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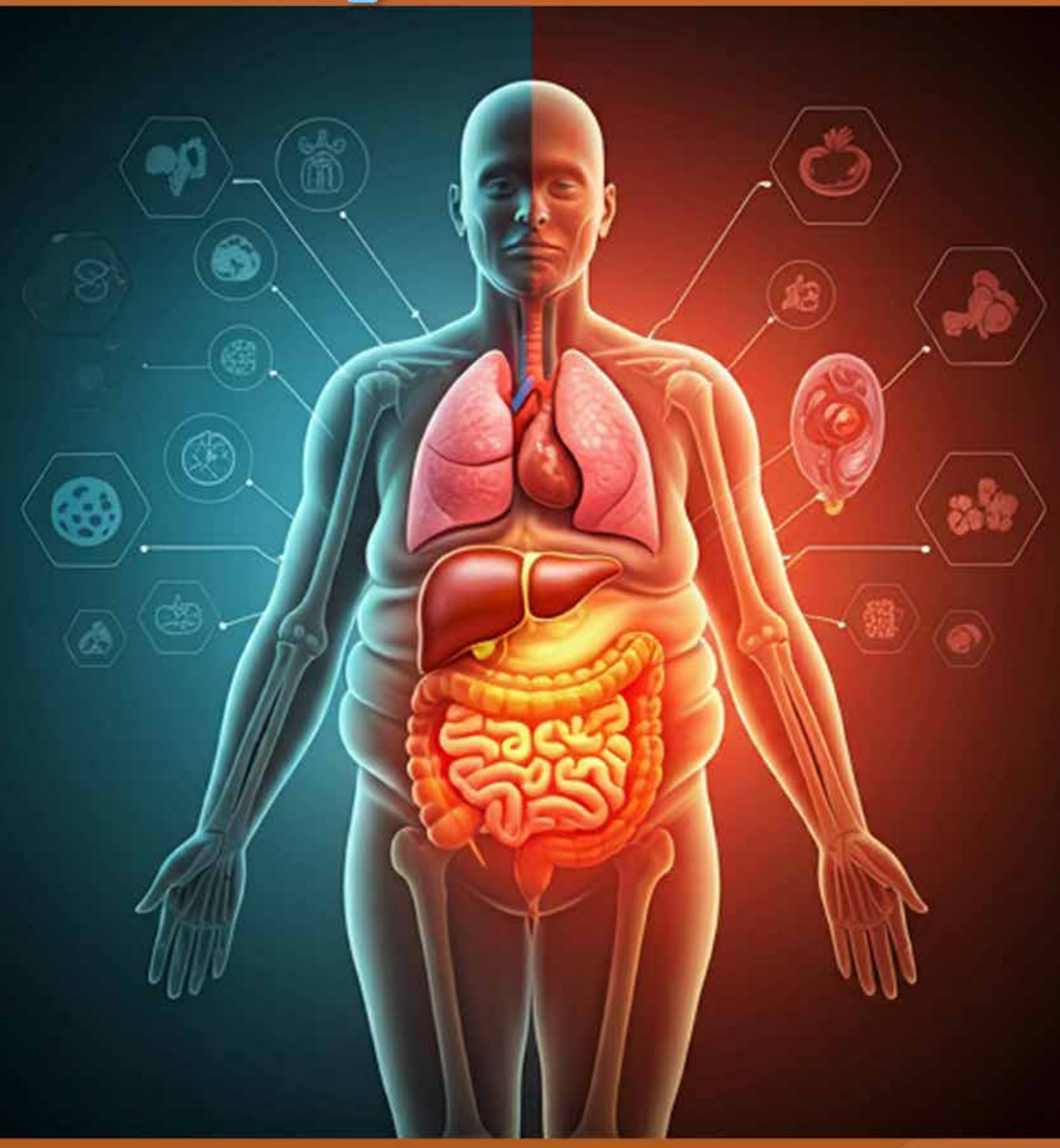

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Opinion: An urgent need of better criteria for the diagnosis and classification of obesity

Harbindar Jeet Singh

Keywords: *Obesity; BMI; leptin; inflammation; body fat; adipose tissue*

According to a recent World Health Organization (WHO) estimate, almost a quarter of the world's adult population is above the ideal body weight,[1] ie. they are either overweight or obese. This fraction has been steadily increasing over the last few decades, and is expected to continue to increase in the foreseeable future unless something is done about it.[2] The WHO defines a body mass index (BMI) of between 25 and 30 kg/m^2 as overweight, and a BMI greater than 30 kg/m^2 as obese.

The consequences of being overweight and obese on health are well recognised and documented. Although initially recognised as a risk factor for a number of non-communicable diseases, which include high blood pressure, ischaemic heart disease, atherosclerosis, diabetes mellitus, chronic respiratory diseases, some types of cancers, dyslipidaemia, fatty liver disease, the WHO, in its right wisdom, declared obesity as a disease in 1997. This was adopted by the American Medical Association (AMA), some 16 years later, where the AMA defined it as a chronic condition, with multiple pathophysiological aspects and complications.[3] In the more recent years, obesity has also been linked to mild cognitive impairment, altered hippocampal structure and function, Alzheimer's type dementia, autonomic and somatic nervous system dysfunction, and to some obstetric, reproductive, perinatal and pelvic disorders. Clearly, obesity is a disease that is responsible for countless other conditions, and desperately in need of a better diagnostic criteria than just the BMI.

Obesity is a state of low-grade inflammation. The exact point on the BMI scale or percentage body fat inflammation begins remains unknown. In other words, the precise relationship between BMI and inflammation needs to be clearly established. It is unknown if this particular point is the same for all populations, races, adults and children, and whether there are gender differences[4] and what factors influence this point. Whether regular physical activity impacts this cut-off point is unknown. Moreover, and equally importantly, the precise factor/s responsible for this low-grade inflammation in obesity remains to be clearly established.

There is considerable evidence in the literature that the distressed adipocytes in obese individuals may be the source of this factor/s that triggers inflammation. In this regard, the increased secretion of leptin and a number of other pro-inflammatory cytokines from the over-stretched, distressed adipocytes in the white adipose tissue may be directly responsible for the inflammation. Being a pro-inflammatory adipokine, leptin causes widespread endothelial activation. In addition to that, raised BMI has been found to disrupt the chromatin accessibility in human adipocytes, which could underlie obesity related inflammation.[5] In this regard, leptin has been found to alter the expression of numerous genes in cells. Studies in our lab have shown that leptin alters the expression of over 5000 genes, including apoptosis-inducing factor, histone acetyl transferase, respiratory chain reaction enzyme, cell necrosis and DNA repair genes. It also downregulates antioxidant enzyme and upregulates tumorigenic genes.[6-8]

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In addition to increased secretion of leptin and other pro-inflammatory adipokines, death of some of the distressed adipocytes increases the recruitment of macrophages into the adipose tissue, which then get polarised into pro-inflammatory M1-like macrophages.[9] These macrophages secrete many pro-inflammatory cytokines, including TNF. The raised circulating levels of leptin and other pro-inflammatory adipokines are the most likely factors responsible for the chronic low-state inflammation that is often noticed in the obese, together, of course, with the accompanying array of metabolic disorders.

Despite the declaration of obesity as a disease, and the overwhelming evidence in the literature implicating it as a risk factor in a number of other diseases, the diagnosis and classification of obesity still continues to rely on the old WHO definition that is primarily based on BMI. There is a clear and urgent need for a better criterion for the diagnosis of obesity if we wish to better manage obesity and obesity-related diseases. The current criteria used for the diagnosis of obesity are incomplete, and have inherent limitations and weaknesses. They do not reflect or detect the silent or insidious pathological changes happening inside the body of the overweight and obese individuals. Unfortunately, there is no information or data in the literature showing the precise BMI or percentage body fat cut-off at which the ill effects of being overweight or obese become apparent. From all probability, these perhaps start to occur at BMIs between 25-30, or even below 25, in some populations. It is not the BMI but the extra adipose tissue mass that is the disease. BMI does not directly assess body fat, and cannot differentiate between lean and fat mass in the body. Skinfold thickness using a skinfold calliper only measures subcutaneous fat, and does not accurately reflect the total percentage of body fat. Bioelectrical impedance analysis (BIA) for the measurement of body composition and body fat percentage is influenced by factors like hydration status, food consumption and physical activity. The accurate methodologies for the measurement of fat mass like dual X-ray absorptiometry and hydrodensitometry are too expensive to be performed in a clinical setting. Whilst it is important to know the exact fraction of body fat, but accurate measurement of percentage body fat in itself does not automatically confirm the presence of disease. There are those, albeit a few, with BMIs of above 30, and live to be 80 years or more with no major health complaints. What we, therefore, need, in addition to the BMI or body fat percentage, are parameters for the detection of altered or disturbed physiological function, particularly those related to adipocyte dysfunction. The most relevant parameters that need to be measured for the accurate diagnosis of obesity as a disease would be those representing adipocyte function or dysfunction, and those showing the presence of endothelial activation and generalised inflammation, together, of course, with the usual anthropometric measurements, such as BMI and waist-hip circumference ratio, etc.

Adipocytes produce a large number of adipokines and cytokines, which, under normal circumstances, serve numerous physiological functions that include regulation of energy balance and body weight, immune function, and reproduction.[10,11] Some of these adipokines are pro-inflammatory and some are anti-inflammatory, and the secretion of these is drastically

altered in obesity. Secretion of pro-inflammatory adipokines is upregulated whereas the secretion of anti-inflammatory adipokines is down-regulated in obesity.[12,13] The hypertrophy of adipocytes, particularly those in and around the viscera, exacerbates hypoxia within the adipose tissue leading to metabolic dysfunction in the adipocytes and dysregulated differentiation and maturation of preadipocytes and even death of some of the adipocytes.[12] This internal milieu within the adipose tissue favours the increased secretion of pro-inflammatory adipokines like leptin, TNF-alpha, IL-6, resistin, chemerin, visfatin, PAI-1, RBP4, lipocalin 2, IL-18, ANGPTL2, CCL2, CXCL5 and NAmPT and decreased secretion of anti-inflammatory adipokines like adiponectin and SFRP5 in obesity. Serum leptin concentration is directly proportional to the adipose tissue mass. This has long been well established. Released constitutively, the secretion of leptin increases further when the adipocytes are hypoxic or distressed. Pro-inflammatory and cell proliferative activities of leptin have also been well documented.[14-16] Incidentally, leptin is also believed to mediate the relationship between blood pressure and fat mass,[17] and leptin injections into rats and mice result in increased blood pressure, proteinuria and serum levels of markers of endothelial activation.[18-20]

Given the information that we have, it is clearly evident that we need a set of tests that will specifically identify the inflammatory state associated with increased adipose tissue mass, not just BMI or the fraction of body fat. The measurements of these inflammatory parameters will certainly help in identifying the disease a lot earlier; perhaps long before its cardiovascular and metabolic manifestations become apparent. Measurement of pro-inflammatory adipokines like leptin and cytokines like IL-6, and TNF-alpha, and serum levels of markers of inflammation like C-reactive protein (CRP) and markers of endothelial activation (eg., endothelial adhesion molecules such as ICAM, VCAM, e-selectin, etc.) are necessary for the diagnosis of obesity. As stated earlier, it is very likely that changes in these parameters may be evident even at BMIs below 25 or between 25 and 29 kg/m^2. As we know that cardiovascular and metabolic diseases also affect individuals in the borderline and overweight population and not just those who are obese.

Parameters on adipocyte morphology could also be included in the diagnosis of obesity as the morphology of adipocytes is altered when in distress. An alteration in any of these would further indicate the presence of disease.

Clearly, the currently used BMI classification of overweight and obesity needs to be re-classified or revised based on the level of adipocyte dysfunction and inflammation rather than based just on BMI or percentage body fat, if we wish to manage obesity as a disease. Like with many other diseases, early diagnosis of obesity is important if we want to combat the scourge of obesity-related diseases, that are fast becoming a burden to the health care systems of most countries. Measures have to be put in place to reduce the prevalence of obesity in the community. These include education in schools and colleges on the importance of a balanced nutrition and regular physical exercise in the maintenance of normal body weight. Obesity in most instances primarily stems

from poor nutrition and low physical activity. Food has become a very important component of our social behaviour and we consume food even when we do not need to. We really need to learn to eat to live rather than living to eat, which is what we are doing at the present time.

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Impact of Academic Stressors on Eating Behaviour Among University Students: Application of Socio-Ecological Model

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Academic stressors can hinder the wellbeing of students and impact their eating habits. In this study, we apply the socio-ecological model to academic stressors and explore the influence they have on eating behaviour among university students. This cross-sectional study was set in a private health sciences university in Malaysia among a sample of 183 pre-university students, which was obtained using systematic random sampling technique. The academic stressors of the participants were assessed using the Academic Stress Questionnaire while eating behaviour was determined using The Three Eating Factor Questionnaire Revised-18 Items. Significant association ($p \leq 0.05$) was found between academic stressors and eating habits. The increase in academic stressors increased the unhealthy eating behaviours: Cognitive Restraint, Uncontrolled Eating, and Emotional Eating. The findings illustrate that academic stressors should be taken into consideration for future university health interventions to promote healthy eating behaviour.

Keywords: *socio-ecological model, academic stressors, eating behavior, student*

Introduction

In 2018, Malaysia was recognised as the fattest nation in Asia and had the second-highest childhood obesity rate among children in ASEAN countries.[1] In less than two decades, the prevalence of overweight and obesity has increased by 80% and 70% in Malaysia,[2] with the prevalence of obesity in teenagers climbing over the last decade from 9.5% in 1997 to 19.6% in 2007.[3] One of the factors that may be contributing to this problem is stress.

Students of the current generation face a plethora of stressors including family, academics, finances and social.[4] Academic stressors in particular, have been linked to affecting eating habits through various pathways.[5] Stress is defined as the negative process which affects an individual's emotions, cognitive behavioural and physiological function to adjust with certain stressors which occur in their life.[6] Stressors are events or situations which can disturb, interfere, or even threaten an individual's function in their daily life. Stressors will affect a person's daily function in order to make adjustments to accommodate to the stress or strain faced by the individual.[7] Academic stress is the response of the body towards academic-related demands when a student is no longer able to adapt to these demands.[8] Academic stressors are factors that lead to academic stress. Eating behaviours refers to patterns of food consumption which include a variety of food choices and it may relate to obesity or malnutrition.[9] University students are considered to have more stressful lives than other people in their various stages of life.[10] Academic stressors can include finance, peers, exams, time management, study methods, lecturers and environment.[11,12] High academic stress can have a negative impact on a student's health, including cardiovascular health.[13] In addition, high academic stress has been correlated with lower well-being, anxiety, depression, changes in appetite, sleeping problems, and reduced academic performance.

One of the most important characteristics determining an individual's health is what is being used to nourish and maintain the body. This is determined by the eating behaviours of individuals. One study on nutrition-related factors and binge eating behaviour

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among Malaysian university students showed that 10 percent of the participants had binge-eating behaviour. [14] In a study by Steptoe *et al*, in 2012, it was found that people who recorded more events of annoyance, irritation, concern, or disappointment ate fast food more often.[15] In a cross-cutting analysis by university students from three European countries, Mikolajczyk concluded that the relationship between stress, depression symptoms and unhealthy food was very different for each country.[15] This implies that the association between stress and food choice can differ based on the country the individual resides in.

Students tend to eat an unbalanced meal or have diets consisting of too much starch, sugar and fat.[16] Unbalanced nutrition due to stress can contribute to the development of diseases, affecting general wellbeing and cognitive abilities. In 2013, a systematic review on stress and eating behaviours among animals indicated that stress influences food habits, with foods rich in fat and sugar being preferred when participants become either physically or emotionally stressed.[17] Stress has been related to "comfort eating," which is overeating high-sugar, high-fat foods and this can contribute to weight gain.[18] Cortisol increases appetite which may cause an individual to eat more in situations causing anxiety.[10] During those times, stress triggers the body to release the hormone cortisol.

Although there are plenty of previous studies on the impact of stress among university students, there are just a handful that explore the relationship of factors of stress and their impact on eating behaviours of an individual.[19] This is especially important in the global context of rising obesity prevalence, where causes of obesity need to be identified and addressed through appropriate intervention and policy measures.[20] This study seeks to determine the effect of academic stress factors on the eating behaviour of university students. By identifying stressors that can result in a shift in eating behaviour, proactive steps can be taken to avoid detrimental health issues.[21]

Materials and Methods

This research employed a cross-sectional quantitative study design. The target population were students enrolled in a science-based pre-university course in a private medical university in Kuala Lumpur, Malaysia. The sampling frame was 353 students and a total sample size of 183 students was derived using the formula derived from the work of Krejcie and Morgan.[36] A random sampling technique was employed for recruiting participants, and data was collected over three months, between 28th August 2020 to 25th November 2020. Participants were at least 18 years old and Malaysian citizens. This targeted population was chosen as this population has just progressed from school to university environment, where the focus is on independent self-management and learning.

Conceptual framework

The social ecological model (SEM) behaviour theory was used as the theoretical framework basis for this research study because the model explores how an individual is connected with and interacts in their environment and society. This model has been previously used for childhood obesity interventions.[22,23] In this study, we have developed a conceptual framework (Figure I) based on this theory, where academic stressors are categorised into various levels of the SEM, all of which influence eating

behaviours. The levels of academic stressors include: I. Individual (gender, age, ethnicity, household income, individual behaviour such as sleeping habits, smoking, and alcohol consumption); II. Interpersonal (relationship with family, friends, housemates, students, and teachers); III. Institutional (academic factors: hours of studying, examinations, missing lectures, and number of assignments); IV. Community (environmental factors: living conditions, moving to new city, and unfamiliar circumstances).

Exposure variables

The exposure variables are sociodemographic factors and academic stressors. Sociodemographic factors include sex, ethnicity, family household income, smoking status, and alcohol consumption. The categories of academic stressors are based on four environmental structures with which an individual can interact, which are: I. Relating to other people (interpersonal); II. Scholarly; III. Personal; IV. Environmental. Each of these variables can have an impact on change in eating behaviour.

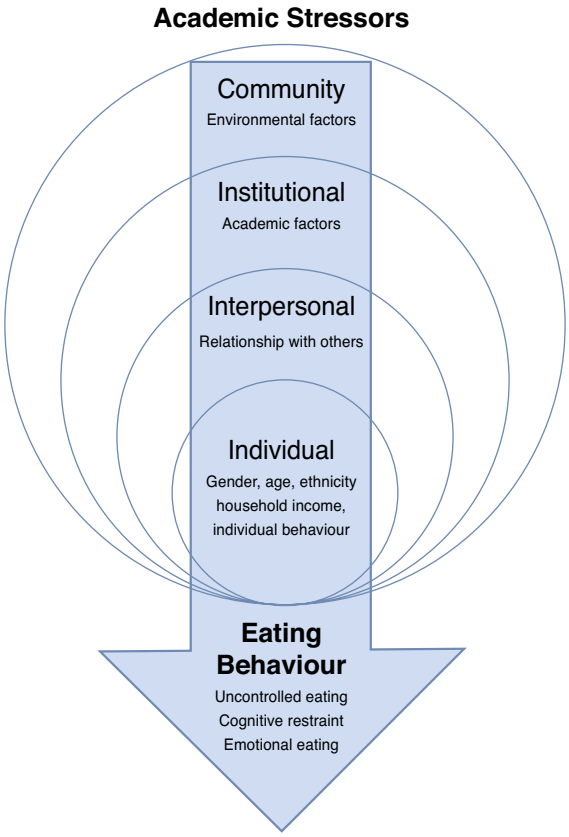

Figure I. Conceptual framework: Application of Socio-Ecological Model (SEM) to academic stressors and their influence on eating behaviour among students.

Outcome variable

The outcome variable is eating behaviour, which is categorised into three types: cognitive restraint, uncontrolled eating, and emotional eating. Cognitive restraint refers to when an individual consciously restricts and controls their food intake without using physiological cues such as hunger. Eaters in this category will consume food less than what the body requires.[24] Uncontrolled eating is a form of binge eating behaviour where an individual has a tendency to overeat with no self-control.[24] Emotional eating is a form of eating behaviour where an individual tends to eat in response to their negative emotions.[24] These three eating behaviours have the potential to be unhealthy.

Data collection procedure

Participants were asked to complete an online, English language, self-administered questionnaire on Google Form platform. A systematic random sampling technique was used with an adaptation of a replacement method to select the students. The first student was selected by an electronically generated random number with the updated list of pre-university course students from the student affairs department of the selected university. After

that, every second student was selected from the list. Emails were sent that included the information sheet, consent form and link to the questionnaire. Approval for distribution of the survey was obtained from university administration after explaining the intent of the research study. Participation was voluntary and if the student did not respond within one month, the next student on the list was sent an invitation to participate. Data collection started on 28th August 2020 and was completed on 25th November 2020.

Study instrument

The questionnaire comprised of three sections: I. Sociodemographic, II. Academic stress, and III. Eating behaviour. Two existing validated questionnaires were used in Section 2 and 3.

Academic stress questionnaire was previously used in an analysis of undergraduate student academic stress in Sweden.[29] It is an open-source self-reported questionnaire that consists of 32 items, grouped into four categories of academic stressors, which include: sources relating to the relationships of the pre-university students with others, scholarly variables, personal variables, and environmental variables. There is an equal number of eight items in each category. For evaluating the degree of stress for each category, the respondents are evaluated based on a 5-point Likert scale, from 1 as not all stressful to 5 as extremely stressful. They were also provided the option of don't know, which was categorised as missing value during data analysis.

The Three-Factor Eating Questionnaire (TFEQ-R18) was used to investigate eating behaviours.[25] The original source of the questionnaire was from the Stunkard Messick TFEQ with 51 items.[26] However, it was revised to produce the Three-Factor Eating Questionnaire Revised-18 item version (TFEQ-R18), which is a self-reported questionnaire measuring three different eating behaviours, which are cognitive restraint (6 items), emotional eating (3 items) and uncontrolled eating (9 items).[25] The revised version (TFEQ-R18) has been widely used in several countries including Malaysia.[27] Respondents are evaluated based on a 4-point Likert scale; whereby higher values would indicate more of the eating behaviours.[25] The internal consistency and reliability coefficient,[24] for all these three scales are: uncontrolled eating is 0.85, emotional eating is 0.87, and cognitive restraint is 0.75. Permission to use the questionnaire is mentioned to be unrestricted use provided the original work is cited properly.[24]

Statistical Analysis

The data obtained was analysed and tabulated using Statistical Package for Social Science (SPSS) (IBM Statistics Version 25 by IBM Corporation, NY, USA). Frequency tables were obtained to check missing data, out of range values and to assess distributions of continuous variables. Mean scores for academic stressors and eating behaviours were calculated based on responses on the Likert scale questionnaires. Pearson correlation test was used for determining association between academic stressors and eating behaviours. The correlation was observed collectively as a group (mean score) and as separate individual categories.

Results

In this study conducted online, 290 surveys were sent out and the response rate was 63.7%, where 183 participants participated in the survey. Normality testing using Kolmogorov-Smirnov normality test, was done for each category of academic stressors and eating behaviours. The results were found to be normally distributed.

The population demographic profile is represented in Table I, which illustrates that 22.4% were males while 77.6% were females. Among the respondents of this study, the majority of the respondents were Chinese (71.6%), followed by Indian (13.7%), Malay (10.4%) and Others (4.4%). The majority of the respondents did not smoke (97.8%) and did not consume alcohol (86.9%).

Table I - Demographic Profile

Demographic	Frequency (N = 183)	Percentage (%)
Gender		
Male	41	22.4
Female	142	77.6
Ethnicity		
Malay	19	10.4
Chinese	131	71.6
Indian	25	13.7
Others	8	4.4
Family Household Income		
≤RM 6000	79	43.2
>RM 6000	104	56.8
Smoking Status		
Yes	4	2.2
No	179	97.8
Alcohol Consumption		
Yes	24	13.1
No	159	86.9

An independent T-Test was conducted to compare the mean of academic stressors which are relating to other people, personal factors, academic factors and environmental factors to the mean sociodemographic/ socioeconomic factors. A significant association was not observed apart from emotional eating to family household income [t (181) = -2.45, p = 0.015] and ethnicities [p<0.05 level F (4, 179) = 8.09, p = 0.000].

An independent T-Test was conducted to compare the mean of academic stressors which are relating to other people, personal factors, academic factors and environmental factors to the mean sociodemographic/ socioeconomic factors. A significant association was not observed apart from personal factors with ethnicities [p<0.05 level F (4, 179) = 2.98, p = 0.03] and environmental factors with ethnicities [p<0.05 level F (4, 179) = 3.55, p = 0.016].

A Pearson product-moment correlation coefficient was computed to assess the association between academic stressors (relating to other people, personal factor, scholarly factor and environmental factor) and eating behaviours (cognitive restraint, uncontrolled eating and emotional eating). The results of the Pearson correlation test in Table II reveal the overall mean of grouped academic stressors to be 3.48 and overall mean of grouped eating behaviour to be 2.23. There was a positive correlation and high significance between these two variables (r = 0.455, p= 0.000). Hence, the increase in academic stressors increases potentially unhealthy eating behaviour patterns.

Table II - Means and association of academic stressors and eating behaviours.

Mean of Academic Stressors	Mean of Eating Behaviours	Pearson Correlation (*r-value*)	*p-value*
3.48	2.23	0.455	0.000

Table III - Association of each academic stressor with each eating behaviour.

FACTORS	Cognitive Restraint		Uncontrolled Eating		Emotional Eating	
	Pearson Correlation	*p-value*	Pearson Correlation	*p-value*	Pearson Correlation	*p-value*
Relating to Other People	0.208	*0.005	0.208	*0.002	0.230	**0.000
Scholarly	0.271	**0.000	0.375	**0.000	0.351	**0.000
Personal	0.361	**0.000	0.392	**0.000	0.396	**0.000
Environmental	0.221	*0.003	0.350	**0.000	0.294	**0.000

**p-value* <0.005 – significant ***p-value* <0.001 – highly significant

Associations between each academic stressor and each eating behaviour were assessed using Pearson correlation and are depicted in Table II. The results show a significant ($p<0.001$) weak to medium strength positive correlation, where correlation of 0.10 to 0.29 indicates weak correlation, and 0.30 to 0.49 indicate medium strength correlation.

There was a significant and positive correlation between "relating to other people" (academic stressor) with cognitive restraint ($r = 0.208$, $p = 0.005$), uncontrolled eating ($r = 0.208$, $p = 0.002$) and emotional eating ($r = 0.230$, $p = 0.000$). There was a significant and positive correlation between "scholarly factor" with cognitive restraint ($r = 0.271$, $p = 0.000$), uncontrolled eating ($r = 0.375$, $p = 0.000$) and emotional eating ($r = 0.351$, $p = 0.000$). There was a significant and positive correlation between "personal factor" with cognitive restraint ($r = 0.361$, $p = 0.000$), uncontrolled eating ($r = 0.392$, $p = 0.000$) and emotional eating ($r = 0.396$, $p = 0.000$). There was a significant and positive correlation between "environmental factor" with cognitive restraint ($r = 0.221$, $p = 0.003$), uncontrolled eating ($r = 0.350$, $p = 0.000$) and emotional eating ($r = 0.396$, $p = 0.000$).

Discussion

The results of this study are significant as there is evidence of an association between academic stressors in university students and their corresponding eating behaviours. Specifically, increase in academic stressors increases potentially unhealthy eating behaviours: cognitive restraint, uncontrolled eating, and emotional eating. Other studies have explored the health impacts of stress and its association with dietary habits. However, these studies focus on stress as a general component, rather than specifying academic stressors. It is pivotal to specify academic stress and eating behaviours so that health promotion interventions can be designed particularly for the high-risk group of young adults in an educational environment.

Our results support the association of increase in uncontrolled eating, cognitive restraint and emotional eating with increase in academic stressors (personal, interpersonal, scholarly and environmental factors). This is supported by findings from a study done in a Brazil college, which states that 43 percent of the students have a high stress level and that depressed individuals consume more.[28] Studies have also shown that overeating and a fixation with food will evolve from stress.[19,28] In addition, individuals that have high carbohydrate and high fat intakes levels are generally susceptible to stress because of their relatively low energy intake which may generate anxious feelings. Burnout and eating disorders are common among students at a private university in Malaysia.[20]

Studies indicate that stress can affect an individual's appetite which leads to either eating more or less than usual and can affect the food preferences of the person, causing him/her to consume high-fat and dense calorie "snack" candy rather than "meal type" foods, such as meat and vegetables.[29] Hyperphagia was reported by 46 percent of women and 17 percent of men under stress in a food selection study conducted among 169 undergraduate students in USA.[30] Gibson *et al*, in United Kingdom observed in their laboratory study that people under stress consumed soft, fatty food in excess of low-fat bland foods or salty foods, with

cake and chocolate as their principal favourite snacks. Physiologically, the impact of stress on the body could lead to energy-rich snacks being consumed rather than meal consumption due to the suppression of intestinal activity through sympathetic (adrenaline-promoted) excitement and easier digestion of snacks than meals.[12] Sleep deprivation has been associated with hyperphagia due to disrupted release of ghrelin and leptin, which neurotransmitters that regulate appetite.[31] That is consistent with the findings of our study, where sleep was identified as a personal factor of academic stressors.

In our study, we found that there was a significant association between emotional eating and ethnicities. This is in line with a study that assessed emotional experiences through different forms of eating patterns across Finnish, French and Pakistani cultures. It was found that there were strong differences among the groups, with some eating in social and luxurious eating pattern when in positive emotions while others eat in solitary with positive emotions.[32] There was also a significant association between emotional eating and family household income in our study. There is increasing research to suggest that youth from lower income households are at risk for loss of control eating. The inability of individuals to satisfy needs successfully may be perceived as a stressor and individuals may engage in emotional eating as an alternative to fulfill their needs.[33] This is depicted in a study among adolescents, which revealed lower household income-to-needs was positively associated with loss of control in eating at higher levels of household food insecurity.[34] Although gender was not found to be a significant factor in regard to eating behaviours in our study, another study found that in comparison with men, women constitute the majority of restricted eaters among stress-induced survivors, suggesting that when stressed, hyperphagia seems to occur for women with pre-existing restraining behaviours in terms of food.[35]

Strengths and limitations

There were several limitations of this study. Firstly, although the sample size was large enough to check for significant associations, it could be larger to improve the power of the study. Secondly, the recruitment of participants was limited to one university that was located in the capital city but not in the city centre. This might affect the generalisability of the results to other student populations due to university specific environmental differences. Future studies are recommended using a larger representative sample size from various universities to build on the knowledge database.

Conclusion

There is a paucity of research looking into perceived determinants of eating behaviours in Asian countries. This study used an ecological framework to determine whether sociodemographic and academic stressors have an association with potentially unhealthy eating behaviours (cognitive restraint, uncontrolled eating and emotional eating). Students' eating behaviours were found to be influenced by all four categories of academic stressors: personal, interpersonal, scholarly, and environmental. Students that are just transitioning from secondary school to university are at precipice, where their seemingly independent choices will determine their health outcomes.

These choices are affected not only by personal beliefs but are far ranging, including university campus food environment, social activities, time management skills and peer pressure. University administrators and researchers are recommended to provide interventions on building self-capacity through self-discipline, resilience and time management skills; providing social support; providing a curriculum that strikes a balance between rigour and healthy learning. Our study brings to the forefront the role of university setting in preparing students to make healthy food choices to life and curtailing the obesity epidemic.

Declarations

Data Availability Statement: The data that supports the findings of this study are available upon request from the corresponding author but restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available. The data are, however, available from corresponding author upon reasonable request.

Compliance with Ethical Standards Statement

Conflicts of Interest: The authors have no relevant financial or non-financial interests to disclose.

Informed Consent Statement: Informed consent was obtained from all individual participants included in the study.

Ethical Approval Statement: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by International Medical University Joint-Committee of Research and Ethics. "(Project ID: MSPH I/2020(05), 25th June 2020)".

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Ensuring the Safety of COVID-19 Vaccines among Rheumatic and Musculoskeletal Disease (RMD) Patients in Seremban: A Cross-Sectional Study Investigating Adverse Reactions

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Introduction: Coronavirus disease 2019 (COVID-19) has severely influenced all aspects of life since its emergence and one of the strategies to end this pandemic rests on the vaccination to achieve herd immunity. While vaccinations are usually a safe and effective tool, the abbreviated development process of the available COVID-19 vaccines has increased uncertainties about the safety among the general population especially among patients with rheumatic and musculoskeletal diseases (RMD).

Methods: A cross-sectional analysis was performed on rheumatic disease (RMD) patients from the rheumatology clinic at Hospital Tuanku Ja'afar Seremban (HTJS), investigating adverse events occurring within one month of receiving COVID-19 vaccines administered from 1st May 2021 to 30th September 2021.

Results: 549 RMD patients were recruited in this study. Pfizer/BioNTech was the predominant vaccine (n = 257, 64.3%), followed by Sinovac (n = 60, 47.2%), Oxford/AstraZeneca (n = 7, 1.3%) and Moderna (n = 1, 0.2%). 330 (60.1%) patients experienced at least one adverse event, none of which required hospitalisation. Common side effects included pain at the site of injection (n = 169, 30.8%), generalised muscle pain (n = 91, 16.4%), fever (n = 90, 16.4%), arthralgia (n = 55, 10.0%), and lethargy (n = 43, 7.7%). Female patients (OR = 0.88, CI 0.79-0.97, p = 0.012), Sinovac recipients (OR = 0.51, CI 0.34-0.76, p = 0.001) and age >50 years (OR = 0.62, CI 0.44-0.89, p = 0.009) had significantly lower risks of experiencing adverse events. Among patients with autoimmune rheumatic disease (AIRD), 28 (6.4%) experienced disease flare. Patients with spondyloarthropathy (SpA) and overlap syndrome were more likely to experience disease flare following COVID-19 vaccination compared to rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) patients (OR = 2.87, CI 1.23 - 6.69, p = 0.014). The use of combination conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) was associated with a tendency toward increased risk of disease flare (OR = 2.34, CI: 0.97–5.64, p = 0.056). However, the use of glucocorticoids (OR = 2.02, CI 0.72–5.61, p = 0.17) and an active disease state (OR = 1.94, CI 0.75–5.02, p = 0.171) did not show a statistically significant impact on the frequency of disease flares.

Conclusions: The study affirms the overall safety of COVID-19 vaccines in rheumatic musculoskeletal disease patients, supporting efforts to address vaccine hesitancy in this population.

Keywords: *Adverse events; COVID-19; Rheumatic and musculoskeletal disease; SARS-CoV-2; Vaccination*

Background

Coronavirus disease 2019 (COVID-19) is a global threat to humanity and has severely influenced all aspects of life since its emergence. Immune dysregulation in various autoimmune rheumatic diseases (AIRD) poses a risk for prolonged viremia and severe COVID-19 due to a few factors such as high comorbidities and high disease activity.[1] One of the strategies to tackle this rests on vaccination to achieve herd immunity. While vaccinations are usually a safe and effective tool, the accelerated development process of the available COVID-19 vaccines has increased uncertainties about safety among the general population, especially among

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patients with AIRD.[2] Furthermore, these individuals were largely excluded from the initial vaccine trials and the evidence of vaccine safety in patients with AIRD is limited.

Connolly *et al*, published the first available data on the safety and reactogenicity of mRNA COVID-19 vaccine among rheumatic and musculoskeletal diseases (RMD) patients. In this study, local and systemic adverse events were consistent with expected vaccine reactogenicity, mainly mild and similar in frequency to those reported in the vaccine trials.[3] Studies on COVID-19 vaccine hesitancy among patients with RMD showed that the main reasons for vaccine refusal were fear of disease worsening and occurrence of adverse events related or regardless to disease.[4]

Our objectives are to explore the safety of COVID-19 vaccination among RMD patients and to identify precipitating factors for the occurrence of adverse events post-vaccination.

Methods

Patient recruitment

Patients with rheumatic and musculoskeletal diseases (RMDs) aged 18 years and older, who were being monitored in the rheumatology clinic at Hospital Tuanku Ja'afar Seremban and had received at least one dose of the COVID-19 vaccine between 1st May 2021 and 30th September 2021, were invited to participate in this cross-sectional study. All participants were informed of the purpose of the survey and verbal consent was obtained before their inclusion. Participant information sheets in two languages (English and Bahasa Malaysia) were also made available at the rheumatology clinic.

Data collection

The survey included demographic data (age, sex and ethnicity), RMD condition (diagnosis, disease activity and treatment), underlying medical illness, and SARS-CoV-2 infection and vaccination history. Information on demographic data and RMD conditions were obtained from the out-patient case notes while SARS-CoV-2 infection and vaccination history were obtained through interviewing the participant, either face-to-face or via telephone calls. Questions on SARS-CoV-2 vaccination included date, type and number of vaccines received, presence of adverse event within a month following the injection and the nature of the adverse event. No identifiable data were recorded.

Statistical analysis

Data collected were entered into IBM SPSS Software version for statistical analysis. Frequency distributions of the demographic variables were summarised using counts (n) and percentages (%). The relationships between categorical variables were analysed using the Pearson chi-square test. To assess the association of demographic and clinical characteristics with the occurrence of adverse events and disease flare-ups, we employed the chi-square test to determine unadjusted odds ratios (ORs) with 95% confidence intervals. A p-value of 0.05 or lower was considered statistically significant.

Operational definition

Disease flare among the AIRD patients was defined as requiring increment or introduction of corticosteroid or addition of immunosuppressants in any patient who had been on a stable dose in the preceding three months before vaccination.

Ethics statement

This study was granted approval by the Joint Committee on Research & Ethics, International Medical University (CSc/Sem6(25)2021) and Medical Review & Ethics Committee (MREC) (22-00880-DMT).

Results

We studied 549 patients with RMD. More than half of the patients (n = 306, 55.7%) were older than 50 years and majority were female (n = 417, 76.0%). Among the participants, 277 (50.5%) were Malay, 149 (27.1%) were Chinese, and 105 (19.1%) were Indian. Four hundreds and fourteen (75.4%) patients received Pfizer-BioNTech, 127 (23.1%) received Sinovac, 7 (1.3%) received Oxford-AstraZeneca and 1 (0.2%) received Moderna. Four hundreds and forty (80.0%) patients were diagnosed with AIRD and 109 (19.9%) with non-AIRD.

A comparison of demographic and clinical characteristics between patients with and without adverse events within a month following the COVID-19 vaccination were included in Table I. Female patients (OR = 0.88, CI 0.797-0.977, p = 0.012), Sinovac recipients (OR = 0.51, CI 0.34-0.76, p = 0.001) and age >50 years (OR = 0.63, CI 0.44-0.89, p = 0.009) had significantly lower risks of experiencing adverse events. No significant differences were observed in adverse event occurring between AIRD and non-AIRD groups (p = 0.447).

Table I: Demographic and clinical characteristics of all RMD patients with and without adverse events within a month following the COVID-19 vaccination.

CHARACTERISTICS *n* (%)	ALL (n = 549)	WITH ADVERSE EVENTS (n = 330)	WITHOUT ADVERSE EVENTS (n = 219)	P VALUE
AGE				**0.031**
< 30	65 (11.8%)	42 (64.6%)	23 (35.8%)	
31-50	178 (32.4%)	119 (66.9%)	59 (33.1%)	
>50	306 (55.7%)	169 (55.2%)	137 (44.8%)	
GENDER				**0.012**
Female	417 (76.0%)	263 (63.0%)	154 (37.0%)	
Male	132 (24.0%)	67 (50.1%)	65 (49.9%)	
ETHNICITY				**0.144**
Malay	277 (50.5%)	165 (59.6%)	112 (40.4%)	
Chinese	149 (27.1%)	99 (66.4%)	50 (33.6%)	
Indian	105 (19.1%)	58 (55.2%)	47 (44.8%)	
Others	18 (3.3%)	8 (44.4%)	10 (53.7%)	

VACCINES				**0.001**
Pfizer-BioNTech	414 (75.4%)	263 (63.5%)	151 (36.5%)	
Sinovac	127 (23.1%)	60 (47.2%)	67 (52.8%)	
CO-MORBIDITIES				**0.606**
none	222 (40.4%)	138 (41.8%)	84 (43.0%)	
1-2	244 (44.4%)	141 (43.0%)	103 (47.0%)	
>2	83 (15.1%)	51 (15.4%)	32 (14.6%)	
AUTOIMMUNE RHEUMATIC DISEASE (AIRD)	440 (80.1%)	268 (60.9%)	172 (29.1%)	**0.447**
RA	219 (49.7%)	125 (57.0%)	21 (43.0%)	
SLE	122 (27.9%)	83 (68.0%)	39 (32.0%)	
SpA	44 (10.0%)	23 (52.3%)	21 (47.7%)	
Overlap syndrome	18 (4.1%)	14 (77.8%)	4 (22.2%)	
Dermatomyositis	11 (2.5%)	9 (81.8%)	2 (18.2%)	
Systemic sclerosis	8 (1.8%)	3 (37.5%)	5 (62.5%)	
Vasculitis	9 (2.1%)	3 (66.7%)	6 (33.3%)	
Others	9 (2.1%)	8 (88.9%)	1 (11.1%)	
NON-AUTOIMMUNE RHEUMATIC DISEASE (NON-AIRD)	109 (19.9%)	62 (56.9%)	47 (43.1%)	
Gout	65 (59.6%)	32 (49.2%)	33 (50.8%)	
Osteoarthritis	16 (14.7%)	9 (56.3%)	7 (43.8%)	
Osteoporosis	10 (9.2%)	8 (80.0%)	2 (20.0%)	

Data are shown as n (%). RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, SpA: spondyloarthropathy

At least one adverse event was recorded in 330 (60.1%) RMD patients, none of which required hospitalisation. The most common symptoms reported were pain at the site of injection (n = 169, 30.8%), generalised muscle pain (n = 91, 16.4%), fever (n = 90, 16.4%), arthralgia (n = 55, 10.0%), and lethargy (n = 43, 7.7%).

The association between COVID-19 vaccination and AIRD flare

In this study, 440 participants (80.1%) had an autoimmune rheumatic disease (AIRD). Among them, 219 patients (49.7%) had rheumatoid arthritis (RA), 122 patients (27.9%) had systemic lupus erythematosus

(SLE), 44 patients (10.0%) had spondyloarthritis (SpA), 18 patients (4.1%) had overlap syndrome, and 11 patients (2.5%) had dermatomyositis. Disease flare was recorded in 28 (6.4%) patients. Fourteen RA patients who experienced disease flare were solely arthritis-related. Six SpA patients experienced flares, with 4 exhibited only arthritis-related symptoms and 2 observed arthritis along with psoriasis flare. Among the 5 SLE patients who flared, 3 were renal-related, 1 had arthritis, and 1 had mucocutaneous flare. Additionally, 3 patients with overlap syndrome experienced arthritis flares.

Among the AIRD, patients with SpA and overlap syndrome were significantly more likely to experience disease flare-ups following COVID-19 vaccination compared to those with RA and SLE (OR = 2.87, CI 1.23–6.69, p = 0.014). The use of combination conventional synthetic disease-modifying anti-rheumatic drug (csDMARDs) was associated with a tendency toward increased risk of disease flare (OR = 2.34, CI 0.97–5.64, p = 0.056). However, the use of glucocorticoids (OR = 2.02, CI 0.72–5.61, p = 0.17) and an active disease state (OR = 1.94, CI 0.75–5.02, p = 0.171) did not show a statistically significant impact on the frequency of disease flares. No case of disease flare was noted among patients who received biologic/targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs) (Table II).

Table II: Clinical characteristics of AIRD patients with and without disease flare within a month following the COVID-19 vaccination.

PARAMETERS	ALL N = 440 (100%)	WITH DISEASE FLARE N = 28 (6.4%)	WITHOUT DISEASE FLARE N = 412 (93.6%)	P VALUE
AGE				**0.123**
< 30	60 (13.6%)	2 (3.3%)	58 (96.7%)	
31-50	145 (33.0%)	14 (9.7%)	131 (90.3%)	
>50	235 (53.4%)	12 (5.1%)	223 (94.9%)	
GENDER				**0.325**
Female	374 (85.0%)	22 (5.9%)	352 (94.1%)	
Male	66 (15.0%)	6 (9.0%)	60 (91.0%)	
ETHNICITY				**0.144**
Malay	210 (47.8%)	10 (4.7%)	200 (95.3%)	
Chinese	119 (27.0%)	6 (5.0%)	113 (95%)	
Indian	95 (21.6%)	9 (9.5%)	86 (90.5%)	
Others	16 (3.6%)	3 (18.8%)	13 (81.2%)	

TYPES OF AIRD				**0.0436**
Rheumatoid arthritis	219 (49.7%)	14 (6.4%)	205 (93.6%)	
SLE	122 (27.9%)	5 (4.1%)	117 (95.9%)	
Spondyloarthropathy	44 (10.0%)	6 (13.6%)	38 (86.4%)	
Overlap syndrome	18 (4.1%)	3 (16.7%)	15 (83.3%)	
Dermatomyositis	11 (2.5%)	0	11	
Systemic sclerosis	8 (1.8%)	0	8	
Vasculitis	9 (2.1%)	0	9	
Others	9 (2.1%)	0	9	
VACCINES				**0.274**
Pfizer-BioNTech	336 (76.4%)	23 (6.8%)	313 (93.2%)	
Sinovac	99 (22.5%)	4 (4%)	95 (96%)	
DISEASE ACTIVITY				**0.654**
Remission/inactive	380 (86%)	22 (5.8%)	356 (93.7%)	
Low	12 (3.1%)	1 (8.3%)	11 (91.7%)	
Moderate	34 (8.6%)	4 (11.8%)	30 (88.2%)	
High	10 (2.3%)	1 (10%)	9 (90%)	
GLUCOCORTICOSTEROID USE				**0.037**
None	395 (90%)	23 (5.8%)	372 (94.2%)	
Low dose (≤ 7.5mg / day)	33 (6%)	2 (6%)	31 (94%)	
Medium (7.5mg – 30mg / day)	12 (2.2%)	3 (25%)	9 (75%)	
TREATMENT				
Cs-DMARDs	338 (76.8%)	24 (7.1%)	314 (92.9%)	
1 cs-DMARDs	178 (52.5%)	8 (4.5%)	170 (95.5%)	**0.063**
≥2 cs-DMARDs	160 (47.5%)	16 (10.0%)	144 (90.0%)	
b/ts-DMARDs	32 (7.3%)	32 (100%)	0 (0%)	
Anti-TNF alpha	16 (2.9%)	16 (100%)	0 (0%)	
Anti-IL6	9 (1.6%)	9 (100%)	0 (0%)	
JAK-i	7 (1.3%)	7 (100%)	0 (0%)	
not on any DMARDs	70 (15.9%)	1 (3.4%)	28 (96.6%)	

Data are shown as n (%). b/ts-DMARDs: biologic/target synthetic-Disease Modifying Antirheumatic Drugs; Cs-DMARDs: conventional synthetic-Disease Modifying Antirheumatic Drugs; IL-6: intermeulin-6; JAK-i: Janus kinase inhibitor; TNF: tumor necrosis factor. ^Chi-Square test was conducted exclusively for the categories of RA, SLE, Spondyloarthritis (SpA), and Overlap Syndrome.

Discussion

Our study provides valuable insights into the adverse effects of COVID-19 vaccination among patients with RMD, shedding light on vaccine safety, tolerability and the occurrence of disease flares post-vaccination.

The predominance of Pfizer-BioNTech recipients in our cohort aligns with global trends given its early availability and widespread distribution. Notably, 60.1% of patients experienced at least one adverse effect within a month post-vaccination, with pain at the site of injection, generalised muscle pain and fever being commonest. All of them were mild and did not warrant hospitalisation.

Our analysis indicated notable differences in adverse events based on gender and vaccine type. Additionally, there was a weak inverse correlation between age and adverse events suggesting that older individuals experienced slightly fewer adverse events. These were similar to previous studies.[5,6,7] mRNA vaccines like Pfizer-BioNTech were often associated with a higher rate of reactogenicity compared to other vaccine platforms. Conversely, the Sinovac vaccine, being an inactivated virus vaccine, tended to have a different safety profile, which aligns with our finding that Sinovac recipients had fewer adverse events.[5] Older adults generally experience fewer adverse events following vaccination and this might be due to age-related differences in immune response and reactogenicity.[6]

There was no significant difference in the occurrence of adverse events between patients with AIRD and those with non-AIRD. This observation aligns with findings from other studies suggesting that COVID-19 vaccines were generally well-tolerated among autoimmune patients.[8,9,10] It is possible that the immune dysregulation seen in autoimmune diseases does not predispose individuals to a higher incidence of common vaccine side effects, although they seem to exhibit increasing susceptibility to develop severe forms of COVID19 infection with higher mortality rates.

Although the overall adverse event rate was similar between AIRD and non-AIRD patients, the study revealed that specific subtypes of AIRD, such as SpA and overlap syndrome, were associated with a higher likelihood of experiencing disease flares following vaccination. This suggests that while the general adverse event rate may be comparable, certain autoimmune conditions might interact differently with the vaccine, leading to a higher incidence of disease flare-ups. This observation is supported by other studies highlighting that patients with certain autoimmune conditions may experience transient exacerbations post-vaccination.[11] Among the patients who had psoriatic arthritis flare also encountered worsening of psoriasis. All of them received Pfizer vaccine. This resonates with findings by Wu *et al*, where most of the patients with psoriasis flare received mRNA vaccines with the onset of flare ranging from 1 day to 90 days.[12]

In this study, glucocorticoid use did not demonstrate a significant association with the frequency of disease flares. This aligns with the findings of a systematic review by Shaun *et al*, which examined disease flare patterns among SLE patients following COVID-19 vaccination. However, the authors did note that a high SLE disease activity score was associated with an increased risk of flares, a finding that contrasts with our results among AIR patients.[13]

It is known that some immunosuppressive or immunomodulatory drugs reduce seroconversion rates, rendering the vaccine less immunogenic and potentially impacting flare rates.[14]

Limitation

This study was cross-sectional, which introduces limitations related to temporal relationships and increases the risk of recall bias. Additionally, majority of the study's participants received Pfizer-BioNTech vaccine. This limited diversity in vaccine types may affect the generalisability of the findings to other vaccines or newer vaccine formulations. This study also did not investigate the impact of vaccine dose on adverse events and disease flares. Examining dose-dependent effects could provide insights into whether higher or lower doses of the vaccine have varying safety profiles for RMD patients.

Conclusion

Our data confirm good tolerability and low frequency of disease flare following COVID-19 vaccination. While most adverse effects were mild and self-limiting, close monitoring and individualised management strategies are essential, especially for patients at higher risk of adverse events or disease flares.

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Effectiveness of Virgin Coconut Oil in Treating Dry Eyes

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Background

There are a few dry eye remedies available in the market. Currently, artificial tears and lubricants are still the most common management for dry eyes.

Objective

We proposed a new method in managing dry eyes.

Methods

A pre-soaked contact lens in virgin coconut oil (VCOCL) is being used as a vehicle to deliver virgin coconut oil (VCO) in dry eyes. VCOCL was prepared in sterilised conditions where daily soft hydrogel contact lenses were immersed in raw VCO. The efficacy of VCOCL in delivering the VCO to eyes was assessed by measuring the Tear Break-Up Time (TBUT) values, corneal staining of the anterior eye, Schirmer Test values and the measurement of residual VCO volume in tears at baseline and at 15 minutes after insertion on subjects with dry eyes. Pre- and post-data were used to analyse all the measurable variables.

Results

This study showed a significant difference in the TBUT, corneal staining, and residual VCO volume for both eyes ($p<0.05$). However, there were no changes in the Schirmer Test value ($p>0.05$). VCOCL was proven to improve tear quality in dry eye subjects and was able to maintain its presence in the eye even after 15 minutes.

Conclusion

This study suggests a new method for dry eye management.

Keywords: *Contact Lens, VCO, Therapeutic, Dry Eye, Tearfilm*

INTRODUCTION

Dry eye is often characterised by increased tear film osmolality and inflammation of the ocular surface, leading to symptoms such as discomfort, blurred vision, and unstable tear film, especially in individuals who wear contact lenses.[1,2] Adequate tear volume is crucial for maintaining overall ocular health, which in turn ensures clear vision.[3]

The remedies commonly used are artificial tears and eye lubricants. Some artificial tears containing hyaluronic acid are well known to relieve dry eye symptoms in dry eye treatment.[4] However, tear substitutes are not specifically designed to improve symptoms, but to prevent the build-up of those pre-existing problems. Some of the formulation of those artificial tears may contain preservatives which potentially cause some side effects and induced irritation after prolonged usage.[5] Many types of artificial tears have attempted to enhance their effectiveness by modifying the composition, viscosity, and/or osmolarity of the solution. Although many of these rewetting drops are available over the counter, they are often known to provide only temporary relief from symptoms or may not be effective treatments at all.[5] Additionally, most of these products have not been scientifically tested for their efficacy.[4]

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Ophthalmic drug delivery system is often prescribed in eye drops and ointment through topical ocular administration. Approximately 95% of the drugs contained in the drops are very likely to be lost through tear drainage.[6] Using therapeutic contact lenses as vehicles for drug delivery were introduced and approved in 1970s in United States on cornea related treatments. This has led to the expansion of inventing a variety options of contact lens materials and parameters in the market and lately high DK silicone hydrogel lenses were used.[7] Therapeutic contact lens of high water content can be used to load the drugs, thus providing longer residence time of the drug on cornea, which has effectively overcome the short residence time of drugs in tears that results in a low corneal bioavailability of 1-5%. Hence, therapeutic contact lens wearer can maintain the efficacy of drug loadings to maintain its efficacy, thus increasing its bioavailability.[8] To solve the dry eye problem for evaporative dry eye patient, the stabilisation of tear film can be achieved by increasing lipid layer thickness. If the quantity of the oily layer is unstable, it will cause the watery layer to be dried up rapidly.[9]

A new horizon in discovery of the benefits of VCO has been emphasised in most systemic diseases either in curing or in treating at the same time. One study has been conducted on efficacy of VCO as ocular rewetting agent on rabbit eyes whereby VCO did not cause harmful effects when used on rabbit's eyes which concludes that it is safe to be used on human's eyes.[10] The fatty acid and anti-inflammatory agents on VCO may act as protective layer over the tear film layers to reduce evaporation, which is useful for those with dry eyes problem.[11,12] However, there is no further study on efficacy of VCO as rewetting agent using contact lenses as its vehicle.

In this study, pure VCO was pre-soaked in daily disposable aspherical soft contact lenses for four hours before the insertion on a dry human eye randomly. The main aim of this pilot study was to evaluate the efficacy of contact lens in virgin coconut oil (VCOCL) used to relieve symptoms of dry eyes.

MATERIAL AND METHODS

Subjects

A prospective, non-randomised, double-masked, placebo-controlled, contralateral – eye comparison clinical study was carried out in Universiti Kebangsaan Malaysia. Approval was obtained prior to commencement of the study from the Institutional Ethics Committee (Universiti Kebangsaan Malaysia, UKM1.21.3/244/NN-2019-042). All subjects were volunteers among the students and staff of the Kuala Lumpur Campus. All subjects were screened from having active ocular allergy/infection, significant eye deformities (ectropion, ptosis, use of systemic medication, uncontrolled diabetes, and pregnancy or lactation), having undergone intra-ocular or extra-ocular surgery or having worn contact lenses regularly in the previous six months were excluded. All subjects were also ensured free from topical eye medication. They were asked to fill out a McMonnies questionnaire.[13] The scores ranged from 0 to 45. Fifty subjects were tested using the McMonnies Test and subjects having McMonnies score greater than 14.5 were accepted as dry eye subjects for this study. Forty-four individuals were enrolled in the study after a brief explanation on this clinical trial and a written consent for the participation in the study were filed. Six subjects were terminated as they were classified as having normal eye condition using McMonnies.

Forty-four subjects aged between 19 to 28 years old (22.39 ± 1.06 years); 10 males (23%) and 34 females (77%) were recruited to participate in this clinical trial at Optometry Clinic Kuala Lumpur Campus. The total numbers recruited were sufficient. The sample size for this study was obtained by using G Power 3.1.9.4 software.[14] The effect size was derived from a previous study with a similar background.[12] Comparing two means and their standard deviations; 3.17 ± 0.99 and 4.05 ± 1.08, the effect size was 0.85. This indicates a medium-to-large effect size, suggesting the effectiveness of one treatment compared to the other. Based on a priori power analysis, the minimum required sample size was determined to be 22 subjects per group. Since only one eye per subject is used, the total sample size was doubled to 44 eyes per group. We were able to retain a sample size of 44 eyes for each group.

Preparation and insertion of VCOCL

Forty-four pieces of daily disposable aspherical soft contact lenses were soaked in individual sterilised lens casings in 5ml of VCO for at least four hours before insertion onto the subject's cornea by another operator. Another 44 pieces of similar contact lenses were soaked in normal saline (CCL) for four hours and acted as controls. All these lenses were labelled to indicate the type of lens inserted to the right and the left eye. Two different operators were used in the preparation of the material. The second operator which handled the insertion of lenses into subjects' eyes and parameter measurements was masked.

In this clinical trial, soft daily disposable aspheric hydrogel contact lenses with a power of -1.00 DS, 58% water content, and an oxygen transmissibility (Dk/t) of 36.7 were used. The -1.00 DS lenses were selected as a standard low-power option for all subjects, as some had a Plano prescription. As vision testing was not part of the study, subjects still had to wear their spectacles for clarity, if needed. All apparatus for VCOCL preparation were sterilised and prepared in a standard lab of controlled temperature 21-23 degrees Celsius.

Subjects were fitted with a VCOCL on one eye and a conventional contact lens which acted as control (CCL) on the other, with the allocation done randomly using a simple randomisation calculator. Both the second operator and the subjects were masked throughout the clinical trial. Measurements were taken at baseline and again 15 minutes after the insertion of the VCOCL. All subjects underwent a 15-minute adaptation period to ensure they could comfortably open their eyes following the VCOCL insertion. All 44 subjects were staggered in a fixed schedule. This assessment was not done concurrently for all subjects. The whole assessment process took three weeks to complete. Each subject spent about 45 minutes at the clinic. All subjects were blinded throughout the assessment. When the entire clinical trial ended, the second operator handed over the results and analysis to the first operator for identification of intervention done.

Parameters Measured

Measurements of residual VCO volume in tears after contact lens wear

After 15 minutes of wearing the contact lens, the lenses were removed from both eyes. Tear samples were collected from the lower tear meniscus (the small pool of tears at the edge of the lower eyelid)

using a glass capillary tube. The collected tears were then dropped onto a piece of oil paper and left to dry at room temperature. Once the tears had fully evaporated, a pattern appeared on the oil paper. This pattern represented the remaining VCO in the tears. The size of the stain on the oil paper, which indicated the amount of VCO left, was measured manually in square millimeters (mm^2). The measurement was repeated three times to help standardise measurements, improving the reliability and reproducibility of results.[15]

TBUT (Tear Break-Up Time)

A 2% fluorescein strip was moistened with a drop of saline and placed in the lateral one-third of lower lid in a non-anaesthetised eye and patient was asked to blink only once or twice to avoid pooling of fluorescein, following which the strip was removed. Using the cobalt blue light of the slit lamp (Type; Haag Streit) the time lapses between the last blink and the appearance of the first randomly distributed dark spots in the fluorescein-stained tear film was the tear break-up time. Values of less than 10 seconds were considered abnormal. Three measurements were taken once sightings of dry spots appear, and the average of the three readings was recorded. The room temperature and humidity were kept constant at 23-24 degree Celsius and 50-60%, respectively.

Corneal Staining

Cornea epithelium was observed under cobalt blue light with slit lamp biomicroscope (Type; Haag Streit). The grading of corneal staining was evaluated using the Efron Grading Scale as reference, from 0 to 4, where – 0 = normal; 1 = trace; 2 = mild; 3 = moderate; 4 = severe.[16]

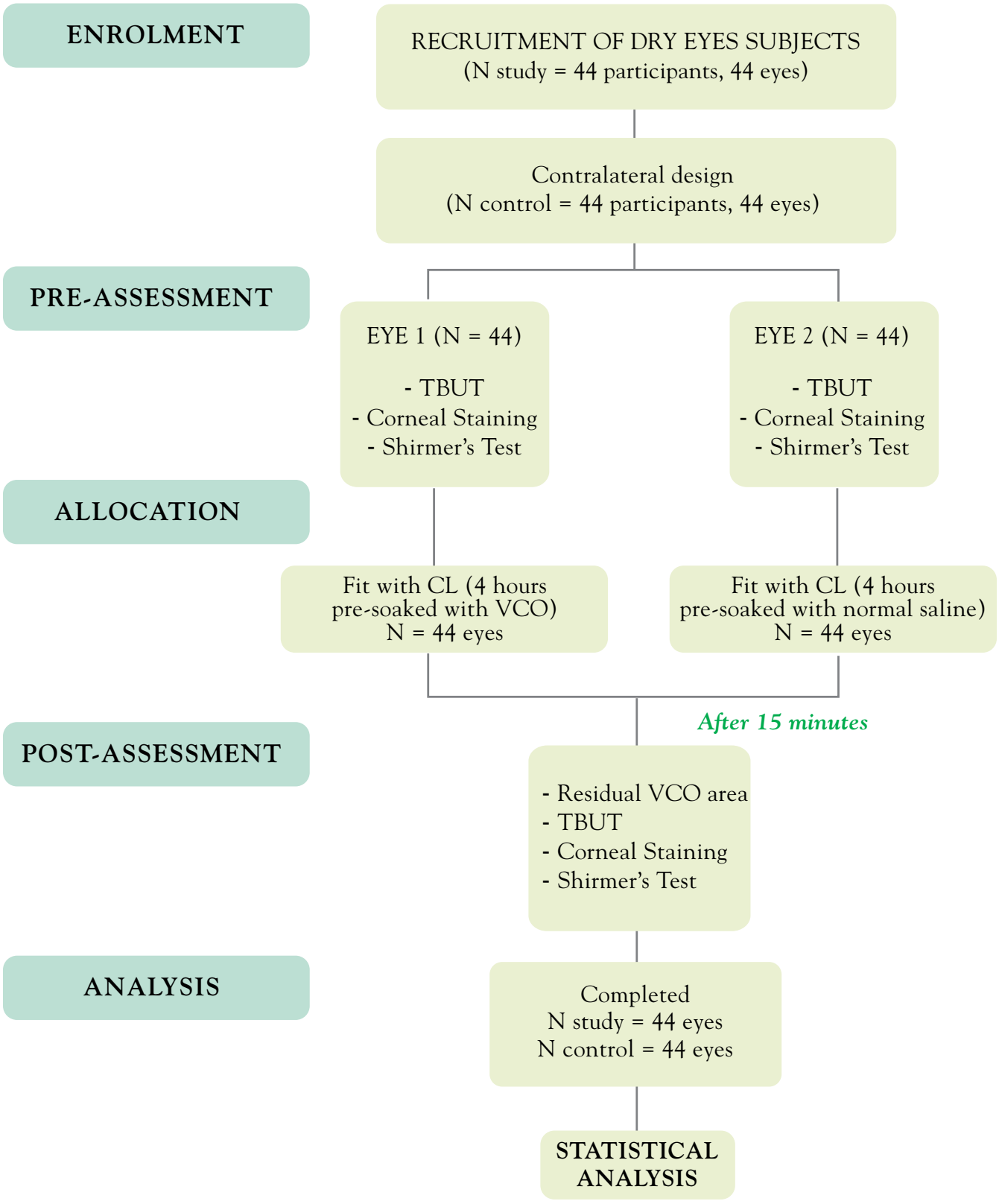
Schirmer's Test (ST)

A standard 35mm Schirmer's strip (Clement Clarke International Limited) was placed over the lateral one-third of lower lid without the instillation of topical anaesthesia. After five minutes, the level of strip wetting (in millimetres) was noted. Reading less than ten millimetres wetting was considered as positive Schirmer's test. An interval of five minutes was kept between two tests. Positive Schirmer's test was considered as Aqueous Tear Deficiency. The amount of wetness on the test paper was immediately measured against a standard scale calibrated in millimetres and recorded in two decimal values.

Statistical Analysis

These analyses were accomplished by using statistical analyses system configured for computer (SPSS 28.0). Shapiro-Wilk test was analysed to evaluate the normality of the data. A p-value of <0.05 was considered significant. However, all the collected data were not normally distributed. Therefore, non-parametric test of Wilcoxon Signed Rank and Mann Whitney U Test were carried out to analyse the data.

Figure I. Flowchart of the participants from screening to study completion.



RESULTS

The results of the TBUT, Schirmer's Test, corneal staining and residual VCO in tears were measured as shown in Table I. Wilcoxon Signed Rank Test were used to compare the value recorded at 0 and 15 minutes for all tests. In addition, Mann Whitney U test was used to compare the differences of every parameter recorded on both eyes after contact lens wear.

Table I: TBUT, Schirmer's Test, corneal staining and residual VCO volume in tears at baseline and 15 minutes after contact lens wear.

Median±IQR	Group	0 min	15 min	%	P value
TBUT (seconds)	VCO CL	3±1	6±2	100	<0.05
	CCL	3±1	4±1	10	
Schirmer's Test (mm)	VCO CL	35±5	35±8	0	0.69
	CCL	35±10	35±13	0	
Corneal Staining (Grade)	VCO CL	1±1	3±1	200	<0.05
	CCL	1±1	1±1	0	
Residual VCO volume in tears after CL wear (mm^2)	VCO CL	NA	12±10	NA	<0.05
	CCL	NA	8±13	NA	

TBUT

The baseline readings for TBUT of both eyes were similar, however, the TBUT values increased in both eyes after 15 minutes of contact lens insertion. As shown in Figure I, the increase in TBUT on VCOCL (3.3 secs) was relatively higher compared to CCL (1.43 secs). Significance difference ($p<0.05$) was observed for TBUT of both eyes.

Schirmer's Test

In this study, Schirmer's test showed no significant difference ($p>0.05$) during pre- (30.66 and 29.11 for VCOCL and CCL, respectively, and post-measurement (29.11 and 27.32 for VCOCL and CCL, respectively). Mann Whitney U test indicated no significant difference, $p>0.05$, between both lenses.

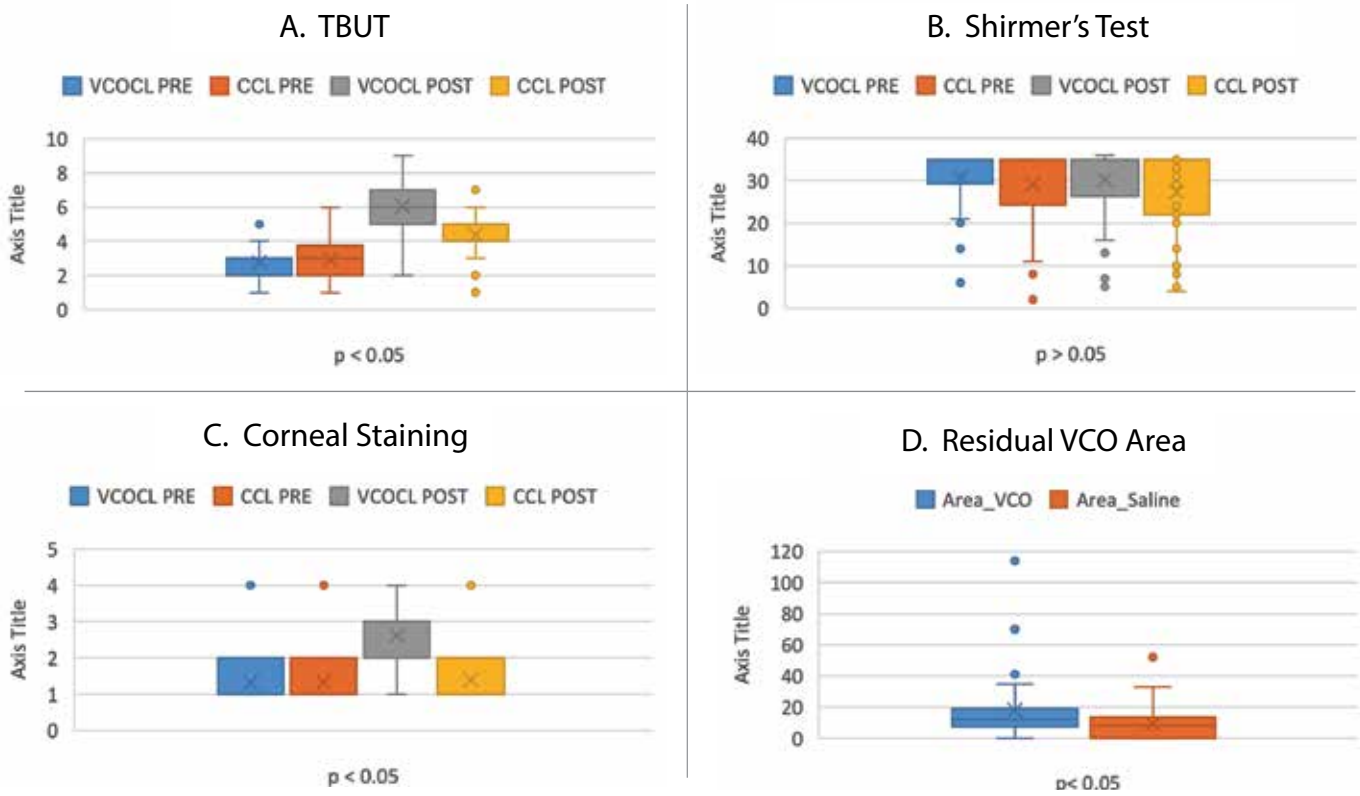
Corneal Staining

Less corneal staining was observed (1.29; $p<0.05$) before and after insertion of VCOCL, whereas no significant difference (0.07; $p>0.05$) was observed for the controlled eye.

Residual VCO area

For the measurement of residual VCO area in tears after 15 minutes of contact lens wear, the area of the VCO pattern on the oil paper of both eyes were compared and significant difference were shown, $p<0.05$. The mean was 10.48 ± 5.05 mm^2 for VCO CL whereas the area min was 5.73 ± 5.05 mm^2 for CCL. Both groups were found to be significant ($p<0.05$).

Figure II: Mean and standard deviation of eyes wearing VCOCL and CCL (A) TBUT, (B) Schirmer's Test, (C) Corneal Staining, and (D) Residual VCO area at 15 minutes compared to the baseline 0 minute.



DISCUSSION

In this study the increment in TBUT was observed due to the medium chain triglycerides (MCTs) that provides the anti-oxidant effects.[13] The VCO behaves differently as compared to animal fatty acid, which is the long chain triglycerides (LCTs) where MCTs is water soluble. This explained the effect of VCO on human tears which promoted improvement in tears quality. The VCO deposited on the CL was then transferred on the cornea surface coated with tears, where the water-soluble properties action took place slowly.

MCTs work by enhancing the lipid layer of the tear film, reducing evaporation, providing anti-inflammatory effects, and stabilising the overall tear film structure. This makes them more effective for long-term relief of dry eye symptoms, especially in cases where tear evaporation is the primary cause of discomfort.[17]

Conventional lipid-based artificial tears often use synthetic oils or longer-chain triglycerides, which may not integrate as effectively into the tear film. These oils might not spread as efficiently or may not form as stable a barrier as MCTs, resulting in less effective tear film stabilisation.

Increment of TBUT value in the control eye was lower compared to the increment in VCOCL eye. The contact lens used in the control eye was immersed in saline instead of VCO. So, this will add moist to the

eye condition but will not prevent it from rapid drying. This condition can be explained further where the insertion of contact lens causes intervention on the tear film. In 2007, silicone hydrogel contact lens was used to treat dry eye patients with chronic graft-versus-host disease. The lenses are known as therapeutic contact lens, it acts as a bandage to stabilise tear film and protect ocular surface from complication such as trichiasis and fibrotic lid change.[18] The indications of using contact lens to serve as drug delivery is well known but it is an uncommon practice as the contact lenses available in the market vary in properties and finding the ideal lens to be used as the vehicle for drugs is still unclear.[19] In this study we used a normal hydrogel lens instead of Silicone Hydrogel as previous research has shown that these lenses absorb deposits better than the Silicone Hydrogels.[20]

As expected, Schirmer's test did not show any effect as this test quantified tears measurement from the combination of reflex and basal tears. Both VCOCL and CCL eyes showed decreased in the results as shown in Figure II. However, the decrease in tear quantity in CCL eye was much more compared to the contralateral eye. The reduction of the results in post contact lens insertion in this parameter was due to the induced reflex tears during the first insertion of Schirmer strip at 0 minute. After 15 minutes wear of contact lens, the eyes were less responsive to foreign body after adaptation, thus results in the decrease in reflex tears. The VCO did not cause changes to tear quantity as MCTs act as internal phase in lipid layers in the tear film to link the drug in ophthalmic emulsion to stabilise the tear film.[17]

The TBUT test is primarily used to evaluate the quality and stability of the tear film, which helps in identifying issues like meibomian gland dysfunction or problems with the lipid layer. On the other hand, Schirmer's Test measures the quantity of tears produced, making it effective in diagnosing conditions that cause tear production deficiencies, such as Sjogren's syndrome. Both tests provide complementary insights into different aspects of tear film function – TBUT for stability and Schirmer's Test for tear volume.

In Figure II, no significant difference in corneal staining was observed in the CCL eye before and after insertion. However, the corneal staining in subjects wearing the VCOCL was more pronounced, likely due to the high viscosity of the VCO.[21] The corneal staining results from the 44 subjects ranged from Grade 0 to Grade 3, indicating none to moderate staining according to the Efron grading scale. This corneal staining is a temporary clinical sign that gradually fades as the VCO is naturally drained from the tear film through the nasolacrimal duct.

In this study, we introduced a new technique to measure residual VCO in tears by using a glass capillary tube to extract tears from the tear prism, representing the amount of VCO in the tear film after lens insertion. This procedure was conducted 15 minutes after contact lens wear. The results revealed a significant difference in the surface area of the VCO pattern on oil paper between the tear samples collected from both eyes. This conventional method proved to be simpler and faster for determining the residual VCO in the tear samples. The findings indicated that VCO remained in the tear layer, and after 15 minutes, the volume of VCO, reflected by the size of the stained area, was significantly greater in the VCOCL eye compared to the CCL eye.

For future studies, a better and more accurate method to measure tear quantity and/or improvisation on tear sample collection can be applied. Since the Schirmer test values remained unchanged, indicating that further research is necessary to understand the full impact of VCO on tear production. Besides that, the duration of the study should be extended to know the period of VCO presence. This study provides a new insight of how the dry eyes subjects can benefit from VCO, and how contact lenses can be used as a vehicle to retain the effect of VCO in the eye.

Dry eye symptoms are a relatively common ophthalmic disease that can manifest in various degrees of severity and can be caused by many factors. While not life threatening, patients may often have to continuously endure discomfort or even pain, which puts a damper in their quality of life. Given the multitude of conditions which Dry Eye Syndrome can originate from, a variety of treatment options is critical to ensure inclusivity and effectiveness.[22]

CONCLUSION

The eye wearing the VCOCL showed a significant increase in TBUT after lens insertion. The greater amount of residual oil in the tears 15 minutes after insertion demonstrated that the contact lens absorbed the VCO and helped retain it in the tear film, thereby reducing tear evaporation and maintaining moisture in the eye. The staining revealed that the new oil layer formed a protective coating over the corneal surface. These findings suggest that VCOCL is safe for use in human dry eyes and offers prolonged effects compared to regular eye drops. Further research could explore its potential as an effective alternative treatment for dry eye symptoms.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Clinical Trial Registration Number NCT06071780
https://register.clinicaltrials.gov/

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