IMPACT OF RAMADAN FOCUSED EDUCATION PROGRAM ON HYPOGLYCEMIC RISK AND METABOLIC CONTROL FOR PATIENTS WITH TYPE 2 DIABETES

by

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Thesis submitted in fulfillment of the requirements
for the degree of
Doctor of Philosophy

February 2017

ACKNOWLEDGEMENT

First of all, I thank Almighty Allah for giving me the strength, and determination to carry out this work. Without the help and blessing from Allah, I would be unable to do anything.

I would like to thank my supervisors who have strongly supported me throughout my PhD journey. In particular, I am indebted to my main supervisor Professor Dr. Mohamed Azmi Ahmad Hassali for his excellent supervision and guidance. Indeed, without his guidance I would not be able to complete this work. Also, I would like to thank my co-supervisors Dr. Alian A Alrasheedy and Dr. Hisham Aljadhey for their continuous support, valuable advice and constructive comments. They have sincerely helped me in conceptualizing the research idea, specific objectives, the research design, interpretation of the results, reviewing the thesis content, as well as proof-reading and editing the thesis. To all my supervisors, thank you very much for your effort and time spent during all the steps of carrying out this PhD. Special thanks to Dr. Alian A Alrasheedy, whom I have consulted so many times about each part of this research. He has continuously given me constructive feedback which immensely contributed to the development of the final version of this thesis. Dr. Alian A Alrasheedy has always generously provided me with his time, understanding, vision, and help. I owe him much of my success and I can only hope to be as good as him when I get to mentor others.

This thesis would have never been completed without the support, encouragement, and thoughtful criticism of Dr. Turki AlHarbi, the in-charge of Chronic Diseases Center who has been always pushing me forwards to finish the requirements of my PhD degree. His positive comments and suggestions have been instrumental in shaping this work.

Finally, I would like to express my deep thanks and gratitude to my husband and my parents who have supported me emotionally, physically, and financially through all the stages of this work. Their patience, understanding, and determination to support were just invaluable.

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ADA	American Diabetes Association
AGI	α-glucosidase inhibitor
ANOVA	Analysis of variance
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
DAR	Diabetes and Ramadan
DBP	Diastolic blood pressure
DKA	Diabetes ketoacidosis
dL	Deci liter
DM	Diabetes Mellitus
DPP4	Dipeptidyl peptidase-4
E2	Estradiol
EPIDIAR	Epidemiology of diabetes and Ramadan
FSG	Fasting serum glucose
FSH	Follicle stimulating hormone
HbA1c	Glycosylated hemoglobin
HDL	High-density lipoprotein
HHA	Hypoglycemic Health Association
IDF	International Diabetes Federation
Kg	Kilogram
LDL	Low-density lipoprotein
LH	Luteinizing hormone

mg/dL	Milligrams per deciliter
mmol/l	Millimoles per liter
N	Number
OIC	Organization of Islamic Conference
PRL	Prolactin
RFEP	Ramadan Focused Education Program
SD	Standard deviation
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TZDs	Thiazolidinediones
UAE	United Arab Emirates
UK	United Kingdom
US	United States
WHO	World Health Organization

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KESAN PROGRAM PENDIDIKAN FOKUS RAMADAN MENGENAI RISIKO HIPOGLISEMIK DAN KAWALAN METABOLIK UNTUK PESAKIT DIABETES JENIS 2

ABSTRAK

Berpuasa di bulan Ramadan dikaitkan dengan kesan yang besar ke atas kawalan glisemik dan keselamatan pesakit di kalangan pesakit diabetes jenis 2 (T2D). Kebarangkalian permasalahan ini mungkin tinggi di Arab Saudi kerana kelaziman kencing manis yang tinggi. Risiko ini berpotensi menjadi bertambah buruk akibat cuaca panas dan tempoh puasa panjang bagi musim Ramadan kali ini di Arab Saudi. Garis panduan semasa mengesyorkan kaunseling dan pendidikan pesakit T2D diadakan sebelum Ramadan. Walaupun risiko yang lebih tinggi di kalangan pesakit Saudi, terdapat kekurangan kajian yang memeriksa kesan program pendidikan Ramadan di kalangan pesakit T2D. Tujuan kajian ini adalah untuk menilai kesan Program Pendidikan Fokus Ramadan (RFEP) terhadap komplikasi akut, kawalan glisemik, dan kesan lain yang berkaitan termasuk berat badan dan parameter metabolik. Intervensi prospektif tidak rawak yang terkawaltelah dijalankan pada tiga peringkat: sebelum, semasa dan selepas Ramadan terhadap 262 pesakit T2D di sebuah pusat perubatan keluarga. Kumpulan intervensi (n = 140) telah menerima sesi pendidikan diabetes fokus secara individu dan pelarasan ubat-ubatan antidiabetik sebelum dan selepas Ramadan, manakala kumpulan kawalan (n = 122) telah menerima rawatan piawai diabetes. Skor hipoglisemik yang telah disahkan telah digunakan bagi kedua-dua kumpulan untuk menilai perubahan risiko. Pesakit dinasihatkan untuk menyesuaikan dos dan masa agen

antidiabetik mengikut saranan Ramadan 2010 Persatuan Diabetes Amerika. Dapatan utama kajian ini adalah perubahan skor hipoglisemia dan HbA1c bagi tempoh 6 bulan susulan selepas intervensi. Data telah dibentangkan dalam bentuk min ± sisihan piawai. HbA1c telah dinyatakan dalam peratusan. Skor hipoglisemik sebelum, semasa, dan selepas Ramadan adalah 14.21 ± 8.50, 6.36 ± 6.17, dan 5.44 ± 5.55 bagi kumpulan intervensi, masing-masing (P <0.001) dan 14.01 ± 5.10, 13.46 ± 5.30 dan 9.27 ± 4.65 bagi kumpulan kawalan, masing-masing (P <0.001). Tahap HbA1c adalah 9.79 ± 1.89, 8.26 ± 1.54, dan 8.52 ± 1.61 sebelum, semasa, dan selepas Ramadan bagi kumpulan intervensi, masing-masing (P <0.001), dan 10.04 ± 1.47, 9.54 ± 1.38, dan 9.59 ± 1.79 bagi kumpulan kawalan, masing-masing (P <0.001). Pengurangan HbA1c dan skor hipoglisemik selepas Ramadan adalah lebih tinggi dalam kumpulan intervensi (-13.0% vs -4.5%, P = 0.004 untuk HbA1c dan -61,7% vs -33.8%, P <0,001 untuk skor hipoglisemik). Kolesterol lipoprotein ketumpatan rendah bertambah baik dalam kumpulan intervensi dari 2.41 ± 0.91 mmol / L sebelum Ramadan kepada 2.28 ± 0.68 mmol / L selepas Ramadan (P <0.001). Tiada statistik yang signifikan diperhatikan pada tekanan darah atau berat badan. Selain itu, tiada perubahan yang diperhatikan dalam kumpulan kawalan. Hasil kajian ini menunjukkan bahawa program pendidikan Ramadan mempunyai kesan positif terhadap pengurangan risiko hipoglisemik, HbA1c, dan kolesterol lipoprotein berketumpatan rendah. Oleh itu, ia boleh disyorkan kepada pesakit yang mempunyai risiko tinggi berhadapan dengan hipoglisemia semasa berpuasa dalam bulan Ramadan.

IMPACT OF RAMADAN FOCUSED EDUCATION PROGRAM ON HYPOGLYCEMIC RISK AND METABOLIC CONTROL FOR PATIENTS WITH TYPE 2 DIABETES

ABSTRACT

Ramadan fasting is associated with significant impact on glycemic control and patient safety among patients with type 2 diabetes (T2D). The burden of the problem is high in Saudi Arabia due to the high prevalence of diabetes. The risk can be aggravated by hot weather and long fasting duration during Ramadan in Saudi Arabia. Current guidelines recommend counseling and educating patients with T2D before Ramadan. Despite the higher risk among Saudi patients, based on the extensive literature review, there is lack of studies examining the impact of Ramadan education program among Saudi patients with T2D. Therefore, the aim of the study was to evaluate the impact of Ramadan Focused Education Program (RFEP) on hypoglycemia risk score and other related clinical & metabolic parameters (HbA1c, lipid profile, blood pressure, body weight and body mass index (BMI). A prospective non-randomized interventional controlled design was run on three phases: before, during and after Ramadan on 262 T2D patients at a large big family medicine center. The intervention group (n=140) received focused individualized diabetic education sessions and antidiabetic medications adjustment before and after Ramadan, while the control group (n=122) received standard diabetic care. A validated hypoglycemic score was used in both groups to assess the change of the risk. Patients were advised to adjust the dosage and timing of antidiabetic agents according to the recommendations for management of diabetes during Ramadan. Primary outcomes were post-intervention change of hypoglycemia score and HbA1c

over a 6-month follow-up. Data were presented as mean ± standard deviation. HbA1c was expressed in percentage. The hypoglycemic scores before, during, and after Ramadan were 14.21±8.50, 6.36±6.17, and 5.44±5.55 in the intervention group, respectively (P<0.001) and 14.01±5.10, 13.46±5.30, and 9.27±4.65 in the control group, respectively (P<0.001). HbA1c levels were 9.79±1.89, 8.26±1.54, and 8.52±1.61 before, during, and after Ramadan in the intervention group, respectively (P<0.001), and 10.04±1.47, 9.54±1.38, and 9.59±1.79 in the control group, respectively (P<0.001). Post-Ramadan reductions of HbA1c and hypoglycemic scores were significantly higher in the intervention group (-13.0% vs -4.5%, P=0.004 for HbA1c and -61.7% vs -33.8%, P<0.001 for hypoglycemic score). Low-density lipoprotein cholesterol improved in the intervention group from 2.41±0.91 mmol/L before Ramadan to 2.28±0.68 mmol/L after Ramadan (P<0.001). No statistically significant effects were observed on blood pressure or body weight in the intervention group. Similarly, no change was observed in the control group. The findings of the current study suggested that Ramadan educational program has a positive impact with reduction of hypoglycemic risk, HbA1c, and low-density lipoprotein cholesterol. Therefore, it could be recommended for patients with increased risk of hypoglycemia during Ramadan fasting.

CHAPTER ONE: INTRODUCTION

1.1 Background

Ramadan fasting is one of the main pillars in Islam (Al-Bukhari, 870 AD). According to Islamic teachings, Muslims should refrain from eating and drinking from dawn time to sunset time during the month of Ramadan. It was estimated that Muslims population worldwide reached approximately 1.6 billion in 2009, making up over 23% of the world population (Pew Research Center, 2009) and is expected to reach 2.76 million by 2050 (Pew Research Center, 2015). The daily fasting hours in Ramadan varies by season and geographic locations. The current Ramadan seasons come during summer months with hot weather and long fasting duration, reaching approximately 15 hours in most Islamic countries including Saudi Arabia (Berbari et al., 2012).

Fasting is regarded by Islam as a way of practicing patience and good manners rather than creating excessive hardship or safety challenge. All healthy non-travelling Muslims are required to fast during Ramadan. However, in certain situations such as illness, long travelling, frail old people, pregnancy, lactation, menstruation, and puerperium, fasting is exempted (The Holy Quran, 632 AD). The International Islamic Fiqh Academy of the Organization of Islamic Conference (OIC) issued a detailed guidance on exemption from fasting (Beshyah, 2009). Patients with very high and high risk of diabetic complications as described by the American diabetic association (ADA) should be advised not to fast whereas patients with low and medium risk are expected to fast (Beshyah, 2009; Al-Arouj et al., 2010; Jaleel et al., 2011).

Diabetes prevalence in Saudi Arabia is approximately 24% and considered one of the highest in the world (Al-Nozha et al., 2004; Guariguata et al., 2014). Additionally, three of the top ten countries with the highest diabetes prevalence worldwide have a

majority of Muslim population (Guariguata et al., 2014; International Diabetes Federation, 2015). Although religiously exempted, the vast majority of patients with type 2 diabetes (T2D) in Saudi Arabia decide to fast Ramadan (Salti et al., 2004; Aravind et al., 2011). Since Ramadan in most Islamic countries including Saudi Arabia is currently practiced in hot weather and long fasting duration, this probably adds more risk of acute diabetic complications. Lack of appropriate education before Ramadan could result in unwanted practices (Pinelli and Jaber, 2011). Acute complications are often seen among diabetic patients who fast in during Ramadan without appropriate medical guidance (Mohamed et al., 2002). Current guidelines recommend that diabetic patients should have counseling and education about the need to modify medication dose and timing, dietary habits, physical activity and self-monitoring of blood sugar, to reduce the risk of acute diabetic complications (Al-Arouj et al., 2010; Suliman et al., 2010).

Ramadan fasting is associated with major changes in eating habits, sleeping patterns, and daily activities that could negatively impact the control of blood glucose, blood lipids, and weight (Hui and Devendra, 2010). In a large population-based cross-sectional study conducted in 13 countries among more than 12,000 patients with diabetes (epidemiology of diabetes and Ramadan "EPIDIAR" study), the researchers found that the change in eating patterns increased the risk of severe hypoglycemia during Ramadan by 4.7-times in type 1 diabetes (T1D) and 7.5-times in T2D. Additionally, the incidence of severe hyperglycaemia during Ramadan increased five times in patients with T2D (Salti et al., 2004). Moreover, according to a study from Pakistan, 21.7% of diabetic patients who fast in Ramadan reported hypoglycemia while

19.8% reported hyperglycemia. The study also found that 4% had major hypoglycemic episodes and 8% had major hyperglycemic episodes during Ramadan (Ahmadani et al., 2008).

The overall effect of Ramadan fasting on biochemical parameters is mild. Reviews that used data from studies published in 1980s through early 2000s showed that the majority of studies reported no change in glycosylated hemoglobin (HbA1c) in patients with T2D (Azizi and Siahkolah, 2003; Benaji et al., 2006). On the other hand, smaller number of studies showed decrease or increase of HbA1c during Ramadan fasting (Azizi and Siahkolah, 2003; Benaji et al., 2006). Similar findings were shown in lipids profile with some studies showed decrease, increase, or no change (Azizi and Siahkolah, 2003; Yarahmadi et al., 2003; Benaji et al., 2006).

In the EPIDIAR study, it was shown that one-fourth of patients treated with oral antidiabetic drugs were able to change their treatment dose (Salti et al., 2004). On the other hand, two-thirds of Arab Americans with T2D consulted their healthcare providers prior to Ramadan fasting (Pinelli and Jaber, 2011). For the majority of diabetic patients, fasting in Ramadan is a safe practice when medical guidance and proper diabetic management are ensured (Azizi and Siahkolah, 2003). Fasting is generally safe in well-controlled patients with T2D who are aware of the disease requirements and compliant with dietary and medicine intake advices (Benaji et al., 2006). A detailed management of patients with T2D during Ramadan fasting has been published (Al-Arouj et al., 2010; Alomi, 2016; International Diabetes Federation, 2016).

A number of studies examined the effect of focused diabetic education on the acute diabetic complications (Bravis et al., 2010; Fatim et al., 2011; Ahmedani et al., 2012). A prospective study in Pakistan showed that the majority of outpatients who attended two educational sessions focusing on changes in dose and frequency of medications, monitoring of glucose, and modifications of diet and lifestyle did not have any serious diabetic complications during fasting (Ahmedani et al., 2012). Additionally, in a retrospective study among UK Muslim population with diabetes, the group that received Ramadan-focused education had significantly (four-fold) lower risk of hypoglycaemic events compared with the control group (Bravis et al., 2010).

1.2 Rationale of the study

Diabetes prevalence in Saudi Arabia is very high and the total Saudi population was approximately 31 million in 2015 (Central Department of Statistics and Information, 2016) (with more than 40% of the population above the age of 30 years) (United Nations, 2011). Therefore, it is estimated that the majority of two million people with diabetes in Saudi Arabia are fasting Ramadan and are at potential risk of acute diabetic complications. The current guidelines recommend that diabetic patients should have counseling and education about the need to modify medication dose and timing, dietary habits, physical activity and self-monitoring of blood sugar, to reduce the risk of acute diabetic complications (Al-Arouj et al., 2010; Suliman et al., 2010; Alomi, 2016; International Diabetes Federation, 2016). Such focused education has been shown in a number of studies to be successful in protecting diabetic patients against serious acute diabetic complications (Bravis et al., 2010; Ahmedani et al., 2012). However, there is currently a limited number of studies examining the impact of such focused education

program among Saudi patients with T2D (McEwen et al., 2015), despite the probable higher risk of Saudi patients and the success of focused education seen in similar studies in other countries (Bravis et al., 2010; Ahmedani et al., 2012). Moreover, the findings derived from studies conducted in other countries cannot be confidently extrapolated to the situation in Saudi. This is due to differences in health systems. Furthermore, the majority of studies have been done during Ramadan falling in cold seasons and there is limited data about Ramadan fasting in hot seasons with long durations (Bragazzi, 2014). Therefore, the aim of this PhD project was to evaluate the impact of Ramadan Focused Education Program (RFEP) on hypoglycemia risk score and other related clinical & metabolic parameters among patients with T2D who insisted to fast Ramadan and were receiving care at a primary care center in Riyadh, Saudi Arabia.

1.3 Significance of the study

The findings of the current study can provide health authorities and health policy makers with valuable data about the impact of this program. Hence, it could be adopted in other centers in Saudi. This can potentially lead to several benefits including both clinical and economic benefits. This is particularly important as diabetes is prevalent in Saudi and may lead to serious complications in Ramadan (e.g. hypoglycemia, hyperglycemia, dehydration, ketosis, and thrombosis) (Azzoug et al., 2015). Moreover, lack of patient education prior to Ramadan and suboptimal self-management may contribute to these complications (Pinelli and Jaber, 2011). Increasing patient awareness regarding the risk of Ramadan fasting and following recommended pharmacological and behavioral changes can potentially improve their adherence to the appropriate diabetic care.

From economical perspective, it has been shown that severe hypoglycemic events represent a substantial cost to the hospitals. For example, Laires et al. (2016) estimated the overall cost per hypoglycemic episode to be €1493 (range: €34–26,818) in Portugal. Therefore, reducing these events would lead to economic benefits to the healthcare system.

The interventions used in the current study included focused tailored diabetic education sessions with adjusting anti-diabetic medications before and after Ramadan. These interventions could be considered as an achievable model in the diabetic care during Ramadan in similar primary health centers. This can reduce diabetic emergencies such as hypoglycaemia, hyperglycaemia and metabolic decompensation including diabetic dehydration, ketoacidosis, hyperosmolar coma, and thrombosis. Therefore, implementing similar programs could reduce the morbidity, loss of activity, and the healthcare costs associated with diabetic complications.

The tailored educational intervention used in the current study was carried out by clinical pharmacist, primary care physician and dietician. Therefore, the current study could provide evidence regarding the importance of the multidisciplinary approach in diabetic care during Ramadan. Additionally, it was shown that interventions that have been tailored to center-specific barriers are more likely to have a positive impact on professional practice (Baker et al., 2010). Center-specific barriers are the locally prevalent barriers and they can be different from one center to another. Hence, barriers in one center or area may not be applicable to other centers or areas. For example, in a well-educated community, the focus will be on the barriers to access rather than the education while in a less-educated community with free healthcare the focus will be on

the education. Therefore, in management of diabetes mellitus, solving center–specific barriers such frequent monitoring of self-blood glucose monitoring through frequent visits and appointments to all disciplines or through phone for close blood glucose monitoring, opening extra clinics during Ramadan for adjustment of doses of anti-diabetic medications either oral anti-diabetic medications, or insulin titration or both and audit of physicians adherence to the guideline and protocols.

1.4 Objectives

The specific objectives of this PhD project are:

1. To examine the impact of Ramadan focused education program (RFEP) on the hypoglycemia risk score.

2. To examine the impact of RFEP on glycemic control.

3. To examine the impact of REFP on the lipid profile.

4. To examine the impact of REFP on body weight and body mass index.

5. To examine the impact of REFP on blood pressure.

6. To examine the impact of RFEP on number of antidiabetic medication and doses.

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

Ramadan is a lunar month; therefore the duration is not fixed and varies from month to month ranging between 29 and 30 days. The lunar year is approximately 10 days shorter than Gregorian year; therefore Ramadan falls in different seasons over time (Ghouri et al., 2012). Studying the effect of an educational program that is based on the management recommendations could potentially help to improve diabetic patient safety during Ramadan. This is critically needed in Saudi Arabia and similar counties which have high prevalence of diabetes, sub-optimal diabetes management, sub-optimal primary care services, in addition to poor knowledge and low educational levels among diabetic patients, especially those with older age (Al-Khaldi and Khan, 2000; Al-Ahmadi and Roland, 2005). In this chapter, the challenges that diabetic patient may face during Ramadan fasting as well as the impact of diabetic educational programs on the patient safety are reviewed.

2.2 Search strategy

The objective of the current search strategy was to identify all published literature examining patients with diabetes (specifically T2D) who are practicing Islamic fasting during the month of Ramadan. The eligibility criteria were peer-reviewed and English language studies published between 1980 and 2015. To identify potentially relevant articles, a computerized English-language searches was performed on databases/search engines accessible at the University library, which include Pubmed, Ovid, Scopus, Blackwell Synergy, Springer link, ScienceDirect, and Google scholar. Additionally four supplemental search methods were used as follows:

- Search of reports from relevant websites such as the American Diabetes Association and the World Health Organization
- Targeted searches for articles used in the reference list of the retrieved literature.
- Author search using the name of the corresponding or first author of the retrieved literature.
- Abstracts, where available on-line, were also identified from relevant conferences and web sites.

The search strategy used a series of keywords to identify the topics of interest, these included different combinations of:

- Ramadan, Islamic fasting, and/or intermittent fasting
- Diabetes, type 2 diabetes, and/or T2D
- Education, educational, health education, and/or awareness
- Glycaemia, glycemic control, glycosylated hemoglobin, hemoglobin A1c, HbA1c
- Hypoglycemia, emergency, complication
- Blood lipids, serum lipids, lipid profile cholesterol
- Blood pressure, hypertension, body weight, BMI
- Impact and/or effect

The abstracts of retrieved articles and documents, when available, were compiled into endnote library along with their pdf to facilitate further in-document search and to facilitate accurate citations.

2.3 Diabetes in Saudi Arabia

Diabetes is a major public health problem both in Saudi Arabia and worldwide. After pooling data from 130 countries, the diabetes burden was shown to be high with approximately 382 million people affected worldwide (Guariguata et al., 2014). Additionally, this large number is expected to increase to 592 million by 2035. Moreover, it was expected that the greatest increase in diabetes burden over the next two decades will be in low-income or middle-incomes, which will make the impact even worse (Guariguata et al., 2014). In Saudi Arabia, the prevalence of diabetes was estimated in a national epidemiological health survey conducted between 1995 and 2000 at approximately 24% among Saudi adults (Al-Nozha et al., 2004). This is approximately three-folds higher than the global prevalence of diabetes which was reported to be 8.3% (Guariguata et al., 2014). The most recent data released by the International Diabetes Federation (IDF) showed that Saudi Arabia comes as the seventh in the list of the countries with highest prevalence of diabetes and list of the countries with the highest number of diabetic children (International Diabetes Federation, 2013; International Diabetes Federation, 2015). Additionally, the IDF prevalence estimates put Saudi Arabia as the highest among all Middle Eastern and North African counties (International Diabetes Federation, 2013). Moreover, the current high prevalence of diabetes risk factors such as obesity and smoking among Saudi adults are expected to increase T2D to 44% in 2022 (Al-Quwaidhi et al., 2014).

The specific reasons of the high diabetes-burden in Saudi Arabia have not been well-examined (Tourkmani et al., 2014). However, the prevalence of traditional risk factors such as obesity, sedentary life style, and smoking were shown to be very

prevalent in Saudi Arabia (Midhet et al., 2010; Al-Daghri et al., 2011; Al-Quwaidhi et al., 2014). Additionally, the huge surge in socioeconomic growth over the last decades contributed to the higher frequency of sedentary life style as well as unhealthy dietary habits including high calorie/fat containing diets (Midhet et al., 2010). Moreover, suboptimal adherence to clinical guidelines and the suboptimal management of diabetes and its risk factors among Saudi patients with diabetes attending primary care centers may have contributed to the high diabetes risk in Saudi Arabia (Alfadda and Abdulrahman, 2006; Harbi et al., 2015).

Diabetes has a negative impact on the morbidity, mortality, productivity and disability. For example, approximately 5.1 million adult patients with diabetes died from diabetes worldwide in 2013, which accounted for 8.4% of deaths from all-causes worldwide (International Diabetes Federation, 2013). Additionally, diabetes is a costly disease to individuals and societies. It was shown that diabetic patients, on average, have healthcare expenditures approximately ten times higher than those without diabetes (Alhowaish, 2013). Moreover, it was estimated that diabetes cost to individuals and societies will increase over the next 2 decades by about 55% worldwide, with a special increase by 96% in the Middle East region (International Diabetes Federation, 2013). Saudi estimates was even higher; showing that the healthcare expenditures on managing diabetes and its complications by the Saudi healthcare system increased by five-folds during the last 2 decades, which represented one dollar for each 11 spent dollars (Alhowaish, 2013). Therefore, the expected substantial increase in the size of diabetes population in Saudi Arabia together with the persistence of its risk factors such as obesity, sedentary life style, and smoking will probably be translated into a huge surge

in the healthcare utilization and allocated costs in the nest 2 decades (Alhowaish, 2013).

2.4 Ramadan in Saudi Arabia

Ramadan is as an intensive training course that train Muslims for positive habits such as patience, silence, renewal of the work spirit, and productive skills. It is meant to be a time for charging the faith battery, self-discipline and self-control, and developing new behavioral and religious habits. Ramadan in Saudi Arabia, like many other Islamic countries, is an opportunity that happens once a year with several changes in the daily activities. These include eating a variety of traditional foods, altered sleep patterns, frequent visits to relatives, in addition to altered time of meals which are reduced from three to two meals (Bakhotmah, 2011; Bahijri et al., 2013). The two meals served are the pre-dawn meal (sohor) and a meal at dusk (Iftar). There is more consumption of carbohydrates specially dates and sugary juices. It is recommended that those who are fasting Ramadan should eat simple but balanced diet that is not much different from normal diet with avoiding high-sugar and high-fat foods (UK National Health Service, 2014). However, bad habits that are frequently seen during Ramadan in the last few decades include excess food intake, shift to high calorie foods such as dates, deserts and treats, and sedentary life style specially during day time (Bakhotmah, 2011; Bahijri et al., 2013). The total energy intake tends to remain unchanged whereas the quality of nutrients are markedly affected (M'Guil et al., 2008; Hui and Devendra, 2010; McNeil et al., 2014). These eating and sleeping changes represent a significant challenge for glycemic control among patients with diabetes (Saberi, 2009).

A cross-sectional study among Saudi families was conducted to identify common dietary habits during Ramadan (Bakhotmah, 2011). Dates were found on the top of food

list consumed during breakfast meal followed by Sambosa (a type pastry stuffed with cheese, meat, or vegetables) and meat soups. On the other hand, fish and fish products were rarely used during breakfast meal. For the sohor meal which was usually prepared in home, rice was found on the top of food list consumed during Ramadan followed by bread and salads. On the other hand, fruits and sweets were the least food items to be consumed during sohor meal (Bakhotmah, 2011).

2.5 Changes during Ramadan fasting among healthy individuals

Ramadan fasting is considered as complete and intermittent fasting that does not require caloric restrictions. It is intermittent because eating and drinking are allowed from sunset to dawn. This is different from the complete or partial continuous fasting that is frequently examined in medical and nutritional books (Roky et al., 2004). The following section will describe the impact of complete and intermittent fasting on several physical and metabolic parameters among otherwise healthy individuals who observe fasting during Ramadan. These include changes in caloric intake, body weight, body water, electrolytes, blood glucose, blood lipids, blood pressure, hematological components, inflammatory markers, hormones, and body systems such as circulatory, renal, immune, and respiratory systems. Most of the studies that examined the physiologic changes during Ramadan used before-after intervention designs without control of confounders such as age, BMI, nutritional status, socioeconomic status, and comorbidity (Rouhani and Azadbakht, 2014). Therefore, several of published Ramadan findings may still need to be further verified using appropriate study designs (Rouhani and Azadbakht, 2014). Additionally, the beneficial effect on some of these changes was shown to be lost or attenuated after Ramadan.

2.5.1 Impact on caloric intake

A number of studies showed that the energy intake among healthy individuals during Ramadan remains largely unchanged (Haouari et al., 2008; Meo and Hassan, 2015). On the other hand, some studies showed that energy intake among healthy individuals during Ramadan slightly increased (Lamri-Senhadji et al., 2009) or decreased (Afrasiabi et al., 2003). The total amount of food intake during Ramadan have been shown to generally decrease in several Muslim populations, however, a slight increase has been noted in some populations such as Saudi and Moroccan populations (Roky et al., 2004). In Saudi population, the food being taken in groups and frequently outside the home as well as reduced physical activity may result in a significant increase in the amount of caloric, fat, and carbohydrate intake (Bakhotmah, 2011).

2.5.2 Impact on body weight

The majority of studies showed that Ramadan fasting is associated with a slight reduction in body fat, body mass index, and waist circumference (Roky et al., 2004; Meo and Hassan, 2015). It was suggested the impact on the body weight parameters may reflect a decrease in the amount of fluid intake (Roky et al., 2004). A meta-analysis of cohort studies (N=21 studies) comparing body weights before and after Ramadan among healthy individuals reported an overall pooled body weight reduction of 0.17 kg (95 % CI = 0.07-0.26 kg), which was significant for men (0.24 kg reduction, 95 % CI = -0.36, -0.12 kg) but not females (0.04 kg reduction, 95 % CI = -0.20, 0.12 kg) (Kul et al., 2014). On the other hand, these changes in body weight are probably temporary. It was shown that the lost weight and fat percent during Ramadan are regained short time

after Ramadan and the reduced BMI is returned to the usual levels before Ramadan (Faris et al., 2012).

In Saudi Arabia, cross-sectional study done among 173 families showed that approximately 60% of these families reported weight gain after Ramadan (Bakhotmah, 2011). The explanations suggested by the studied families were consumption of foods rich in fat and carbohydrates, relative lack of physical exercise, and increase in food consumption (Bakhotmah, 2011). Although the weight gain and dietary patterns were self-reported without additional tools to confirm the findings, this study may show the traditional dietary habits in Saudi Arabia could have negative and supersizing health outcome during Ramadan.

2.5.3 Impact on body water and electrolytes

The reduction of fluid intake during daytime in Ramadan results in a state of dehydration. This is manifested by increased measures of hematocrit, hemoglobin, plasma osmolality, and urine osmolality (Bouhlel et al., 2008). It was shown that Ramadan fasting can result in changes in electrolyte such as decrease in calcium, iron and magnesium and an increase in phosphate blood levels (Roky et al., 2004). However, this seems to be temporary situation as the post-Ramadan total body water was not much different from that reported before Ramadan fasting (Bouhlel et al., 2008). Additionally, serum sodium and potassium was not affected by Ramadan fasting (Meo and Hassan, 2015).

2.5.4 Impact on fasting blood glucose levels

In normal individuals, blood glucose concentration is maintained within the physiological range by the balance between the blood levels of insulin and other glucose increasing hormones (Meo and Hassan, 2015). A meta-analysis of 16 cohort studies comparing fasting blood glucose before and after Ramadan among healthy individuals reported a slight (-1.10 mg) but statistically significant reduction in glucose levels (Kul et al., 2014). The reduction in blood glucose levels is noticed in the afternoon time. This may be explained by the increase in insulin sensitivity and glucose uptake by peripheral tissues as a response of caloric restriction and physical activity during the day (Gnanou et al., 2015).

Insulin secretion is stimulated by feeding in healthy individuals. Insulin secretion promotes the storage of glucose as glycogen in liver and muscle. Since no food is taken during fasting, the levels of blood glucose gradually decrease which result in reduction of insulin secretion. As a consequence, the secretion of glucose-raising hormones such as glucagon and catecholamines increase to help glycogen breakdown and gluconeogenesis (Cryer et al., 2003). Later during the fasting day, the continuous low insulin levels result in depletion of glycogen stores and increase fatty acid release from adipocytes (Al-Arouj et al., 2010). More details on hormonal regulation of blood glucose levels are shown in Figure 2.1.

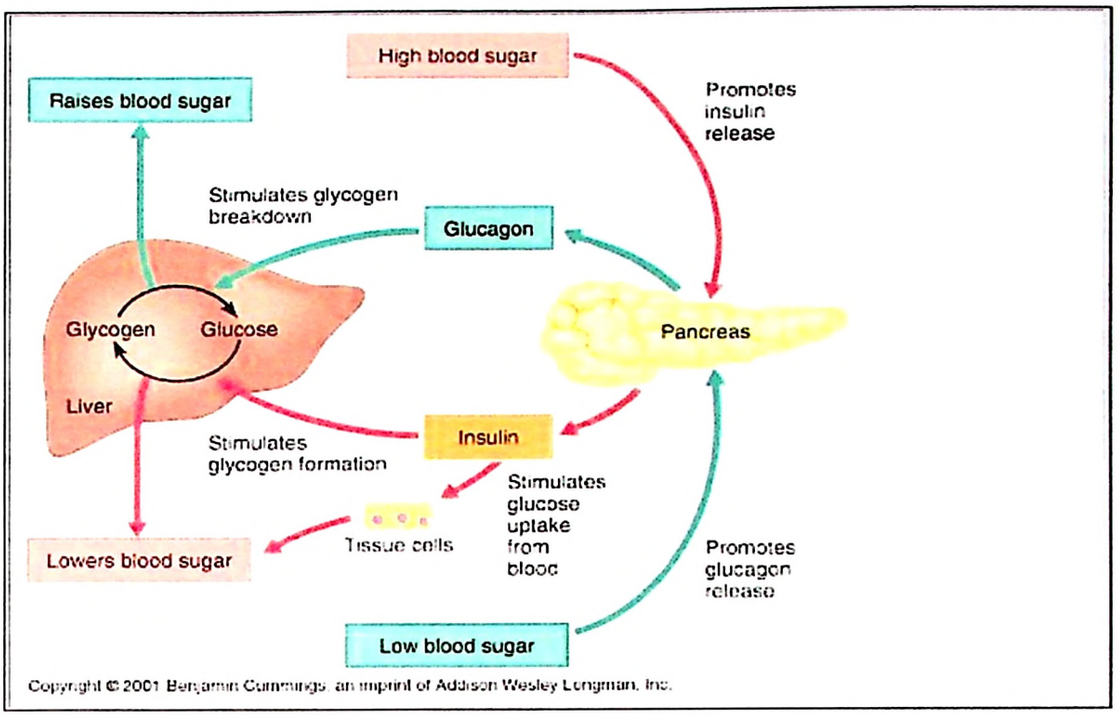

Figure 2.1: Hormonal regulation of blood glucose levels (Source: Marieb, 2001)

2.5.5 Impact on blood lipids

Several studies showed that Ramadan fasting has a positive impact on the level of blood lipids, decreasing serum total cholesterol, triglyceride, low-density lipoprotein (LDL) cholesterol but increasing high-density lipoprotein (HDL) cholesterol (Roky et al., 2004; Marbut et al., 2005; Meo and Hassan, 2015). Such beneficial impact on blood lipids seems to be gender-specific where these changes were more observed among men than women. The meta-analysis by Kul et al. comparing blood lipids before and after Ramadan found that both gender had reduction in LDL levels after Ramadan but differential impact concerning other lipid components. In males, there was reduction in the levels of total cholesterol, LDL cholesterol and triglyceride. In females, the level of HDL cholesterol was increased without increase in the levels of total cholesterol and

triglyceride (Kul et al., 2014). Overall findings from this meta-analysis showed that Ramadan fasting is associated with significant improvement of LDL levels but minor impact on other lipid parameters (Kul et al., 2014).

2.5.6 Impact on blood pressure

A number of studies suggested that Ramadan fasting could have a positive impact on the systolic and to less extent diastolic blood pressure among healthy individuals (Roky et al., 2004; Shehab et al., 2012; Salim et al., 2013; Meo and Hassan, 2015; Samad et al., 2015). In a meta-analysis of 25 studies that examined the impact of Ramadan fasting on cardiovascular risk factors in normal healthy adults, two out the three studies that reported the impact on blood pressure showed reduction in both systolic and diastolic blood pressure after Ramadan (Salim et al., 2013). The range of reduction was -3 to -7 mmHg systolic and -2 to -3 mmHg diastolic. In a study that measured the blood pressure before Ramadan and at multiple points after Ramadan, repeated measures showed a significant drop in both systolic (-7.6 mmHg) and diastolic (-3.2 mmHg) blood pressure in normotensive non-smoker middle aged men (Samad et al., 2015). Another study showed a significant drop of systolic blood pressure four weeks after Ramadan among a group of healthy multi-ethnic middle-aged volunteers (Shehab et al., 2012).

2.5.7 Impact on hematological parameters

The majority of the studies that examined the impact of Ramadan fasting on the blood cells and hemoglobin values showed mild or no changes (Roky et al., 2004). In a follow up study that examined hematological and coagulation factors during Ramadan and two months after among healthy individuals who fast Ramadan, fibrinogen level and factor VII activity were the only hematological and coagulation factors to show significant reduction after Ramadan (Sarraf-Zadegan et al., 2000). In another similar study that examined hematological parameters at the beginning and at the end of Ramadan, platelets were the only hematologic parameter to show marked reduction (Akrami Mohajeri et al., 2013). Additionally, hemoglobin and T-lymphocyte cells were shown in some studies to decrease during Ramadan (Roky et al., 2004).

2.5.8 Impact on inflammatory markers and immune status

It is also shown that fasting Ramadan could be helpful in controlling inflammation by reducing the levels of pro-inflammatory CXC chemokines, cytokines IL-1β, IL-6, and tumor necrosis factor (Akrami Mohajeri et al., 2013; Meo and Hassan, 2015). The pro-inflammatory markers have been associated with the development of atherosclerosis and the promotion of the oncologic process (Meo and Hassan, 2015). On the other hand, Ramadan fasting was shown to have no or mild effect on the immune system. For example, the levels of serum IgG concentrations that decreased during Ramadan remained within the normal range. Additionally, there was reduction in concentration of salivary IgA and increase in the lymphocyte number (Develioglu et al., 2013).

2.5.9 Impact on hormonal secretion

Ramadan fasting has significant impact on sex hormones in both males and females. In a study that examined the impact of Ramadan fasting on sex hormones in single healthy men, there was decrease in testosterone level, increase in FSH levels, but no change in LH levels (Mesbahzadeh et al., 2005). In another study that examined the changes in hormonal levels in women before and after Ramadan, there were no change in testosterone, estradiol (E2), prolactin (PRL), luteinizing hormone (LH), and follicle stimulating hormone (FSH) (Caglayan et al., 2014). Few studies examined the effects of intermittent fasting during Ramadan on the circadian variations in the secretion of cortisol and melatonin hormones. It was found that Ramadan fasting could have a two-hour delay in the acrophase of cortisone section but with consistency of the mean hormone level during the 24 hours (Bogdan et al., 2001; Roky et al., 2001). Additionally, circadian changes in nutrient oxidation rates were reported in Ramadan with more increase in fat oxidation and decrease in carbohydrate oxidation, as an adaptive mechanism to maintain the body-weight during fasting (El Ati et al., 1995).

2.5.10 Impact on renal function and urinary excretion

Ramadan fasting was shown not to negatively impact the kidney function in healthy subjects (Cheah et al., 1990). As expected during Ramadan, when the water intake is avoided during the day time, the 24-hour urine output is reduced and urinary osmolarity is increased. Additionally, the urine acidity and the urea concentration were shown to decrease (Roky et al., 2004). In a study that evaluated the effect of Ramadan fasting on calculus formation, there was a reduction in urine volume, calcium, phosphate, and magnesium but an increase in the concentration of uric acid, sodium,

potassium, citrate, and phosphate (Miladipour et al., 2012). Interestingly, these changes do not support the hypothesis that Ramadan fasting is a risk factor for calculus formation (Miladipour et al., 2012).

2.5.11 Impact on cardiovascular system

Several studies showed that fasting Ramadan have beneficial impacts on BMI, lipid profile, and blood pressure (Salim et al., 2013; Meo and Hassan, 2015). For example, a literature review of 11 studies that examined cardiovascular risk factors among healthy individuals showed an overall improvement in blood cholesterol along with reduction in body weight and both mean systolic and diastolic blood pressures (Salim et al., 2013). Additionally, the beneficial effects on inflammatory and coagulation markers such as interleukin-6 and C-reactive proteins, and D-dimer may provide anti-atherosclerotic effect on blood vessels (Salim et al., 2013). Moreover, the incidence of acute coronary syndrome , heart failure and cerebral stroke was not shown to be higher during Ramadan as compared with non-Ramadan times (Salim et al., 2013; Meo and Hassan, 2015).

2.5.12 Impact on respiratory system

A study that examined spirometry measures before, during, and after Ramadan among healthy individuals showed no major changes during Ramadan as compared with pre-Ramadan values (Siddiqui et al., 2005).

2.5.13 Impact on eyes and tears

It was shown that Ramadan fasting may cause decrease in tear proteins, lysozyme, lactoferrin and alpha amylase enzymic activity (Sariri et al., 2010). Additionally, it was shown that Ramadan fasting may be associated with increase in the intra-ocular pressure and tear secretion in the early morning period as a result of the fluid loading at the pre-dawn meal. However, by the end of fasting day these changes tend to diminish due to dehydration (Kerimoglu et al., 2010).

2.5.14 Impact on pregnancy

Although pregnant women are exempted from Ramadan fasting according to the Islamic teaching (The Holy Quran, 632 AD), some pregnant women are observing partial or complete Ramadan fasting. In the few studies that examined the pregnancy outcome among women who fast and those who did not fast, Ramadan fasting in healthy women with appropriate nutrition was shown to have no effect on intrauterine growth, pregnancy duration and anthropometrical measures of infant (Ziaee et al., 2010; Moradi, 2011). However, fasting in the first trimester may increase the relative risk of low weight birth (Ziaee et al., 2010). The clinical guidelines recommends against fasting if the pregnant women had chronic diseases such as diabetes (Al-Arouj et al., 2005; Al-Arouj et al., 2010).

2.5.15 Impact on sleep pattern

Since Muslims eat exclusively between sunset and sunrise, Ramadan fasting may induce altered sleep patterns with more daytime sleeping and late night sleeping (Roky et al., 2001; Bahijri et al., 2013), as shown in Figure 2.2. Altered sleep patterns may impact