Article published online: 2025-10-31

Original Article

Physiological Responses to Relative Hypoglycemia in Uncontrolled Type 2 Diabetes Mellitus: A Pilot Study

A. Wahab Norasyikin[1] Nur Hazurreen Harryzan[1] Ching Soong Khoo[1] Shamsul Azhar Shah[2]

[1] Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur, Malaysia
[2] Department of Community Health, Faculty of Medicine, Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur, Malaysia

Address for correspondence Norasyikin A. Wahab, MMED (UKM), Department of Medicine, Hospital Canselor Tuanku Muhriz, Jalan Yaacob Latif, 56000 Cheras, Kuala Lumpur, Malaysia (e-mail: Naw8282kt@gmail.com).

J Diabetes Endocrine Practice

Abstract

Objective To evaluate the hormonal, cardiac, and neuronal responses during relative hypoglycemia in uncontrolled type 2 diabetes mellitus patients.

Methods Fifteen uncontrolled type 2 diabetes mellitus patients underwent insulin infusion at 0.05 U/kg/h, titrated at 1 U/h every 10 minutes, until they developed symptoms of hypoglycemia with a glucose level >3.9 mmol/L. Blood samples for glucose, cortisol, glucagon, and epinephrine, as well as electrocardiogram and electroencephalogram readings, were taken before insulin infusion and repeated once hypoglycemic symptoms developed. Data were analyzed using paired *t*-tests and Wilcoxon signed-rank tests. The *p*-value of <0.05 was considered significant.

Results The median glucose level during relative hypoglycemia was 6.7 (4.3–7.3) mmol/L, and 86.7% of patients experienced autonomic symptoms. The mean glucagon level was significantly higher at baseline than during relative hypoglycemia (4,842.93 vs. 4,300.13 pg/mL, $p = 0.041$). During relative hypoglycemia, 66.7 and 60% of patients had declined glucagon and cortisol levels, respectively. Meanwhile, 53.3% of patients experienced an increase in epinephrine levels. There was no significant change in cortisol and epinephrine levels during relative hypoglycemia compared to baseline. The electroencephalogram showed generalized background attenuation in eight patients, and none had electrocardiogram changes.

Conclusion This study demonstrates that relative hypoglycemia, in uncontrolled type 2 diabetes mellitus, only leads to autonomic symptoms without significant counter-regulatory hormonal, cardiovascular, and neurological changes. Clinically, recognizing relative hypoglycemia is crucial to avoid misinterpreting it as true hypoglycemia and to highlight its potential role in causing impaired patient awareness of subsequent true hypoglycemic episodes. The small sample size and potential confounding factors warrant cautious interpretation, and larger studies are needed to confirm these findings and to develop strategies for monitoring and managing relative hypoglycemia in clinical practice.

Keywords
► relative hypoglycemia
► type 2 diabetes mellitus
► cortisol
► glucagon
► epinephrine
► electroencephalogram

DOI https://doi.org/10.1055/s-0045-1812065.
ISSN 2772-7653.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Hypoglycemia is a common and potentially serious complication of diabetes management. The incidence of hypoglycemic episodes in people with type 2 diabetes mellitus (T2D) ranges from 2.2 to 3.7 events per month, and 46.5% T2D patients experience recurrent episodes.[1] Traditionally, hypoglycemia is defined based on Whipple's triad: typical hypoglycemic symptoms, plasma glucose level <3.9 mmol/L, and symptoms resolved following glucose normalization.[2] In response to hypoglycemia, counter-regulatory hormones (glucagon, epinephrine, and cortisol) act to restore euglycemia via gluconeogenesis and glycogenolysis.[3–7] The severity of hypoglycemia is classified into three levels. Level 1 is defined as plasma glucose below 3.9 mmol/L but remains ≥ 3.0 mmol/L, a threshold that normally triggers neuroendocrine responses. In diabetes, this level is considered clinically significant regardless of symptoms. Level 2 is characterized by glucose <3.0 mmol/L, with neuroglycopenic symptoms becoming more pronounced and requiring immediate correction. Level 3 represents severe hypoglycemia, defined not by a specific glucose value but by altered mental or physical function necessitating assistance from another person to restore normoglycemia.[8]

Symptoms of hypoglycemia include autonomic symptoms (trembling, palpitations, sweating, anxiety, or hunger) and neuroglycopenic symptoms (difficulty concentrating, confusion, weakness or stroke-like symptoms, drowsiness, or headache).[2]

Hypoglycemia significantly affects both the brain and cardiovascular system. Recurrent hypoglycemia is associated with cognitive decline and increased risk of dementia, likely due to neuronal injury in glucose-sensitive brain regions such as the cortex and hippocampus.[9,10] Electroencephalogram (EEG) studies show reduced frequency and increased amplitude of brain activity when blood glucose levels drop below 3.5 mmol/L.[11]

Cardiovascular effects, including systemic inflammation, endothelial dysfunction, abnormalities in coagulation and fibrinolysis, arrhythmias, electrocardiographic (ECG) abnormalities such as QT interval (QTc) prolongation, ST-segment depression, and T-wave flattening, are primarily driven by catecholamine surges.[12–16] Interestingly, certain patients with poorly controlled diabetes experience classical hypoglycemic symptoms despite normal glucose levels (≥ 3.9 mmol/L). This phenomenon is known as relative hypoglycemia or pseudohypoglycemia.[17] Despite its clinical relevance, the physiological impact of relative hypoglycemia remains poorly understood. To date, no published studies have comprehensively examined the hormonal, neurological, and cardiovascular responses associated with relative hypoglycemia in this population.

Therefore, this study aimed to assess changes in cortisol, glucagon, and epinephrine levels, as well as alterations in EEG and ECG at baseline and during episodes of relative hypoglycemia in patients with uncontrolled T2D.

Method

This was a cross-sectional pilot study done from July 2020 to June 2021. Patients were recruited from the endocrine clinic, Hospital Canselor Tuanku Muhriz (HCTM). The patient selection was based on purposive sampling with no control group included. The study was approved by the Research Ethics Committee of Universiti Kebangsaan Malaysia and funded through a fundamental grant (research code: FF-2020-360). Informed written consent was obtained from patients who experienced relative hypoglycemia. This is defined as individuals having had at least two episodes of hypoglycemic symptoms (such as giddiness, tremor, sweating, palpitation, hunger, nausea, tingling, weakness, vision changes, headache, confusion, drowsiness, and difficulty speaking and concentrating) with a documented blood glucose level >3.9 mmol/L and the symptoms resolved after taking a meal. The study was conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and complied with the Declaration of Helsinki of 1964 and its subsequent amendments. Fifteen uncontrolled T2D patients (HbA1c level greater than 8%), aged between 18 and 60 years, were recruited. None of the patients has ischemic heart disease, epilepsy, chronic kidney disease with eGFR <60 mL/min/1.73 m^2, a history of documented hypoglycemia (blood glucose <3.9 mmol/L), or is on prolonged steroid or traditional medications.

Procedure

The procedure was performed at the endocrine laboratory, HCTM, which is equipped with emergency facilities and has medical personnel present throughout the procedure. All patients had fasted overnight (for at least 8 hours) and the morning dose of the antidiabetic medications was omitted (►**Fig. 1**). Each patient was assessed for hypoglycemic symptoms before the procedure using a hypoglycemia symptom checklist. Two cannulas, sized 22G and 20G, were inserted at the left and right antecubital fossa for insulin infusion and blood taking, respectively. A three-way stop cock was connected to the left cannula for insulin administration as an emergency measure if the patient's blood glucose dropped to <3.9 mmol/L. Ten mL of blood was withdrawn from the right cannula for baseline blood glucose, cortisol, glucagon, and epinephrine levels. The echocardiogram (ECHO), ECG, and EEG were done at baseline. The ECG and EEG leads were attached to the patient throughout the procedure. Short-acting insulin (Actrapid) was infused intravenously at 0.05 U/kg/h, and the dose was titrated by 1 U/kg/h every 10 minutes. The glucose level was monitored every 5 minutes using an Accu-Chek glucometer. Insulin infusion was stopped once the patient developed symptoms of hypoglycemia, and blood was drawn to determine the glucose level. If the glucose level was >3.9 mmol/L, all procedures, including blood taking, ECG, and EEG, were repeated. Oral glucose was administered as needed to reverse the symptoms, and the glucose level was monitored every 10 minutes for a total of

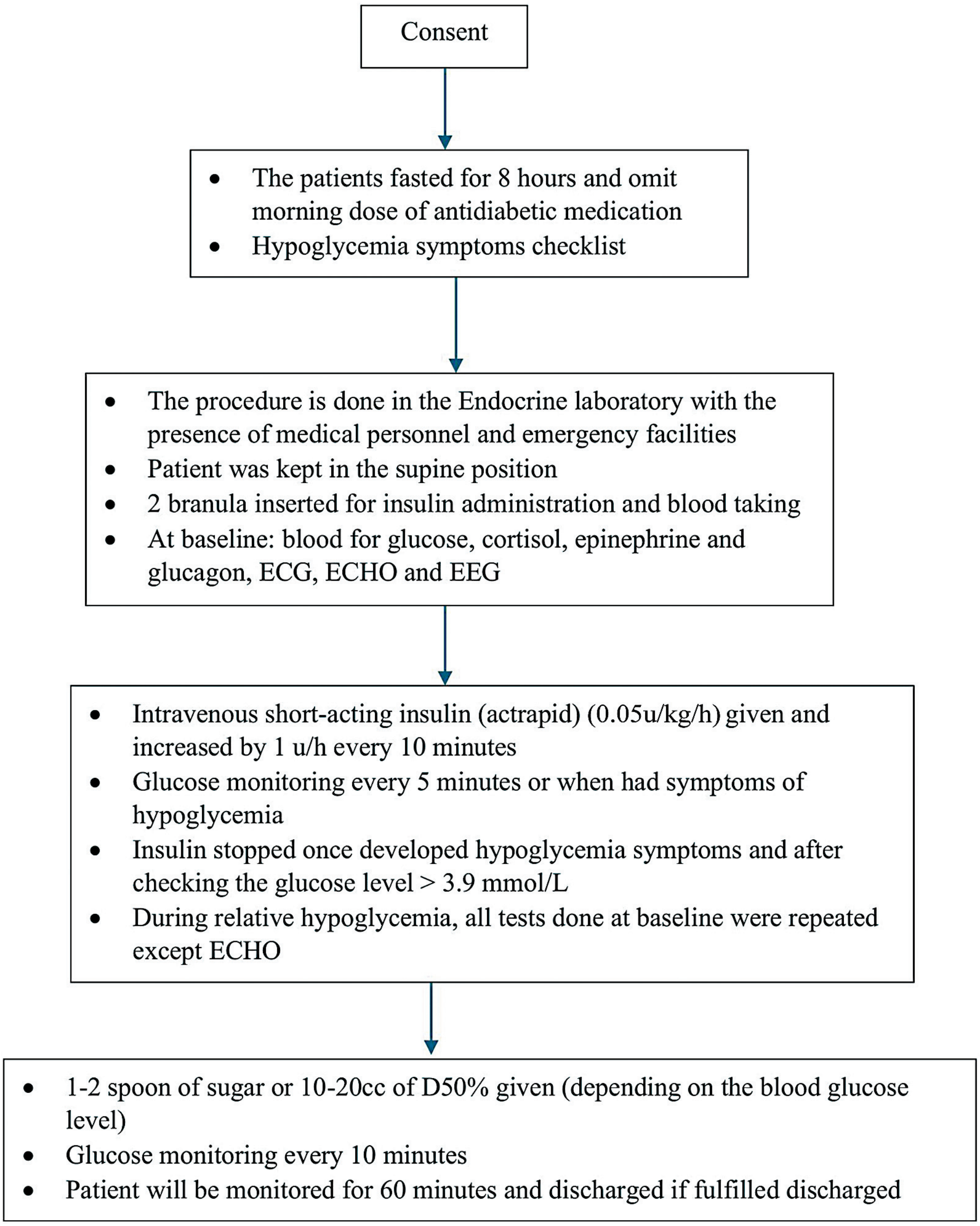

Fig. 1 Flow chart of the study procedure.

60 minutes. The patient was kept in the laboratory for monitoring until they became entirely asymptomatic and fulfilled the safe discharge criterion checklist.

The ECG was analyzed for heart rate, ST depression, T-wave inversion, ectopic beats, and QT interval. The EEG was monitored throughout the procedure and analyzed by a certified neurologist to detect any changes in amplitude, frequency, the presence of delta and theta wave activities, or attenuation of EEG waves.

Cortisol Assay

Serum cortisol assay was taken and centrifuged for 10 minutes at 3,000 rpm using commercially available chemiluminescent microparticle immunoassay with ARCHITECT Cortisol assay (detection range: 27.59–1,650 nmol/L, with a limit of detection of less than 22.07 nmol/L).

Glucagon and Epinephrine Assay

Serum glucagon and epinephrine were taken and centrifuged for 15 minutes at 2,000 rpm. The sera were processed using an ELISA Kit from Elabscience (Catalogue No: E-EL-0045/E-EL-H2237). The ELISA Kit employs the competitive ELISA principle, with a sensitivity value of 18.75 pg/mL and a detection range of 31.25 to 2,000 pg/mL for both glucagon and epinephrine. All samples were assayed in the same batch analysis to avoid inter-assay variation.

Statistical Analysis

The sample size was calculated using a power and sample size calculation. Data were analyzed using the Statistical Software Product and Services (SPSS) version 26.0. Normally distributed data were expressed as mean ± standard deviation, while nonnormally distributed numerical data were expressed as median ± interquartile range. The analysis of the association between numerical and categorical data was performed using a paired *t*-test and a Wilcoxon signed-rank test, depending on sample distribution. The *p*-value of <0.05 was considered significant.

Results

A total of 15 uncontrolled T2D patients were recruited, with a mean age of 47.27 ± 9.59 years, ranging from 31 to 59 years old. The median duration of T2D was 5 years (range, 3 years). The mean HbA1c and fasting glucose levels were 10.4 ± 1.4% and 11.25 ± 3.58 mmol/L, respectively. The median glucose level during relative hypoglycemia was 6.70 (4.5–7.3) mmol/L. Other demographic data are shown in ►**Table 1**. During relative hypoglycemia, 86.7% (13) of patients had autonomic symptoms, mainly experiencing hunger, palpitations, and sweating. Only 13.3% (2) of patients had both autonomic and neuroglycopenic symptoms, namely, giddiness (►**Fig. 2**).

The mean glucagon level was significantly higher at baseline compared to relative hypoglycemia (4,842.93 vs. 4,300.13 pg/mL, $p = 0.041$). Approximately 66.7% (10) of patients experienced a decrement in glucagon levels during relative hypoglycemia. Approximately 53.3% (8) of patients experienced an increase in epinephrine levels during relative hypoglycemia, while 46.7% (7) of patients had a decrease in epinephrine levels. During relative hypoglycemia, 60% (9) had a reduced cortisol level, 33.3% (5) had an increment, and only 6.7% (1) of patients had no difference (►**Fig. 3**). However, the difference in epinephrine and cortisol levels between baseline and during relative hypoglycemia was statistically not significant, as shown in ►**Fig. 3**.

The baseline EEG showed symmetrical and reactive posterior dominant alpha rhythm, ranging from 8 to 12 cycles per second in all 15 patients. Approximately 53.3% (8) had generalized attenuation in the EEG background during relative hypoglycemia. There was no generalized or focal slowing of the brain activity during relative hypoglycemia. There was no significant difference between EEG changes with cortisol

Table 1 Demographic and biochemical data of the study population

Parameter	Mean ± SD
Age (year)	47.27 ± 9.59
Weight (kg)	76.67 ± 12.19
BMI (kg/m^2)	30.2 ± 4.29
Medications: (*n*, %)	
Insulin	2 (13.3%)
OHA	5 (33.3%)
Insulin and OHA	8 (53.3%)
OHA (*n*, %)	
Biguanide (metformin)	13 (86.7%)
SGLT2 inhibitor (dapagliflozin)	5 (33.3%)
Sulphonylureas (gliclazide)	2 (13.3%)
DPP4 inhibitor (vildagliptin)	2 (13.3%)
Insulin (*n*, %)	
Human insulin	11 (73.3%)
Glargine	4 (26.7%)
Premixed Ryzodeg	1 (6.7%)
ECG	Sinus rhythm
ECHO	Ejection fraction more than 60% with no regional wall motion hypokinesia
Pre-insulin infusion	
Blood glucose at baseline (mmol/L)	9.69 ± 2.25
Post- insulin infusion	
Blood glucose during relative hypoglycemia (mmol/L)	6.70 (4.5–7.3)[a]

Abbreviations: BMI, body mass index; DPP4 inhibitor, dipeptidyl peptidase 4 inhibitor; ECG, electrocardiogram; ECHO, echocardiogram; OHA, oral hypoglycemic agent; SD, standard deviation; SGLT2 inhibitor, sodium-glucose transport protein 2 inhibitor.
[a]All values are expressed in mean ± SD, except blood glucose during relative hypoglycemia, expressed in median (IQR).

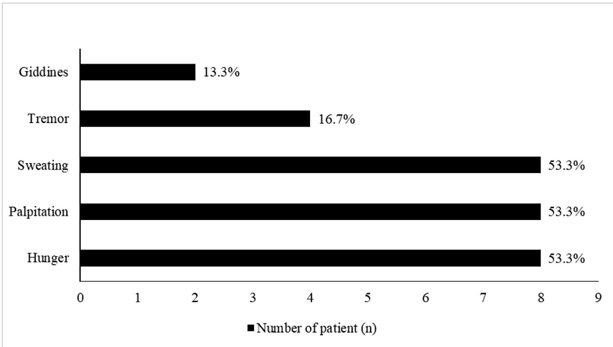

Fig. 2 Autonomic and neuroglycopenic symptoms during relative hypoglycemia.

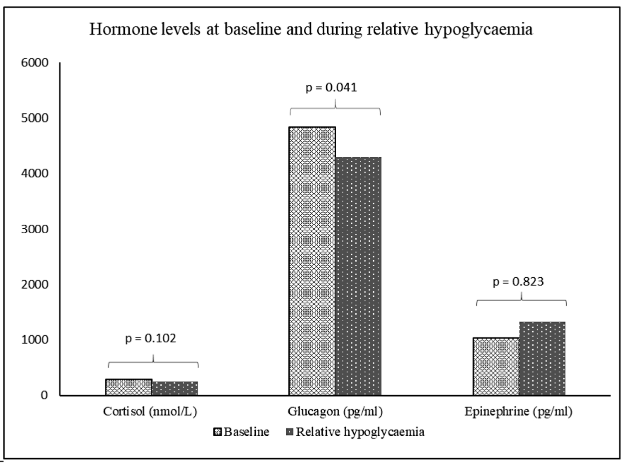

Fig. 3 Hormone levels at baseline and during relative hypoglycemia.

($p = 0.556$), glucagon ($p = 0.645$), and adrenaline ($p = 0.406$) levels. All baseline ECGs demonstrated a sinus rhythm with no ST changes. Similarly, during relative hypoglycemia, none of them had ST depression, T wave inversion, prolonged QT interval, or arrhythmias.

Discussion

Relative hypoglycemia is a diabetes complication where the threshold for detecting and responding to low blood sugar levels is higher than normal. Under normal conditions, the response occurs when blood sugar drops to 3.9 mmol/L or below. The initial response involves the rapid secretion of glucagon and epinephrine, followed by cortisol to restore circulating glucose levels.[3,4,18] Activation of the sympathoadrenal system causes both adrenergic and cholinergic symptoms as well as neuroglycopenic symptoms once glucose supply to the brain is reduced.[18] The median glucose level when patients developed autonomic and neuroglycopenic symptoms of hypoglycemia was 6.7 mmol/L. This explains why our T2D patients are poorly controlled because they are reluctant to have tighter glycemic control as a result of their perceived hypoglycemic symptoms.

Lund demonstrated that in T2D patients, fasting and basal glucagon levels were elevated and failed to be suppressed upon ingestion of nutrients.[19] Hyperglucagonemia occurs due to insulin resistance and the diminished suppressive effect of insulin on the alpha cells in the pancreas, resulting in hypersensitivity to glucagon secretion and leading to hyperglycemia.[3] Boden et al also observed that basal glucagon concentrations were higher in patients with T2D than in controls.[20] All our patients had a high baseline glucagon level compared to levels during the episodes of relative hypoglycemia. We observed a reduction in glucagon levels during relative hypoglycemia, likely due to the exogenous insulin infusion, as physiological insulin would inhibit glucagon release.[21] This finding was not observed in definite hypoglycemia because the glucagon level would be elevated once glucose levels drop to less than 3.9 mmol/L.[3,19]

Our study showed that 53.3% of our patients experienced an increase in epinephrine levels during relative hypoglycemia compared to their baseline levels. This finding was consistent with previous studies that showed an early release of epinephrine in hypoglycemia compared to other hormones.[3,4,22] Schwartz et al demonstrated that activation of epinephrine secretion in hypoglycemia occurred at a glucose level of 69 ± 2 mg/dL (3.45 mmol/L), which is higher than the glucose level needed to secrete glucagon (68 ± 2 mg/dL [3.4 mmol/L]) and cortisol (58 ± 3 mg/dL [2.9 mmol/L]).[3] A study by Mitrakou et al showed that the secretion of glucagon and epinephrine occurred at higher plasma glucose levels between 72 and 80 mg/dL (3.6–4.0 mmol/L).[4] Amiel et al observed that epinephrine release occurred at a glucose level of 3.15 mmol/L, which is higher than the levels of glucagon and cortisol at 2.75 mmol/L.[22] In our study, the stress and anxiety during the procedure could be the confounding factors for the increment of epinephrine levels during relative hypoglycemia.

Our study also showed normal cortisol levels at baseline in all patients, and 60% had cortisol decrement during relative hypoglycemia. Tesfaye and Seaquist showed that the cortisol secretion occurs approximately at a glucose level of 3.2 mmol/L.[23] However, studies by Amiel et al and Mitrakou et al demonstrated that the activation of serum cortisol occurs at lower glucose rates, 53 ± 2 mg/dL (2.65 mmol/L) and 55 ± 2 mg/dL (2.75 mmol/L), respectively.[4,24] These findings were consistent with our study, in which cortisol release needs a lower glucose level to activate the adrenocorticotropic hormone secretion.

A previous study found that EEG signals began to appear at a glucose level of 3.3 mmol/L, characterized by a slow rhythm and a reduction in frequency, accompanied by diffuse theta and delta activities.[25] Pramming et al reported that no EEG changes would occur at blood glucose levels >3 mmol/L, but increased theta activity was observed when blood glucose levels were at 2.0 mmol/L.[26] In our study, 53% (8) of patients had generalized attenuation of EEG background during relative hypoglycemia, and five of them had a concomitant increment in epinephrine. The background attenuation of EEG is defined as background activity consisting of amplitudes less than 20 microvolts. This can be a nonspecific and low-amplitude EEG that can happen in an anxiety state.[27] None of our patients had diffuse or focal slowing in the EEG.

In our study, those with background attenuation with concomitant elevated epinephrine levels were likely due to anxiety during the procedure rather than relative hypoglycemia. A previous study had shown that up to 9% of patients with anxiety states may have low voltage in their EEG.[28] None of our patients experienced any cardiac symptoms or ECG changes during relative hypoglycemia, in which sympathoadrenal counter-regulation was not activated; hence, there was no significant deleterious effect on the heart. Since this is only a pilot study, a multi-center, larger-scale study is required to elucidate the counterregulatory changes in relative hypoglycemia.

Conclusion

Our study showed that relative hypoglycemia only causes autonomic symptoms, without significant changes in the counterregulatory hormones and cardiovascular or neurological systems. The novelty of our study, albeit a pilot one, lies in examining the true changes that occur during relative hypoglycemia in T2D patients. Our study findings will provide a foundation for future research involving a larger cohort to explore the short- and long-term effects of relative hypoglycemia on hormonal, cardiovascular, and neurogenic responses. Hence, there is a need to develop strategies for monitoring and managing relative hypoglycemia in clinical practice.

Author Contribution

N.A.W.: conceptualization, formal analysis, funding acquisition, investigation, methodology, data curation, analysis, resources, supervision, and writing—review and editing. N.H.H.: data curation, formal analysis, investigation, methodology, and writing—original draft. C.S.K.: conceptualization, methodology, analysis, supervision, and writing—review and editing. S.A.S.: conceptualization, data curation, analysis, methodology, and writing—review and editing.

Compliance with Ethical Principles

The study was approved by the Research Ethics Committee Universiti Kebangsaan Malaysia (FF-2020-360). Written informed consent was obtained from all participants prior to the study.

Ethical Approval

Research Ethics Committee Universiti Kebangsaan Malaysia.

Funding

Fundamental grant: Universiti Kebangsaan Malaysia (FF-2020-360).

Conflict of Interest

None declared.

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