GLYCAEMIC CHANGES FROM CONTINUOUS GLUCOSE MONITORING AMONG CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES BEFORE AND DURING FASTING MONTH IN RAMADAN

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LIST OF ABBREVIATION AND NOMENCLATURE

HUSM	: Hospital Universiti Sains Malaysia
HPJ	: Hospital Putrajaya
CV	: Coefficient variant
CGMS	: Continuous glucose monitoring system
T1DM	: Type 1 Diabetes Mellitus
MARD	: Mean absolute relative difference
MDI	: Multiple daily injection
SMBG	: Self-monitoring blood glucose
SG	: Sensor glucose
ISPAD	: International Society of Paediatric and Adolescent Diabetes
GV	: Glycaemic variability
MAGE	: Mean amplitude glycaemic excursions
HBGI	: High blood glucose level
AUC	: Area under the curve
LBGI	: Low blood glucose level

ABSTRAK

PERUBAHAN GLISEMIK DARIPADA PEMANTAUAN GLUKOSA BERTERUSAN DALAM KALANGAN KANAK-KANAK DAN REMAJA YANG MENGHIDAPI DIABETES JENIS 1 SEBELUM DAN SEMASA PUASA DI BULAN RAMADAN.

Objektif: Kajian adalah bertujuan untuk melihat perubahan dan membuat perbandingan antara parameter paras gula sebelum dan semasa Ramadan menggunakan pemantauan glukosa berterusan di dua buah hospital. Selain itu, kajian juga bertujuan mengkaji perubahan paras gula semasa berpuasa dan selepas berbuka puasa serta membuat perbandingan data pemantauan glukosa berterusan antara kanak-kanak yang mempunyai paras gula yang terkawal dan tidak terkawal.

Kaedah: Sebanyak 24 pesakit (12 perempuan) dipilih diantara umur purata mereka 13.6±3.1, HbAlc 9.6±1.9% dan tempoh sakit 5.4±3.4 tahun. 91.7% pesakit menggunakan rawatan pelbagai suntikan harian (MDI) dan 8.3% mengunakan infusi insulin subkutaneus berterusan (CSII). Semua telah berpuasa tanpa komplikasi. Analisis pemantauan glukosa berterusan menunjukkan tiada perubahan semasa dalam hiperglisemia, semasa dalam hipoglisemia, dan semasa dalam julat (TIR) untuk kedua-dua tempoh sebelum dan semasa berpuasa Ramadan. Kepelbagaian pada perubahan paras gula seperti yang ditunjukkan oleh LBGI, HBGI, dan MAGE adalah serupa.

Keputusan: Sebanyak 24 pesakit (12 perempuan) dipilih di antara umur purata mereka 13.6±3.1, HbAlc 9.6±1.9% dan tempoh sakit 5.4±3.4 tahun. 91.7% pesakit menggunakan rawatan pelbagai suntikan harian (MDI) dan 8.3% menggunakan infusi insulin subkutaneus berterusan (CSII). Semua telah berpuasa tanpa komplikasi. Analisis pemantauan glukosa berterusan menunjukkan tiada perubahan semasa dalam hiperglisemia, semasa dalam hipoglisemia, dan semasa dalam julat (TIR) untuk kedua-dua tempoh sebelum dan semasa berpuasa Ramadan. Kepelbagaian pada perubahan paras gula seperti yang ditunjukkan oleh LBGI, HBGI, dan MAGE adalah serupa.

Kesimpulan: Kanak-kanak dan remaja T1DM boleh berpuasa dengan selamat pada bulan Ramadan, dengan syarat mereka diberi pendidikan fokus Ramadan dan patuh kepada SMBG. Puasa Ramadan, dengan sendirinya, tidak dikaitkan dengan kemerosotan paras gula dalam jangka masa yang singkat.

Kata Kunci: Diabetes Mellitus Jenis 1, T1DM, Ramadan

ABSTRACT

GLYCAEMIC CHANGES FROM CONTINUOUS GLUCOSE MONITORING AMONG CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES BEFORE AND DURING FASTING MONTH IN RAMADAN

Objective: We aimed to observe the changes and compare the glycemic parameters using CGMS before and during Ramadan using from 2 centers, and also to study glycemic variability during fasting and after breaking fast and to compare CGMS data from children with good and poor glycemic control.

Method: This study was conducted in 2 tertiary centers: Hospital Putrajaya (HPJ) and Hospital Universiti Sains Malaysia (HUSM) from February to May 2020. Muslim T1DM patients between ages 8 to18, who expressed intention to fast were recruited and given Ramadan focused education. Self-monitoring of blood glucose (SMBG) and retrospective CGMS by iPro2® (Medtronic) was used to assess the glycaemic changes.

Results: A total of 24 patients (12 female) were included with their mean age 13.6±3.1, HbAlc 9.6±1.9% and duration of illness 5.4±3.4 years. 91.7% were on multiple daily injections (MDI) and 8.3% on continuous subcutaneous insulin infusion (CSII). All had fasted without complications. CGMS analysis showed no changes in time in hyperglycaemia, time in hypoglycaemia, and time in range (TIR) for both periods before and during Ramadan fasting. Glycaemic variability as reflected by LBGI, HBGI, and MAGE, were also similar.

Conclusion: T1DM children and adolescents could fast safely in Ramadan, provided they are given focused education and compliant to SMBG. Ramadan fasting, in itself, is not associated with short-term glycaemic deterioration.

Keywords: Type 1 Diabetes Mellitus, T1DM, CGMS, Ramadan,

CHAPTER II

THE TEXT

2.1 Section A:

Introduction

Introduction

Fasting from early dawn (*Sahur*) until sunset (*Iftar*) during Ramadan, the 9th month in Muslim Calendar, is one of the major five pillars of Islam and is compulsory for all healthy adult Muslims, as well as children and adolescents from the time of puberty [1]. Depending on the geographical regions and time difference of sunrise and sunset, the duration of daylight fasting could differ from as short as 11 hours to as long as 20 hours per day. This long hour of enduring practice has raised concerns in particularly among the type 1 diabetes mellitus (T1DM) patients who are on insulin. T1DM has been reportedly to be associated with higher risk of developing acute metabolic complications such as hypoglycaemia, hyperglycaemia, diabetic ketoacidosis, dehydration and thrombosis while observing fasting in Ramadan month[2–4]. Exemption has been stated and provided by religious authorities for people with serious medical conditions including diabetes (*The Quran. 2:183-5*)[2]. Despite exemption, however, most Muslims including those children and adolescents with T1DM has been observed to be persistent on Ramadan fasting.

In 2001, the Epidemiology of Diabetes and Ramadan (EPIDIAR) study, which had included 12,243 Muslim diabetes patients living across 13 countries, reported that 42.8% of patients with type 1 diabetes mellitus (T1DM) and 78.7% of those with type 2 diabetes mellitus (T2DM) had fasted for at least 15 days during Ramadan[5]. This was followed by CREED study[4] in 2010, which included 3394 patients in 4 different regions, namely Middle East, Asia, North Africa and Europe with T2DM cohort of 3250 patients, had similarly reported 94.2% of patients with T2DM had fasted for at least 15 days and up to 63.6% of them fasted every day [6]. Both these studies, however, only included diabetes patients more than 18 years old. More recently, the DaR Global survey published by International Diabetes

Federation (IDF) in December 2020[7], had reported that among the 370 interviewed T1DM patients younger than 18 years old, across 13 major Islamic countries including Malaysia, 75% of them had been reported to be observing fasting in the Ramadan month for the mean days of 22 days[7]. Among those fasted, their mean HbA1c was reported to be at 9.5 ± 2.00% with 55.6% of them reported having at least once daytime hypoglycaemia[7]. Only 71.2% of them had conducted regular SMBG during Ramadan month and 50.7% had received Ramadan focused education[7]. Another recent perspective survey by the Arabic Society of Paediatric Endocrinology and Diabetes (ASPED) had also reported that almost 80% of the physicians looking after children and adolescents with diabetes would allow their patients to fast if they had wished to, provided they had reasonable glycaemic control, good hypoglycaemia awareness and were willing to frequently monitor their blood glucose levels during the fasting[8].

In line with above, the International Society of Paediatric and Adolescent Diabetes (ISPAD) has also recently published their consensus guidelines for Ramadan month[9] stating that Muslim children and adolescent with diabetes (T1DM) could observe fasting during Ramadan month, provided they have fulfilled the criteria of reasonable glycaemic control, good hypoglycaemic awareness and willing to frequently monitor their blood glucose [10]. Instead of discouraging and preventing these paediatric T1DM patients from their religious decision, effort and direction have been shifted and focused to educate and empower them on safer fasting during Ramadan month. Similarly, the latest guidelines recently published by the International Diabetes Federation-Diabetes and Ramadan group (IDF-DAR) in year 2021[4], even though listing T1DM as being one of the risk criteria, have incorporated other important predictive aspects, such as presence of hypoglycaemia with or without awareness, level of glycaemic control, frequency of SMBG, presence of complications, pregnancy,

cognitive function, physical labour, duration of fasting hours, previous Ramadan experience before stratifying them into low, moderate or high risk categories[4]. Of note, being young children or adolescents is not one of the implicated risk factors. These practical guidelines have received support and endorsement from the Egyptian Official Fatwa Authority[4] dated on January 11, 2021, indicating only that diabetes at highest risk (> 6 points) are advised against fasting in Ramadan month, whereas those at moderate risk (3.5-6 points) are preferred to fasting in Ramadan but have to follow medical recommendations with regards to glucose monitoring and medications modifications[4]. Patients, however, still have the right not to fast, if they were concerned about their safety or wellbeing[4].

Malaysia, being one of the main Islamic Country in the Southeast Asia region with more than 60% of its multi-ethnic population composed of Muslims have similarly demonstrated the above trend in Ramadan month[31]. Many or rather most of the Muslim T1DM children and adolescents have been observed to be participating in Ramadan fasting, despite some have been advised against fasting by the health care providers, due to their higher risks. This observation could be possibly related to personal religious obligation and spiritual need, as well as local socio-cultural inclination. Acknowledging the need of these Muslim children and adolescents with T1DM, aimed to observe the changes and compare the glycemic parameters using CGMs before and during Ramadan using from 2 centres, and also to study glycemic variability during fasting and after breaking fast and to compare CGMS data from children with good and poor glycaemic control.

2.1 Section B

Study protocol

2.2.1 Documents submitted for ethical approval

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Research title:
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1.0 Introduction

This is a collaborative study in between 2 tertiary hospitals equipped with the sub-specialty of paediatric endocrinology, namely Hospital Putrajaya (HPJ) and Hospital University Sains Malaysia (HUSM). This study involves the principal investigator, the trainee of paediatric endocrinology, who needs to go through 3 years training and currently attached to HUSM in the 2nd year. The supervisors for this research will consist of both the consultant paediatric endocrinologists from HPJ and HUSM. The co-researchers of the research involve the paediatric postgraduate master student, as well as the lecturer biostatistician in HUSM.

This research is designed as an observational cohort study with 2 centers as mentioned. The research is planned to start by February 2020 until May 2020, which include the Ramadan month, tentatively from 24th April 2020 until 24th May 2020. The researchers will measure the glycaemic changes of Type 1 Diabetes Mellitus (T1DM) children and adolescents using continuous glucose monitoring (CGMS) for both the periods before Ramadan and during Ramadan month.

This research is under the grant support from National Institute of Health (NIH), with reference: KKM/NIHSEC/800-3/2/2 Ilid 9 (69), and has obtained approval from Medical Ethics Research Committee (MREC), with reference: KKM/NIHSEC/P19-348 (12).

2.0 Problem statement & Study rationale

There are limited numbers of paediatric diabetes studies involving T1DM during Ramadan month and the prior international studies mostly utilize SMBG or retrospective data to generate glycaemic profiles. Most of the recently conducted CGMS studies, majority involves the adults and other diabetes types, specifically T2DM. In contrast, T1DM is more

prevalent in the paediatric population and there is a need to better understand the glycaemic profiles of these young T1DM children and adolescents when they attempt religious fasting in Ramadan month. By conducting CGMS study among T1DM children in Ramadan month, we could discover and have a complete view over the exact glycaemic pattern among local children, which may differ from the international community. Lastly, to be able to produce local data and enable better recommendation for Ramadan fasting for T1DM children.

3.0 What is the use of your study finding?

1. To help to prepare and facilitate these young T1DM patients and to monitor them closely while they attempt for religious fasting in Ramadan month because of the potential complications
2. To provide better glucose monitoring and complement the SMBG practice at home
3. The CGMS results would enable the patients to better understand their own glycaemic pattern and gain invaluable experience
4. To detect hypoglycaemia unawareness among the subjects

4.0 Literature review

Following is some background literature review and the rationale of performing this research. Fasting during Ramadan, which is the 9^{th} month of Islamic lunar calendar, is one of the main five pillars of Islam religion and compulsory for all healthy Muslims adults, as well as adolescent from the time of completing puberty ([1]). During Ramadan, fasting starts from early dawn (Sahur/Sehri) till sunset (Iftar), which could last from 12-15 hours duration, depending on the geographical location. As from Sunnah (the way of prophet Mohamed), an individual becomes subject to Shari'a rulings that apply when specific features of puberty are

attained. These are one of the following: wet dreams, growth of coarse hair in the pubic area, reaching the age of 15, or onset of menstruation ([2]). A number of physiological effects on the homeostatic and endocrine processes could occur in healthy individuals who are fasting. Ramadan fasting not only alters the timing of meals but it also disturbs the sleeping pattern and circadian rhythms, all of which can affect a person's metabolic state ([3]). Fasting in diabetic patients, especially those with Type 1 Diabetes Mellitus (T1DM), is thought to be associated with higher risk of complications like hypoglycaemia, hyperglycaemia, diabetic ketoacidosis, dehydration, and thrombosis ([3]). Similarly, feasting after breaking fast in Iftar also carries risks for those with diabetes ([3])

The landmark Epidemiology of Diabetes and Ramadan (EPIDIAR) study ([4]) published in 2014, involving total 13 multi-country with majority Muslim population, in which total 1,070 patients with T1DM and 11,173 patients with T2DM recruited, with the mean age of 31 years old and 54 years old respectively, had reported that during Ramadan there was a 4.7-fold and 7.5-fold increase in the incidence of severe hypoglycaemic complications in patients with T1DM and T2DM, respectively, compared with non-Ramadan periods ([4]). The incidence of severe hyperglycaemia was also found to be increased during Ramadan (3-fold and 5-fold in patients with T1DM and T2DM, respectively) ([4]). This study had also given the prevalence estimates of fasting during Ramadan in the Muslim world and it is reported that as high as 42.8% of adults with T1DM and 78.7% of those with T2DM fasted for at least 15 days during Ramadan. This paper concluded and emphasized that the overall lower incidence of hypoglycaemia is possibly due to hypoglycaemia unawareness, insufficient monitoring (SMBG), limited use of intensified therapies or restriction of definition of hospitalisation ([4]). To highlight, this is an adult based study, which uses SMBG

instead of CGMS for blood sugar monitoring.

Another adult-based study published in July 2017, the CREED study ([5]), also a multi-country study covering total 4 regions, i.e.: Middle East, Asia, North America and Europe, designed to describe the characteristics and multiple approaches to management of people with diabetes who fasted during Ramadan 2010. A total of 3394 subjects were selected, of which the T2DM cohort consisted of 3250 with mean age of 54 years old and only 144 T1DM patients. It was reported that 94.2% of patients with T2DM enrolled in the study fasted for at least 15 days, and 63.6% fasted every day for the full month, again highlighting the determination of these Muslims to fast during Ramadan despite their medical condition. It was reported that among those who had fasted during Ramadan, for the entire T2DM cohort, there was 16.8% of incidence of hypoglycaemia for those treated with insulin, as compared to only 5.3% incidence of hypoglycaemia in those treated with oral anti-diabetic medication. It also reported that a prior hypoglycaemia event has an increased odds ratio of 7.8 (with 95% CI 5.31-11.45) of hypoglycaemia while fasting in Ramadan month. Again in this study, the hypoglycaemia event is only recorded by SMBG and not CGMS.

IDF-DAR (International Diabetes Federation), in collaboration with Diabetes and Ramadan International alliance has published its Practical Guidelines in April 2016 ([3]) and it has highlighted that there is immediate need for more studies to gather more evidence for better recommendation. According to the pre-existing evidence, the guideline has suggested that there are 3 categories of diabetes patients, Group 1: the very high risk group, Group 2: the high risk group and Group 3: the moderate or low risk group. T1DM patients belong to the first 2 groups, regardless of their glycaemic control. It is recommended that diabetes patients who are in the first two categories of IDF-DAR risk should not fast in Ramadan

month. Yet, in the community, there are many diabetes patients that have chosen to take the risk for fasting in Ramadan month despite the supposed medical advice. It is not known to what extent that this guideline is being practiced at the community level.

Similarly, the earlier international guideline, published by American Diabetes Association (ADA) in 2005 ([6]) also categorized the diabetes patients into different risk groups. They emphasized that management of diabetic patients in Ramadan should be individualised and pre-Ramadan assessment and education is of utmost importance. The paper concluded that T1DM should be strongly discouraged from fasting, especially those with hypoglycaemia unawareness. Other ensuing guidelines such as the South Asian Consensus ([7]) have a similar framework with the IDF-DAR guideline ([4]). Malaysian CPG for Management of T1DM in Children and Adolescent, launched in 2015 ([8]) , has suggested that young T1DM patients who wish to perform fasting in Ramadan month should have good glycaemic control, performs regular self-blood glucose monitoring (SMBG) and should be fasting under medical professional supervision ([8]). Different factors, such as the types of diabetes and medication, level of glycaemic control, associated comorbidities and personal circumstances, are used to assess individual risk for fasting in Ramadan month ([8]). Again, this local guideline is mostly based upon the international recommendations due to the absence of local data.

The most recent guideline ([9]) was published in June 2019 by the ISPAD (International Society for Paediatric and Adolescent with Diabetes) entitled “Clinical Practice Consensus Guidelines: Fasting during Ramadan by young people with diabetes”. This paper has provided some useful practical recommendations specifically for paediatricians caring for

young diabetes. In contrast to previous guidelines, they have not attempted to classify the different risk types of diabetes patients relating to the practice of fasting in Ramadan. Instead, they have chosen to emphasize on the importance of pre-Ramadan education and blood sugar monitoring while fasting for those children and adolescents with T1DM who intend to fast. They have acknowledged and reported that the current data on the management of children and adolescents with diabetes who choose to fast during Ramadan are still limited. They have also highlighted the need for well-designed, randomized controlled trials to determine the optimal insulin regimens to minimize glucose fluctuations throughout the fasting and eating hours.

Among the available research evidence of Ramadan fasting in paediatric T1DM are being discussed as followed. Describing a paediatric study published in 2010 ([10]) by Al-Alwan et al., whereby due to limited resources in developing countries, Ramadan fasting involving T1DM children with poorly controlled diabetes using SMBG was performed. A total of 20 T1DM children aged 8-14 years old with mean HbA1c 10 % were recruited. 11 out of 12 subjects in the fasting group had completed a full month of fasting and only 1 had stopped due to hypoglycaemia. The Hba1c, lipid profile and body weight were reported as not statistically different for the pre and post Ramadan period. This study population is rather similar to our community and has highlighted that these young T1DM with poor glycaemic control could actually complete their fasting in Ramadan month. Another prospective observational study by Al-Khawari et al [(11)], which was conducted in Royal London Hospital, London, UK & Al-Amiri Hospital, Kuwait City, Kuwait, involves T1DM who choose to fast during Ramadan (23rd Sept-23rd Oct, 2006). A number of 22 patients were recruited and their blood sugar monitoring was based on SMBG**.** It reported that 18 patients fasted > 13 days

and 4 patients fasted less than 4 days. Comparing the basal bolus (n=13) vs. premixed insulin regime (n=9), the incidence of mild hypoglycaemia episodes were 60% vs. 44%, respectively. There was no severe hypoglycaemia or DKA. Following, Bedowra Zabeen et al. ([12]) had conducted a prospective observational study during Ramadan 2012 (20 July – 18 Aug 2012) in Dhaka, Bangladesh, with total subjects 33 patients and only performing SMBG (2-3 times/day). It reported that 60.6% completed fasting. The mean blood glucose, HbA1c, body weight in 2 groups (success vs broke fast) showed no significant difference. They reported briefly 5 children developed hypoglycaemia in both groups but did not elaborate further details.

Another larger prospective observational study relating to Ramadan fasting in T1DM children has been conducted by Amany El-Hawary et al. ([13]) in Mansoura University, Egypt in Ramadan 2013 (10^{th} July-7^{th} August 2013). For this study, the author had managed to instruct the subjects to perform SMBG for 4 times per day. Total 53 patients had been recruited. They reported that 28 patients (52.8%) completed Ramadan 29 days fasting. 25 broke fast, of which 11 patients fasted < 7days, 6 patients fasted 8-14 days, 8 patients fasted 15-27 days. There was a positive correlation between the fructosamine improvement and the number of days fasted during Ramadan month. They also reported significant hyperglycaemia at three time points, pre-Iftar, pre-Sahur and midday in Regimen-I (intermediate insulin) compared to Regimen-II (long-acting insulin) and Regimen-III (self-mixing insulin) (p=0.004). They reported 6 subjects reported symptomatic hypoglycaemia, but did not elaborate further on the episodes.

However, the main limitation of these above studies has been in the SMBG, as most of the glycaemic events are self-reported by the subjects. It is known that many of the diabetes patients especially among those of younger age or long-standing diabetes could be having hypoglycaemia unawareness, due to autonomic neuropathy ([14]). Therefore, the exact glycaemic picture and changes in Ramadan month during fasting could be masked due to the intermittent and self-reporting nature of SMBG, among the T1DM patients.

Since the advent of CGMS technology about 10 years ago, numerous studies have been performed using CGMS and the majority involved adult patients. Quoting one of the first adult studies by Nader Lessan et al. ([15]) published in May 2012 in Diabetes Care that had looked into the glycaemic pattern of diabetes patients using CGMS during non-fasting period outside Ramadan month with fasting period in Ramadan month. The study had involved CGMS with at least 3 consecutive days monitoring each subject. This prospective observational study was performed in University of Sharjah, Abu Dhabi, UAE, with total 63 subjects, 56 diabetes patients (50=T2DM, 6 = T1DM) and 7 healthy volunteers. The mean age is 44.9 years old with mean HbA1c 7.2%. It had reported significant difference in mean CGMS curve during and outside Ramadan period, as well as great inter and intra-individual variability for both the CGMS traces. The difference observed happened during post-iftar and pre-sahur. The magnitude of excursion was greatest for those treated with insulin. Comparing the fasting and non-fasting period, this study concluded that no statistically significant difference in terms of mean interstitial glucose, mean amplitude of glycaemic excursion (MAGE), high and low blood glucose indices (HBGI/LBGI). There were also no significant differences in the number of high or low glucose excursions, or time spent in euglycaemia, hypoglycaemia, and hyperglycaemia. This study had included adults with unspecified

diabetes, with whom the majority being T2DM. This is in contrast to our study that aims to look at young children with T1DM. Furthermore, the above study population appeared to be selective as most the subjects have good glycaemic control with the mean HbA1c 7.2% (SD1.2).

Quoting one of the handful of CGMS studies among T1DM relating to Ramadan fasting ([16]), published by Walid Kaplan et al. in Diabetes care 2015, involving young T1DM patients with mean age of 15 years old. A total of 21 patients were recruited and CGMS was applied only during fasting in Ramadan month. It was reported that the subjects are able to fast 85% of the days. Hypoglycaemia (from CGMS traces) during fasting hours had been reported as much as 14.2%, as compared to eating hours 2.5%. Hyperglycaemia, on the other hand, was reported as 12% in fasting hours as compared to 17% in eating hours. Mild hypoglycaemia was observed in 16.7% (4 hours) & hyperglycaemia 29.3% (7 hours). Looking closer into this study, we realized that there were different types of CGMS devices used among the subjects. 18 patients were using the Medtronic MiniMed Paradigm 722 insulin pump coupled with the Medtronic iPro CGM system, whereas the other 3 patients were using Medtronic Guardian REAL-Time CGM system and they were not blinded. Insulin adjustment could be made and the adverse event of hypo or hyperglycaemia could be avoided. Hence, the expected outcome of the glycaemic changes during Ramadan month from our study would be different from this study above.

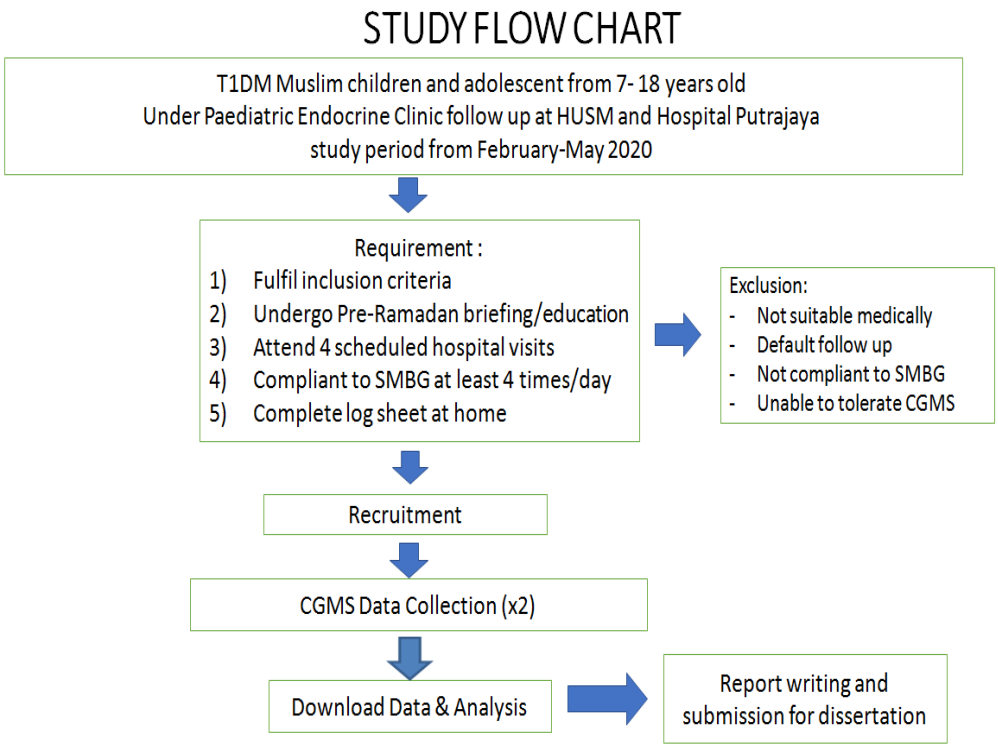
Lastly, quoting a recently published systematic review and meta-analysis looking at glycaemic profile of Ramadan fasting among young T1DM patients by Loh HH et al (2019) which had pooled 17 observational studies with total 1,699 patients, including 203 subjects

with continuous subcutaneous insulin infusion (CSII) and 1,496 subjects with non-CSII, which refers to multiple daily injection (MDI) & premixed insulin group. They had reported that the non-CSII group had less non-severe hypoglycaemia, 22% (95% CI 13-34) as compared to the CSII group who had more non-severe hypoglycaemia, 35% (95% CI 17-55). The non-CSII group however had reported severe hypoglycaemia, 7.1% (95% CI 5.8-8.5%), and none of the CSII group had severe hypoglycaemia. They had also reported that the non-CSII had significantly more hyperglycaemia, ketosis and higher incidence of discontinue fasting as compared to the CSII group (12% vs. 8.8%; 2.5% vs. 1.6%; 55% vs. 31%, respectively). The author had concluded that their meta-analysis relating to the glycaemic effects during Ramadan fasting among young T1DM children have been confounded and limited by the fact that variable definitions of hypoglycaemia have been used in each study (Ranging from 3.9-4.4mmol/L, with or without symptoms), as well as the majority use of SMBG, which relied on self-reporting of individual subjects. Furthermore, different brands of glucometer also carry different accuracy profiles and hence further affecting the SMBG. Out of the 17 observational studies being analysed, only 2 studies had used CGMS devices in their reporting of glycaemic profiles.

Malaysia, with its official religion and more than 60% of its population being Islam, is one of the major Muslim countries in the world. It has a steadily growing population of diabetes mellitus patients, which includes both T1DM and T2DM. According to the National Health and Morbidity Survey (NHMS) in 2015, the overall prevalence of diabetes mellitus (known and undiagnosed) among adults of 18 years and above in this survey was reported as 17.5% (95% CI: 16.6, 18.3). There was a general increasing trend in prevalence with age, from 5.5% (95% CI: 3.9, 7.7) in the 18-19 years age group, reaching a peak of 39.1% (95%

CI: 33.6, 44.9) among the 70-74 years age group. The prevalence of diabetes in Malaysia had increased a relative of 15%, from 15.2% (2011) to the current 17.5%, compared to the relative increase of 31.0% between 2006 (prevalence: 11.6%) and 2011. For diabetes mellitus patients among the paediatric population in Malaysia, referring to DiCARE in 2012 (18), T1DM is still the predominant among children and adolescents and is observed in 71.8% of paediatric diabetes patients. The median age of diagnosis was 7.6 (interquartile range: 4.6, 10.8) years with diabetes duration of 3.3 years. The majority (42.3%) of patients with T1D were between 10 to 15 years old and 57.5% presented with diabetic ketoacidosis. A positive family history for T1D or T2D was reported in 50.2% of patients. About 11.8% of patients with T1D were overweight. Among adults, T1DM was prevalent in only 0.6% of the population.

5.Study flow chart



6.0 Target Research Question(s)

What would be the glycaemic changes observed, relating to the practice of Ramadan fasting among the young T1DM children and adolescents during Ramadan month?

7.0 Objective

General

To observe the glycaemic changes, using continuous glucose monitoring system (CGMS) among the children and adolescents with T1DM before and during fasting in Ramadan month.

Primary objective

a. To describe the glycaemic parameters* from the CGMS data among T1DM children and adolescent during the non-fasting period before Ramadan month

Secondary objective

b. To compare these glycaemic parameters* from the CGMS data among T1DM children and adolescent in between the non-fasting period before Ramadan and during fasting in Ramadan month

8.0 Research study

An observational cohort study

9.0 Hypothesis

There are no difference in the glycaemic parameters from CGMS during fasting and non-fasting period in among T1DM patients.

10.0 Study area

Paediatric clinic (outpatient) Hospital University Sains Malaysia

Kubang Kerian, and Hospital Putrajaya.

11.0 Study period

4 months (Feb 2020 – May 2020)

12.0 Study population

Patients who are under Paediatric endocrine clinic follow up. Those patients who fulfil the inclusion and exclusion criteria will be included in the study.

Reference population	All the Muslim T1DM children and adolescents in both east and west peninsular Malaysia.
Source population	All the Muslim T1DM children and adolescents who is under the paediatric endocrine clinic follow-up in both HUSM and HPJ.
Target population	All the Muslim T1DM children and adolescents who is under the paediatric endocrine clinic follow-up in both HUSM and HPJ and they have intentions to fast in Ramadan month.

Sampling frame	Paediatric endocrine clinic attendance list both HUSM and HPJ

13.0 Subject criteria

1. All T1DM patients who are under paediatric endocrine clinic in HUSM and HPJ.
2. All of them need to fulfilled inclusion criteria

Inclusion criteria:

1. Muslim T1DM patients age 7-18 years old who wish to fast in Ramadan month.

2. On all types of insulin therapy

a Continuous subcutaneous insulin infusion (CSII)

b Multiple daily injections (MDI)

c Conventional insulin therapy (Pre- mixed)

3. Suitable after medical assessment.

4. Compliant to SMBG and hospital appointments.

Exclusion criteria:

1. Patient with history of severe hypoglycaemia within 3 months prior to Ramadan , recurrent hypoglycaemia, hypoglycaemia unawareness and DKA within 3 months prior to Ramadan.

2. Patient with acute illness, pregnancy and chronic dialysis

14.0 Sample size estimation

- For specific objective 1 & 2, descriptive statistics, referring to mean & SD for CGMS parameters. No sample size calculation required.
- For specific objective 3, the analytical statistics needed would either involve paired t test or Wilcoxson Sign Ranked test, as appropriate, to compare the glycaemic parameters from CGMS data before and during fasting in Ramadan month
- Using PS software (t test), setting α= 0.05, power=0.8

Sample size

The sample sizes were calculated using the PS: Power and Sample Size Calculator v 3.1.6 (2018). Data values to calculate the sample size was quoted from: Nader Lessan, "Glucose Excursions and glycemic control during Ramadan fasting in diabetic patients : Insight from continuous glucose monitoring (CGMS)", published in Diabetes and Metabolism 41 (2015)

The researchers used the following formula to calculate for each objective according to the strata. The definition of the formula is as below:

$$n = \frac{(t_{n-1,\,\alpha/2} + t_{n-1,\,\beta})^2}{d^2}$$

- α: The Type I error probability for a two-sided test. This is the probability that we will falsely reject the null hypothesis.

- *n*: For independent t-tests n is the number of experimental subjects. For pair test n is the number of pairs.
- *β*: 1-Power. For paired tests it is the probability of correctly rejecting the null hypothesis of equal population means given n pairs of patients, a Type I error probability α and a true difference in population means of *d*.
- *d: A* difference in population means
- *t*: For paired designs it is the standard deviation of difference in the response of matched pairs.

Objective		***α***	**Power**	***d***	***t***	**Sample pairs needed**
Mean, Min, Max	*Mean glucose (mmol/L)*	0.05	0.8	1.0	1.2	13 pairs
	Minimum glucose (mmol/L)	0.05	0.8	1.0	1.6	22 pairs
	Maximum glucose (mmol/L)	0.05	0.8	1.0	4.6	168 pairs
Hypoglycaemia duration (hr)		**0.05**	**0.8**	**0.16**	**0.38**	**41 pairs**
Hypoglycaemia duration (hr)		0.05	0.8	5	7.49	20 pairs
Time in range (hr)		0.05	0.8	1	6.98	384 pairs

Statistical analysis

SPSS version 22 statistical analysis software (SPSS Inc., Chicago, IL, USA) was used. CGMS data were downloaded from Medtronic Care-link Pro to Microsoft Excel (2010) and transcribed into SPSS. Descriptive statistics were used to characterize demographics. Normality was tested by Shapiro–Wilk test and graphical assessment of normality. Continuous variables were presented as mean (SD) or median (IQR) based on their normality

distribution; categorical data were presented as frequency (percentage). Glycaemic variability (GV) was calculated using EasyGV Excel version 9.0.R2 (https://www.phc.ox.ac.uk/research/resources/easygv) that was developed by Nathan R Hill, (©University of Oxford 2010-2016)[21]. All CGMS metrics were compared by paired t-test (for normally distributed data) or Wilcoxon Signed Rank test (for not normally distributed data), as appropriate, whereas Chi-Squared test and Fisher Exact test were used to assess for differences in the categorical variables, as appropriate. A value of $p < 0.05$ is considered statistically significant. As for number of glucose excursions/CGMS day the incidence rate is compared using 2 sample Poisson Rate as no prior reference data available for calculation of sample size. Looking through all the specific objectives above, the sample size required to achieve the statistical power would be at least 40 subjects. Taking into consideration of the operational cost and the availability of only 10 Ipro2 devices, as well as short duration of Ramadan month, the total population size was limited to 40 subjects.

15.0 Sampling method, subject recruitment, and withdrawal criteria.

All patients who fulfil the inclusion criteria are enrolled after parental consent. All eligible participants within the study period's recruitment will be included. All participants will be given a 3 monthly follow-up as part of their clinical care. For this study we only met the subject twice during the study period. All questionnaires and blood taken are only done during their 1st visit. If the subject did not want to be part of this study. They are still given 3 months' follow-up and basic blood investigation to be taken as part of their clinical care. The subsequent follow-up and treatment will be handled by treating physicians based on the subject health conditions and appropriate treatment and care will be given to the subject. The researchers are not involved in subsequent follow-up. For this study, we only need their information and the subject glycaemic parameters.

Ramadan-focused education and single-day workshops were conducted for both patients and their caregivers before Ramadan, involving the paediatric endocrinologists, diabetes educator nurses, and dieticians. Total 4 clinic visits were performed throughout the study period; 2 clinic visits before and another 2 during Ramadan. Standardized diabetes assessment and Ramadan-focused education were provided during clinic visits. Individual insulin adjustment and dietary advice were provided according to the published international guidelines [3–5].