RESEARCH GROUP: Optometry and Vision Science

Project Title: Myopia and Circadian Rhythm: Understanding myopic progression and intervention

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Level: PhD

Background to the project:
Myopia (short-sight) is a refractive error usually resulting from excessive ocular growth. Its prevalence is escalating: myopia is predicted to affect half the world’s population by 2050. In East Asia the majority of adults are already myopic and our research group recently demonstrated a doubling of prevalence of myopia in UK teenagers since 1960. This is of concern because myopic eyes are at increased risk of ocular pathology and visual impairment. Myopia is now considered a major (and growing) public health issue, associated with significant costs to both the individual and society.

Many factors contribute to the onset and progression of myopia; genetics, lifestyle and visual environment have all been shown to have significant roles. Manipulation of the latter two factors shows potential for reducing incidence and progression. The most promising interventions include increasing time spent outdoors and application of pharmacological agents such as the anti-cholinergic agent atropine sulphate or adenosine antagonist 7-methylxanthine. The mechanism(s) by which these environmental and pharmacological interventions influence refractive status are currently unclear, but both aim to control excessive eye growth. Disruption of retinal circadian rhythm (CR) has been proposed as a key element promoting dysregulation of eye growth and hence myopia. Recent reports support this hypothesis, including work from our research group which has identified, for the first time in humans, significant differences between circulating serum levels of melatonin (Mel) and dopamine (DA) in myopes and non-myopes. Both DA and Mel are intrinsically tied to CR and form a mutual inhibitory relationship whereby Mel negatively influences DA release in both neural and ocular tissue, including the retina. Both Mel and DA have been shown to influence eye growth in animal models of myopia. However, no previously published studies have examined the relationship between systemic/ocular CRs, Mel and myopia in humans. Neither have previous studies investigated the effect of atropine on human Mel expression or systemic/ocular CR. A better understanding of CR in myopic and non-myopic individuals at different stages during the development and progression of myopia is urgently needed to inform and accelerate the further development of effective and acceptable anti-myopia strategies.

Objectives of the research project:
The proposed research aims to:

1. Establish whether salivary measures of Mel are an appropriate surrogate for serum measures of Mel in future studies comparing refractive groups.
   Salivary Mel status has previously been shown to accurately reflect serum MEL levels. Study 1 will establish if it provides a sensitive enough measure to reveal differences in Mel status between refractive groups previously established using serum.
   HO: salivary measures of Mel do not differ between refractive groups.

2. Establish the relationship between myopia and ocular and systemic CRs at different stages during myopia development.
   Disruption of CR has been proposed as a driver promoting myopic eye growth. This study will investigate ocular and systemic CR in non-myopic and myopic groups at different stages of refractive development: (a)
stable adult myopes vs non-myopes, (b) actively progressing myopes during teenage years vs non-myopic peers and (c) pre-myopic young children at high risk of developing myopia vs young children at low risk for future myopia. Data from the NICER study has provided methods for identifying recruits to group (c). Ongoing NICER study work will identify potential recruits for groups (b) and (c). Group (a) will be recruited from staff/students. Ocular CR will be characterised through measures of retinal/choroidal thickness, melanopsin-derived pupil response and axial length and systemic CR characterised through measures of Mel, sleep pattern and quality.

H0: refractive error is not significantly associated with correlates of ocular or systemic CR at any stage of myopia development.

3. Investigate the effect of low dose atropine eye drops on ocular and systemic correlates of CR in adult participants.

Although low dose (0.01%) atropine is becoming an accepted treatment for myopic progression, it is presently unclear how it influences eye growth or its effect on ocular/systemic CR. Topical application of atropine has been shown to depress release of Mel in animal eyes⁹. This adult study will seek to establish the effects of topical instillation of low dose atropine on ocular/systemic correlates of CR and the outcomes of this study will provide a platform for future studies and funding applications.

H0: low dose atropine eye drops have no effect on ocular or systemic correlates of CR in adult myopes and non-myopes.

**Methods to be used:**

The following measures will be used in the proposed studies:

1. **Blood Sample**: Fasting serum sample (10ml) taken in the morning and analysed for Mel using liquid chromatography followed by on-line solid phase extraction and tandem mass spectrometry (LC-On-Line SPE-MS/MS).

2. **Saliva Sample**: A saliva sample (225µl), collected through the ‘passive drool’ method, analysed for Mel content using ELISA technique.

3. **Refractive error**: Refractive error measured using the Shin-Nippon Nvision-K5001 autorefractor.

4. **Ocular biometry**: Ocular biometry (axial length and corneal curvature) measured using the Zeiss IOLMaster.

5. **Ocular structure**: Retinal structure (retinal and choroidal thickness) measured using the Spectralis Ocular Coherence Tomographer (OCT) with EDI (Enhanced Depth Imaging).


7. **Sun Exposure Questionnaire**: A previously validated sun exposure questionnaire will gather information on outdoor activity, frequency of sun exposure and sun protection habits.

8. **Sleep Quality Questionnaire**: The Pittsburgh Sleep Quality Index will provide information on sleep quality over the previous month.

9. **Sleep pattern and activity**: The Actiwatch-2, a validated activity and sleep tracker worn on the wrist (day/night) for two weeks prior to data collection, will objectively quantify sleep/wake patterns and activity.

**STUDY 1: Do salivary measures of Mel capture differences between refractive groups?**

Twenty healthy adult (18-24 years) myopes and 20 healthy adult non-myopes will have Mel levels in fasting blood serum (measure 1) and saliva samples (measure 2) compared. Sample size calculations (power 90%; confidence 95%) indicate that 17 myopes and 17 non-myopes are needed to determine differences in Mel status between groups⁷. The outcome of this investigation will determine whether serum or salivary measures are used in Studies 2 and 3.

**STUDY 2: What is the relationship between myopia and ocular and systemic CRs at different time points of myopia development?**

Twenty-five healthy participants in each participant group a, b and c described above will undergo measure 1 or 2 (depending Study 1’s outcome) and 3-9 first thing in the morning after an overnight fast. Measurements 2-6 will be repeated a maximum of five times throughout the day¹⁰. Sample size calculations based on diurnal variation in
choroidal thickness estimate that 25 participants are sufficient to determine differences in choroidal thickness between groups10.

STUDY 3: Do low dose atropine eye drops affect ocular and systemic correlates of CR?
Ten healthy adult (18-24 years) myopes and 10 healthy adult non-myopes will have measures 1-9 assessed at baseline. Five participants in each group will receive one drop of 0.01% atropine sulphate into each eye and the remainder will receive one placebo drop. These eye drops will be instilled daily at the same time over a period of five days and measures 1-9 repeated daily. Following a ‘wash-out’ period (of at least one week) participants will cross-over and the same five-day procedure will be repeated with the participants who previously received atropine eye drops receiving placebo eye drops and vice-versa.

Skills required of applicant:

The applicant will be required to be a qualified Optometrist with BSc (Hons) 2:1 or 1st class degree. He or she will be required to have excellent administrative and organisational skills, good time management skills, good IT skills (data input, data management and analysis) and the ability to synthesise data and present results appropriately. They will require good interpersonal skills and manual dexterity.

References: