ac.jp/ja/press-releases/2019/1/23/28-50831/

[Glossary]

[1] Crocetin:
A natural yellow pigment found in gardenia and saffron, crocetin is a carotenoid with potent antioxidant activity. Crocetin has been shown to increase expression of EGR-1, one of the genes related to the suppression of myopia progression. Furthermore, it has also been shown to suppress two indicators of myopia, axial length (AL) elongation and change in refractive power, in the myopia disease mouse models (Mori K et al. *Scientific Reports*. 2019).

[2] Axial Length (AL):
The distance from the cornea to the retina. Myopia occurs when the axial length (AL) is too long to focus on the retina (and instead focus in front of the retina). The strength of myopia increases with AL. Excessive axial elongation during childhood is said to be strongly related to the progression of myopia.

[3] EGR-1:
A gene known to suppress myopia. Myopia was traditionally considered to be genetic, but in recent years it has been found that environmental factors such as lifestyle also play an important role in myopic progression. In particular, a number of research teams have reported that myopia progresses as outdoor activity shortens, and a previous study conducted at the Department of Ophthalmology, Keio University School of Medicine discovered that violet light (360–400 nm wavelength), which is abundant in the outdoor environment, can suppress myopia progression. It has been confirmed that when myopia models were exposed to this range in the visible light, axial length (AL) elongation was suppressed, and early growth response 1 (EGR-1), a gene known to suppress myopia, significantly increased (Torii H et al. *EBioMedicine*. 2017).

[4] Spherical Equivalent Refraction (SER):
The power of refraction. Light that enters the eye is refracted by the cornea and crystalline lens to form a focal point. The power of that refraction is called the spherical equivalent refraction. Refractive power is measured in optical units called diopters (D). Myopia occurs when the refraction of the cornea and crystalline lens is strong relative to the axial length (AL) focusing images in front of the retina. The greater the negative refractive power, the further myopia has progressed.

[5] Choroid:
The choroid is a layer of tissues that surround and nourish the retina. As myopia progresses and axial length (AL) increases, pathological changes such as decrease in choroidal thickness are known to occur.

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