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Title	Effect of glycaemic excursions on QT interval in diabetes patients
Author(s)	Nadeem, Asma
Publication Date	2023-09-19
Publisher	NUI Galway
Item record	http://hdl.handle.net/10379/17911

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Effect of Glycaemic Excursions on QT Interval in Diabetes Patients

A thesis submitted to the University of Galway

for the requirements for degree of Master of Science by Research

By

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Supervisor

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March 2023

Declaration

I, Asma Nadeem, hereby declare that all the work in this thesis is entirely my own work. I have not obtained any other degree from University of Galway or from any other University on basis of this work.

Signed: _____  . Date: _27/03/2023____

Abstract

Glucose excursions in Diabetes Mellitus patients are associated with increased risk of cardiac morbidity and mortality (Kaul, Tarr, Ahmad, Kohner, & Chibber, 2013). With the evidence from several clinical trials, it is understood that the hyperglycaemia contributes to increased cardiovascular disease (CVD) risk, particularly cardiac arrythmia due to prolongation of QT interval in Electrocardiogram (ECG). On the other hand, there is considerable evidence from meta-analysis of clinical trials that suggest a strong association of hypoglycaemia with prolongation of QT and CVD outcomes. There are various other factors that are also related to QT-prolongation.

The aim of this research is to synthesise available literature to analyse and establish a clear understanding of effect of glucose excursions on QT interval which consequently increases CVD risk. Objective of the thesis is to study the relationship of glucose excursions with QT-interval in electrocardiogram to understand the extent of the effect of hyper- and hypoglycaemia on QT-interval.

A systematic approach for literature review and evidence synthesis has been employed to collect available clinical evidence and to analyse the reported outcomes.

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, three databases, PubMed, Cochrane and Embase were searched for evidence published between 2000 and 2022. The search resulted in a total of 3039 records reporting clinical trials, observational studies, case reports and meta-analysis. After removing the duplicates (n=440), 2599 articles were selected for title and abstract review followed 250 full paper reviews for eligibility of inclusion. A total of 77 articles were selected for review and 43 studies were selected for meta-analysis based on data availability. The meta-analysis is performed on all data, and sub-groups based on sub-types of diabetes and healthy population. These 43 studies were further grouped as 17 experimental studies, 18 observational studies and 8 case reports.

A pooled analysis of experimental studies showed a positive effect in both hypoglycaemia (Cohen’s d = 1.14; 95% CI 1.01-1.26) and hyperglycaemia (Cohen’s

d = 0.5; 95% CI 0.38-0.63) compared to normal glucose levels. Hypoglycaemia has a strong effect compared to hyperglycaemia in both healthy volunteers and diabetes patients. QTc was also prolonged in all case reports (>460 ms). Similarly, results show that QTc is prolonged in hypoglycaemia, reported in observational studies (Cohen's d = 0.58; 95% CI 0.01-1.18). It is observed that diabetic population has more QTc prolonged cases than healthy population. QTc is more prolonged in hypoglycaemic population (34.23 ms; 95% CI 30.71-37.75 ms) than hyperglycaemic population (11.04 ms; 95% CI 8.30-13.78 ms).

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Acknowledgment

I would like to thank and want to express my sincerest gratitude to all those who have contributed their valuable assistance and provided me help, guidance and support in completion of my degree. Firstly, I would like to express my sincere thanks to my supervisor, Prof. William Wyns, for his constant guidance, valuable advice, patience and educational support in both research and personal development. This work would not have been possible without his constant guidance and support. I am thankful to my graduate research committee, Prof. Osama Suliman, Dr Roisin Dwyer, Dr Adnan Elahi, for their support during my MS.

I am hugely grateful to Dr Andrew Simpkin, Beatrice Charamba and Dr Conon Judge for their expert advice on statistical methods and systematic review.

I would also like to thank Dr Sandra Ganly, David Connolly, Eileen Coen, Dr Cathal Ó Flatharta, Dr Mattia Lunardi, and my colleagues at Smart Sensors Lab for their support and motivation in completing my research degree.

Lastly, I would like to thank my family for their support throughout my life and specially when I decided to come back to education after a long career break. I cannot forget the support and encouragement that my husband, kids and parents (late) have given me during past few years. I also cannot forget all the motivation and encouragement given by my sisters and my friends which kept me determined.

Asma Nadeem

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1. Introduction

1.1 Background

1.1.1 Diabetes Mellitus

Diabetes Mellitus (DM), commonly known as Diabetes, was first documented by Egyptians as condition characterised by weight loss or polyuria (more frequent urination than normal). Diabetes occurs when blood sugar (also referred as blood glucose) level is too high. Regulation of the levels of glucose in the blood is based on a negative feedback loop and acts via the release of insulin and glucagon. When glucose levels in blood are high, a specific group of cells, known as β-cells of the islet of Langerhans in the pancreas, are triggered to release insulin. Insulin lowers the level of glucose in blood. On the other hand, when the glucose level in blood is low, the α-cells of the pancreas are stimulated to release glucagon. Glucagon signals the liver to convert stored glycogen into glucose which is released into the blood to compensate for low glucose level. This process of achieving a balanced level of glucose in blood through release of specific hormones is called homeostasis (Kaul, Tarr, Ahmad, Kohner, & Chibber, 2013). The states when glucose levels are too high, too low, or normal in the blood are called hyperglycaemia, hypoglycaemia and normoglycemia, respectively. The word glycemia means the level glucose (sugar) in blood. In a healthy human weighing 70 kg, approximately 4 grams of glucose is present in the blood. The level of blood glucose varies during the day as to meet the needs of human body function where the stored glucose is delivered via blood to various organs of body (Wasserman, 2009). The level of blood glucose in most part of the world is measured using molar concentration in mmol/L (millimoles per litre). However, in United States (US) and some other regions a mass concentration measured in mg/dL (milligrams per decilitre) is used. These two units are interconvertible where 1 mmol/L is equivalent to 18 mg/dL (Kulkarni, 2005).

There are three major types of diabetes that affect majority of the all the diabetes patients: Type 1, Type 2, and Gestational diabetes (Prevention, 2014). Other less common types include monogenic diabetes, cystic fibrosis-related diabetes, and those caused by rare endocrine syndromes. Type 1 diabetes is where the blood glucose level

is too high because the body cannot make insulin. This happens when the immune system attacks the β-cells in pancreas that make the insulin, restricting production of natural insulin in body. The insulin allows the glucose in blood to enter in the body cells to deliver energy. In the type 1 diabetes, the body still breaks down the carbohydrate from food and drink and turns it into glucose. When this glucose enters in the bloodstream, there is no insulin to allow it into the body cells. Therefore, more glucose builds up in the bloodstream, leading to high blood sugar levels (Adeghate, 2006). Patients with type 1 diabetes are treated with insulin delivered via injection through insulin syringes or pumps. In type 2 diabetes, which is the most prevalent type, the body does not produce enough insulin, resulting in accumulation of glucose in bloodstream (Adeghate, 2006). High sugar levels in the blood can seriously damage vital body organs, including heart, eyes, and feet. This condition can develop at any stage of life. According to World Health Organization (WHO), up to 95% people with diabetes have type 2 diabetes (WHO, 2016). The third more common type of diabetes, Gestational Diabetes, develops during pregnancy, when blood glucose level is too high, and body is not able to produce enough insulin to regulate. This type of diabetes is a temporary condition that generally goes away after the childbirth. However, the patient must take extra precautions and in some cases a treatment during the pregnancy.

1.1.2 Heart Electrical Activity

The heart conduction system is a network of nodes, cells and signals that controls the heartbeat. An electric signal travels through heart each time when heart beats and in result of these signals different parts of hearts expand and contract. As shown in Figure 1, the heart generates its own electrical signal. This electrical signal is produced by a tiny structure known as the sinus node, located in the upper portion of the right atrium. From the sinus node, the electrical signal spreads across the right atrium and the left atrium (the top two chambers of the heart), causing both atria to contract. This pushes their load of blood into the right and left ventricles, the bottom two chambers of the heart. All the flow of blood in body and heart is controlled by these expansions and contractions. The cardiac electrical signal controls the heartbeat in two ways. First, since each electrical impulse generates one heartbeat, the number of electrical

impulses determines the heart rate. In normal sinus rhythm, that rate will be between 60 and 100 beats per minute.

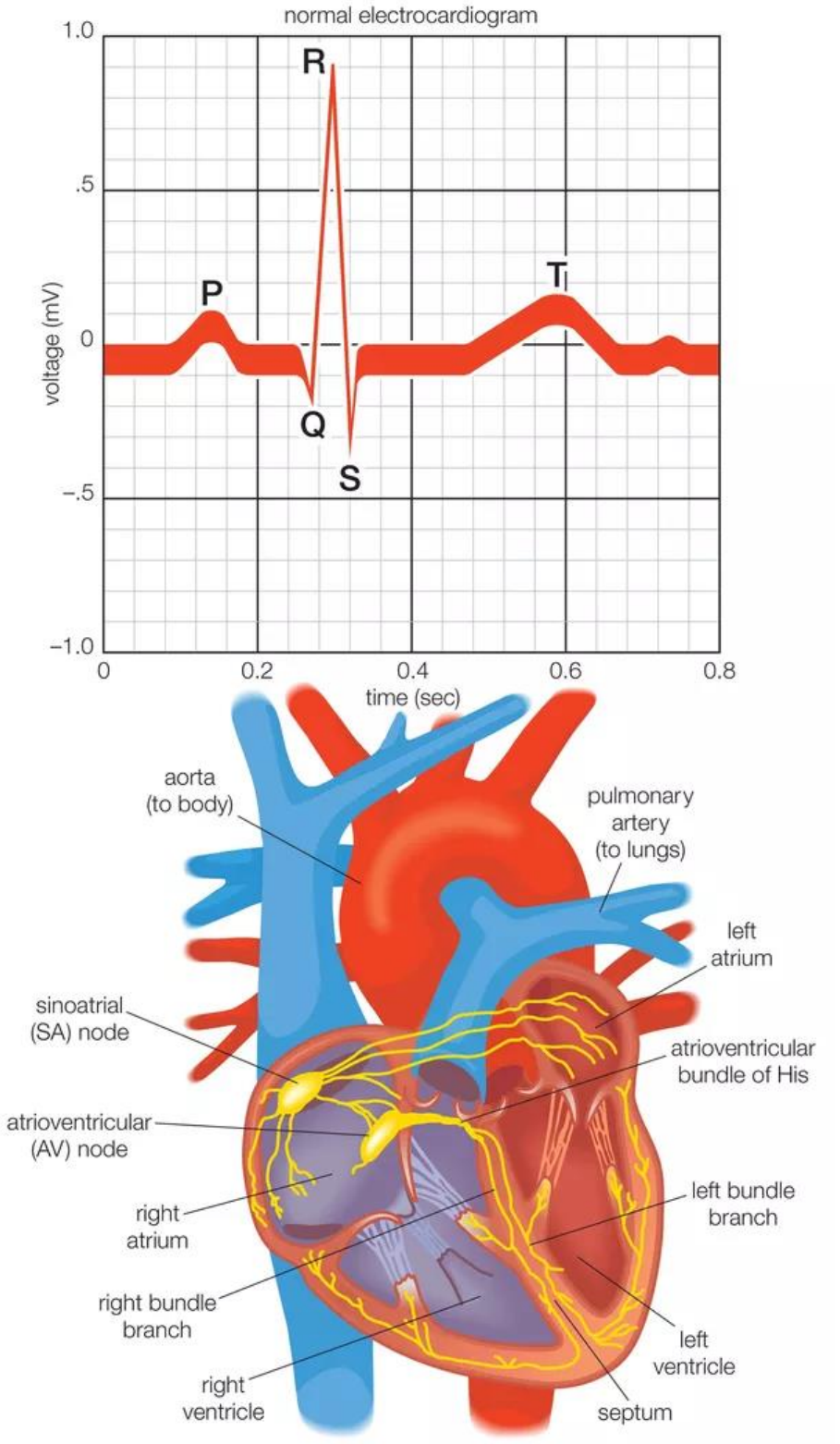

Figure 1. Structure of heart and pathways of electrical activity to create heart rhythm. Image sourced from Encyclopaedia Britannica/UIG/Getty Images

The sinus node signal also controls electrical conduction of the heart's steps as it spreads across the heart. It causes the cells of heart muscle to contract in the correct sequence and ensures regular, efficient, and coordinated heartbeats (Sampson, 2015). The electrical signal produced by the heart electrical activity, shown in the top half of the Figure 1, is recorded on a chart using a process called electrocardiography, and the graph is called electrocardiogram (ECG).

1.1.3 Electrocardiogram (ECG)

Electrocardiography is performed by placing several electrodes on the skin at various locations around the heart and limbs. These electrodes measure electrical signal (voltage) that result from depolarization (when heart muscle contracts) and repolarization (when heart muscle expands or relax) during the cardiac cycle (heartbeat) (Taccardi, 1997).

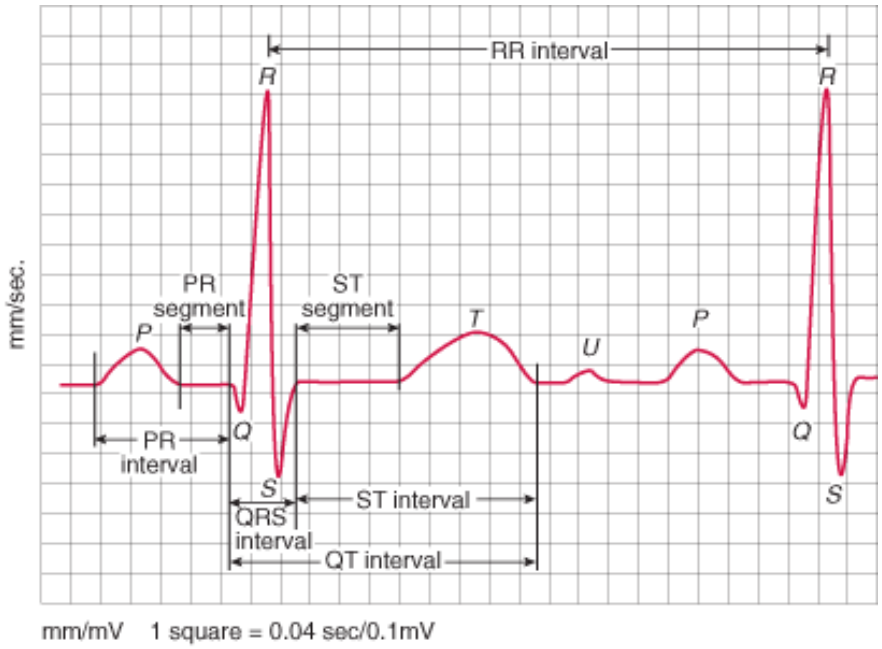

Figure 2. A typical ECG showing major features including segments, waves and key points.

The ECG shows characteristics in the form of waves and segments representing different activities of heart, and any abnormality in these characteristics indicate associated abnormality of heart function. The major features of an ECG are explained as follows:

- **P-wave**: The P-wave represents depolarization (contraction) of the atria.

- **PR interval**: The PR interval is measured between the start of the P-wave and the start of the QRS complex. The PR interval determines whether the electrical pulse transmission from atria to ventricle is normal.
- **PR segment**: The PR segment is the baseline, also known as isoelectric line, which is measured between the end of P-wave and the start of QRS complex. The base line is used as reference in measuring amplitudes of the ECG.
- **QRS complex**: The QRS complex represents depolarization (contraction) of the ventricles. Although it may not always include a Q-wave, R-wave and S-wave, it is still referred to as QRS complex. As the left ventricle is considerably large compared to right ventricle, the amplitude of QRS complex is dominated by the left ventricle contraction.
- **ST segment**: The ST segment connects the QRS complex and the T wave. It represents the periods when ventricles are depolarized (relaxed); therefore, the voltage potential is same as the reference line.
- **T-wave**: T-wave represents repolarization of the ventricles.
- **U-wave**: Sometimes the electrical activity of the ventricular papillary muscle is out of phase with the rest of the ventricles and will record as a "U" wave that shows after the T wave.
- **RR interval**: The RR interval is measured as time between two consecutive R peaks (maximum value of R-wave). RR interval, also referred as inter-beat interval, is often used as a measure of duration of complete cardiac cycle.
- **QT interval**: QT interval measures from the start of the QRS complex to the end of the T wave. This is an important segment because it captures the beginning of ventricular depolarization through the plateau phase to the ventricular repolarization. It covers the entire ventricular activity. The QT interval is used as a clinical measure of cardiac function to assess cardiovascular disease as well as risk. As the QT interval is affected by the heart rate, it is normally standardised for clinical use. The standardisation of QT interval is called QT correction, and the standardised QT interval is referred as QTc (corrected QT interval). There are several methods of QT correction where the most commonly used are Bazett's method and Fridericia's method. Details of these methods and comparison of advantages and limitations is provided in (Funck-Brentano, 1993).

Changes in normal ECG occur because of cardiac abnormalities, such as cardiac rhythm disturbance (in conditions known as atrial fibrillation and ventricular tachycardia), inadequate coronary artery blood flow (in conditions known as myocardial ischemia and myocardial infarction), and electrolyte disturbance (in conditions known as hypokalaemia and hyperkalaemia).

1.1.4 Effect of Diabetes on Cardiac Electrocardiogram

Heart disease is common in people with diabetes. Over time, high blood sugar can damage blood vessels and the nerves that control the heart. Data from Heart Association from 2012 shows that 65% of people with diabetes will die from heart disease or stroke. Heart disease and stroke risk is more than twice in people with diabetes compared to those with normal sugar level. Patients with diabetes mellitus have a two to ten-fold higher risk of sudden cardiac death (Svane, 2020). With the evidence from several clinical trials, it is understood that the high glucose level (hyperglycaemia) contributes to increased cardiovascular disease (CVD) risk, particularly cardiac arrythmia due to prolongation of QT interval in Electrocardiogram (ECG), which is also known as torsade de pointes.

The blood glucose plays a direct role in modulating QTc, with both hypo- and hyperglycaemia prolonging QTc in healthy volunteers as well as in patients with diabetes (Taubel, 2022). The QT interval is primarily controlled by various ion channels (Na+, Ca+, K+) that directly influence cardiac depolarisation and repolarisation. The QT interval represents the cumulative surface depolarisation and repolarisation of the myocardium and varies with heartrate. There is a considerable evidence from meta-analysis of clinical trials that suggest a strong association of low glucose levels (hypoglycaemia) with prolongation of QT and CVD outcomes (Goto, 2013). QT interval prolongation is a common finding in up to 44% of patients with diabetes (Li, et al., 2012). Several studies have reported QT prolongation in hyper- or hypoglycaemia; however, there is no literature compiling the evidence to assess the extent of the effect of these glucose excursions on QT interval in these contrasting cases of glucose excursions.

1.2 Aims and Objectives

The primary objective of the thesis is to study the relationship of glucose excursions (high or low levels of blood sugar) with QT interval in electrocardiogram and understand the role and nature of co-contributors to QT prolongation**.** For this research, a systematic approach has been employed to gather and synthesise the available literature for over past 20 years. The data reported in literature was extracted and analysed to compare the effect of glucose excursions on QT interval, and a relative effect of hyper- and hypoglycaemia is reported in this thesis.

2. Methodology

2.1 Search Method

The literature published between 2000 and 2022 was searched using PICO (population, intervention, comparison, and outcome) search methodology form three major databases: PubMed, Embase and Cochrane. The terms used for population, intervention, comparison, and outcome are given in the Figure 3.

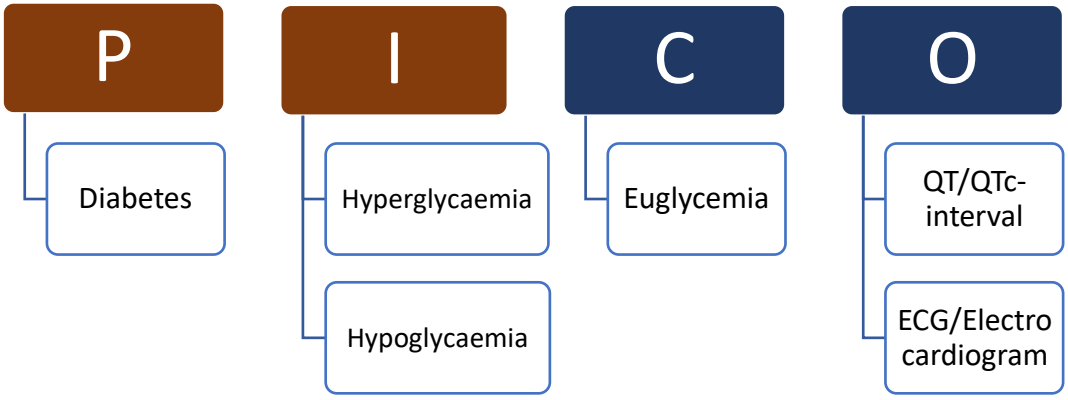

Figure 3. PICO search terms used for evidence synthesis.

I used Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) method for the systematic review and meta-analysis reported in this thesis. The PRISMA flow diagram is shown in Figure 4. The search resulted in a total of 3,039 articles published between 2000 and June 2022. After removing the duplicates, a total of 2,599 abstracts were reviewed to select papers for full review based on the screening criteria. The screening criteria was to include papers published in English language: 1) reporting both retrospective and prospective observational studies on diabetes and QT interval; 2) experimental studies involving glucose clamps; 3) case reports publishing cases of severe glycaemic events; 4) clinical trials reporting continuous glucose measurement and ECG data. A total of 250 papers fulfilled the screening criteria which were further reviewed for final selection through full text review. Based on the inclusion criteria of papers reporting paired quantitative data on glucose and QT-interval in human were selected. Finally, a total of 43 papers were selected for meta-analysis.

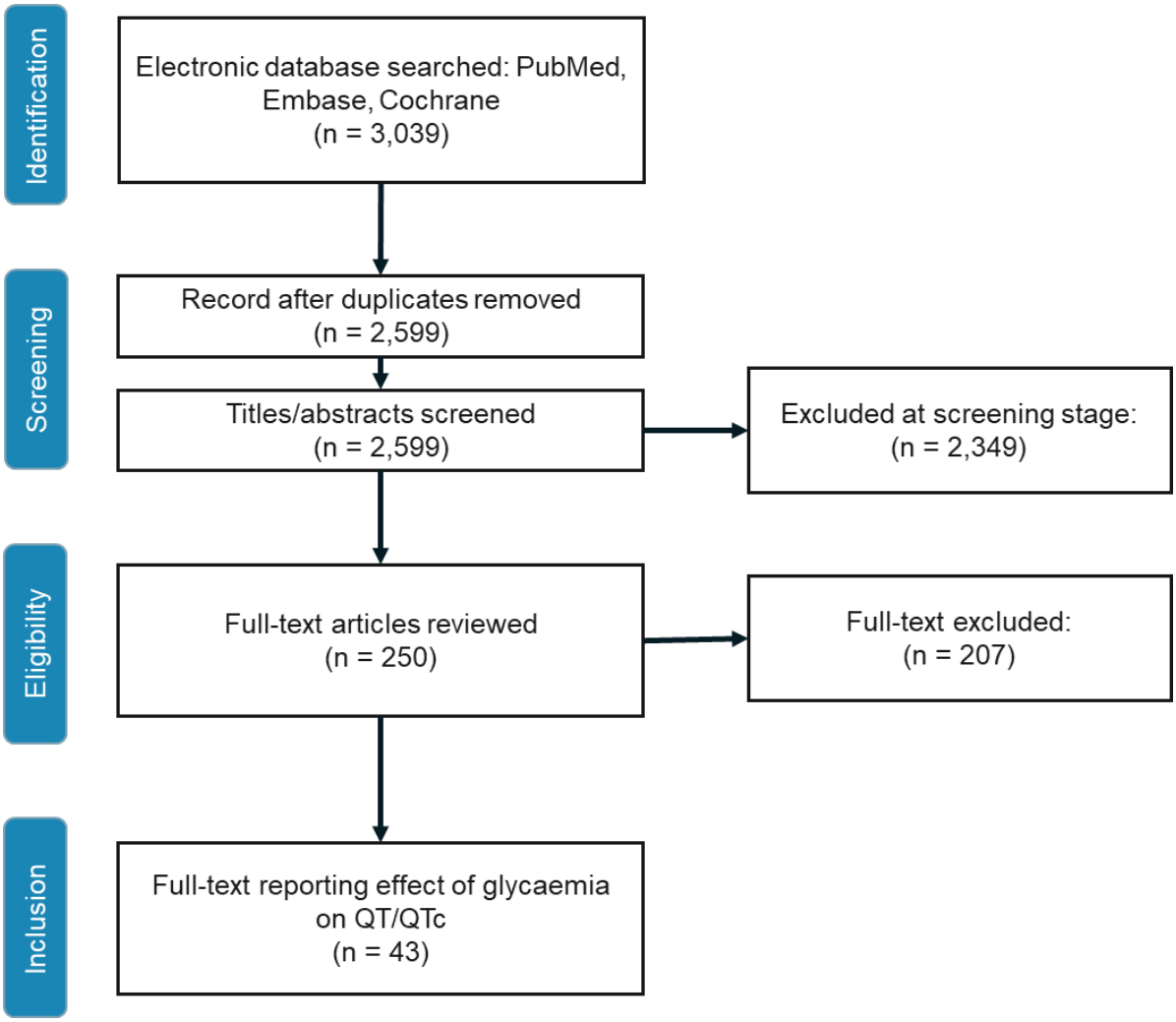

Figure 4. PRISMA flow diagram for the systematic review and meta-analysis reported in this thesis.

The meta-analysis is performed on all, and sub-groups based on sub-types of diabetes and healthy (or non-Diabetic) population. The summary of data extracted is presented in tables and meta-analysis including pooled effect size and subgroup analysis is presented in graphics form in chapter 3.

2.2 Data Extraction and Missing Data

The published literature is hugely diverse and report diverse data for various clinical settings and studies. The papers selected for the review and meta-analysis have data in various formats and for various settings, therefore, I needed to process the data including unit conversions and statistical presentation for comparison. At first, all data from the selected 43 papers were extracted and pooled in a table with details of data and units. This included all primary data for meta-analysis as well as the auxiliary data. Following that the data was analysed for potential mismatches and missing fields.

No interpolation is used to create missing data as the selection of 43 papers was done considering that these provide minimum required data for analysis. The conversion of measurement units and reported statistics were done where required.
It is important to note that the data collected and processed by the sources may have limitations that are beyond my control. As the data is collected using various devices and in varying conditions by the authors of the papers reviewed in this analysis, it is expected that the precision and accuracy of the devices may vary across all data analysed. In addition, the methods used to calculate QT intervals may have additional errors and observer bias for manual methods.

In this analysis, I have standardised all units and statistics to those listed in Table 1.

Table 1. Measurement units and statistics used for meta-analysis.

Name of Unit/Metric/Measurement	**Format/Unit used**
Glucose concentration	mmol/L (millimoles per litre)
ECG intervals (e.g. QT interval)	ms (millisecond)
Age	years
Sample, population statistics	Mean±SD (Mean and Standard Deviation)

The unites and statistics, that were not in the format listed in Table 1, were converted using following methods.

2.2.1. Median, Range, and Interquartile Range to Mean and Standard Deviation Conversion

I used the estimation method proposed in (Wan, 2014) which provides an improved estimation compared to (Hozo, Djulbegovic, & Hozo, 2005) and also cater for additional scenarios as provided in Table 2. Following formulae were used for various cases where data was presented either in the form of median (m), lower (a) and upper (b) values, and sample size (n), or where first (q_1) and third quartile (q_3) values were given instead of lower and upper values.

Table 2. Estimation of Mean and Standard Deviation from Median and Range data.

Data Scenarios	Mean Estimation	Standard Deviation Estimation
m, a, b, n	$\bar{X} \cong \frac{a + 2m + b}{4}$	$\bar{S} \cong \begin{cases} \sqrt{\frac{(a-2m+b)^2}{4} + (b-a)^2} \Big/ 12 & n \leq 15 \\ \frac{(b-a)}{4} & 15 < n \leq 70 \\ \frac{(b-a)}{6} & n > 70 \end{cases}$
m, q_1, q_3, n	$\bar{X} \cong \frac{q_1 + m + q_3}{3}$	$\bar{S} \cong \frac{q_3 - q_1}{1.35}$

2.2.2. Standard Error to Standard Deviation Conversion

The standard deviation (*S*) was calculated from standard error (*SE*) using following equation:

$$\bar{S} = SE \times \sqrt{n}$$

n is the sample size.

2.2.3. Mean Difference and Confidence Interval to Standard Deviation Conversion

In a number of studies, the mean value and confidence interval (CI) was given which needed to be converted to mean and standard deviation. The standard deviation for each group is obtained by dividing the length of the confidence interval by a constant *k*, and then multiplying by the square root of the sample size (*n*):

$$\bar{S} = \frac{(CI_{ul} - CI_{ll})}{k} \times \sqrt{n}$$

CI_{ul} and CI_{ll} are upper and lower limits of confidence interval. The constant *k* is 3.92 (which is 2 × 1.96) for 95% confidence interval, 3.29 for 90% CI and 5.15 for 99% CI (Higgins, 2019).

2.2.4. Combining Standard Deviations

In the cases where summary analysis was missing and I needed to combine standard deviations from different samples, following formula was used:

$$\bar{S} = \sqrt{\frac{(n_1 - 1)S_1^2 + (n_2 - 1)S_2^2}{n_1 + n_2 - 2}}$$

Where S_1^2 and S_1^2 are standard deviations of two samples and n_1 and n_2 are samples sizes.

2.3. Analysis Methods

The data from all eligible studies were collected in a spread sheet. Using the methods described above, all data was converted and standardized to the units given in Table 1. A pooled analysis was performed to study association of glucose level with QTc interval in diabetes patients as well as healthy individuals. The effect size was calculated using standardized mean difference (Cohen's d) formula as following:

$$d = \frac{(QTc_{mean}^{int} - QTc_{mean}^{cont})}{\sqrt{\frac{(QTc_{sd}^{int})^2 + (QTc_{sd}^{cont})^2}{2}}}$$

Where QTc_{mean}^{int} and QTc_{mean}^{cont} are corrected QT interval means from the intervention and control groups, and QTc_{sd}^{int} and QTc_{sd}^{cont} are standard deviations of the corrected QT intervals from the two groups. The intervention arm in this scope is glucose clamp to induce either hyper or hypoglycaemia and the control group is clamped to maintain euglycemia.

For the 8 case reports that are reviewed in this study, the data from patients attending emergency department due to extremely high (hyper) or low (hypo) glucose levels were compared with healthy population data from a large population study. As there's large difference between the sample sizes, a visual analysis is presented where the median and range of the two samples are shown on a scatter plot of the patient data from case reports. Additionally, the effect size (Cohen's d) was calculated and reported in this thesis.

Moreover, visual analysis by clustering and scatter plots were performed and reported for all studies reported in this review. This analysis is performed for all data, subgroups and subpopulations to study association of glucose excursions with QTc.

3. Results

The meta data from all 43 studies included in this thesis is listed in Table 3. These include 8 individual case reports, 17 interventional studies reporting glucose clamp and 18 observational studies. The summary analysis of all studies and review of subgroups is presented in the following.

Table 3. Meta data from all studies included in this review.

Author	Population Size (N)	Age (Year)		Glucose (mmol/L)		QTc (ms)		Population Type
		Mean	SD	Mean	SD	Mean	SD	
(Middleton, et al., 2017)	11	62.8	10.2	2.77	0.51	432.6	16.9	T2DM
(Chow, et al., 2014)	11	67.3	4.33	<3.5	N/A	402	49	T2DM
				>5	N/A	384	36	
(Cha, et al., 2016)	208	68.1	12.1	1.9	0.8	460	33	T2DM
				>5	N/A	433	33	
(Beom, et al., 2013)	9	73.2	77	<3.33	N/A	447.6	18.2	T2DM
				>5	N/A	417.2	30.6	
(Murphy, et al., 2004)	44	12.4	9.8	4.3	1.3	412	22	T1DM
				10.3	2.6	401	19	
(Novodvorsky, et al., 2017)	37	34	4.3	3.5	N/A	413	30	T1DM (Day)
						405	27	T1DM (Night)
(Bachmann, Auderset, Zumsteg, Szinnai, & Donner, 2019)	25	13.2	2.7	<3.7	N/A	411	15	T1DM
				>5	N/A	405	18	
(Christensen, et al., 2010)	14	56	10	≤3.5	N/A	432	33	T1DM
				>5	N/A	422	30	
(Gill, Woodward, Casson, & Weston, 2009)	25	36	7	<3.4	N/A	445	40	T1DM
				≥5	N/A	425	23	
(Laptev & Ryabykina, 2013)	150	13.8	2.9	<3.9	N/A	434	28	T1DM
				≥3.9	N/A	428	28	
	26	67.8	8	<3.9	N/A	440	27.4	T2DM

(Makrilakis, et al., 2018)				>3.9	N/A	428	14.3	
(Mylona, Liatis, Anastasiadis, Kapelios, & Kokkinos, 2020)	154	73.2	16.2	2.14	0.73	442	48.2	DM (Type N/A)
	95	70.7	10.3	>3.9	N/A	401	29.6	
(Andersen, 2021)	21	62.2	8.3	5.7	0.3	407	6.1	Non-Diabetic
				2.5	0.4	458	12.1	
				15.6	1.3	415	6.8	
	21	62.8	6.5	2.5	0.4	459	11.9	T2DM
				16.4	1.8	425	6.4	
(Due-Andersen, et al., 2008)	18	40.15	11.9	2.6	0.3	419	12.4	T1DM
				>3.9	N/A	410.5	16.6	
(Laitinen, et al., 2008)	18	35	4.2	5	N/A	408	21	Non-Diabetic
				3	N/A	429	29.4	
(Jacqueline, 2014)	13	43	10.3	8.5	3.7	390	34	T1DM
				3.4	0.3	430	34	
	10	25	3.1	5.4	0.3	370	31	Non-Diabetic
				3.4	0.3	440	63	
(Koivikko, et al., 2008)	16	32	8	5	0.3	410	31	T1DM
				2.25	0.1	419	35	
	8	34	10	5	0.3	428	34	Non-Diabetic
				2.25	0.1	448	38	
(Lee, et al., 2005)	8	35	8	5	N/A	391	30	T1DM
				2.5	N/A	448	34	
(Kimura, et al., 2017)	37	68.6	1.38	7.21	0.26	412	4.54	Hyperglycemic group (Hb1Ac≥6.5%)
	37	64.6	1.87	6.2	0.2	402	3.42	Normoglycemic group (Hb1Ac<6.5%)
(Robinson R. , et al., Mechanisms of abnormal	17	28	6.4	5	N/A	406	18	Non-Diabetic
				2.5	N/A	480	25	

cardiac repolarization during insulin-induced hypoglycemia, 2003)								
(Lee, et al., 2004)	8	33.8	6.5	5	N/A	378	14.1	T1DM
				2.5	N/A	439	28.3	
(Christensen, et al., 2014)	10	42.5	7.5	8.1	0.6	402	6.1	T1DM
				2.5	0.3	429	12.7	
(Ireland, Robinson, Heller, Marques, & Harris, 2000)	17	27.7	6.4	4.5	0.5	399	23	Non-Diabetic
				2.42	0.2	459	22	
(Landstedt-Hallin, Englund, Adamson, & Lins, 1999)	13	56.7	3.75	5.2	0.1	427	22	T2DM
				2.7	0.2	491	47	
(Novodvorsky, et al., 2018)	18	35	7	5	N/A	422	27	T1DM
				2.5	N/A	459	34	
(Chow, et al., 2015)	12	53.5	7.8	5.2	0.3	417	20.8	T2DM
				2.7	0.6	493	72.1	
	11	52	8.4	5.2	0.3	412	27.5	Non-Diabetic
				2.6	0.6	469	32.1	
(Færch, et al., 2015)	9	56	9.8	5.2	0.3	421	18	T1DM
				2.6	0.2	433	18	
(Kobayashi, et al., 2018)	219	60	13	9.79	2.99	430	22	T2DM
(Ko, Chan, Critchley, & Cockram, 2000)	192	56.6	12.9	9.7	3.8	398	30	T2DM
(Gan, Wong, Cheung, & McLean, 2009)	107	63	1.1	11	0.3	430	3	DM
(Gordin, Forsblom, Rönnback, & Groop, 2008)	13	25.4	1.4	16.9	0.7	412	27.2	Non-Diabetic
				5.1	0.3	378	18	
	22	25.9	5.6	18	0.8	415	23.4	T1DM
				7	0.6	390	28.1	

(Charamba, et al., 2021)	17	52.5	13.2	13.56	N/A	415.27	N/A	T1DM
				7.41	N/A	405.3	N/A	
(Vanina, 2007)	24	52.4	6.9	13.9	N/A	422.6	34	T2DM
				6.9	N/A	415.5	25.6	
	13	48.5	5.9	13.9	N/A	401.9	5.1	Non-Diabetic
				6.9	N/A	394.6	19	
(Robinson R. , Harris, Ireland, Macdonald, & Heller, 2004)	22	40.4	17.2	>5	N/A	Δ27	15	T1DM
				<2.5	N/A			
(Monya-Tambi, Castillo, & Syed, 2014)	1	75	0	1.22	N/A	519	0	T2DM (Case Report)
(Forster, Baillie, & Strain, 2012)	1	75	0	2.69	N/A	467	0	T2DM (Case Report)
(Ukena, Mahfoud, Neuberger, & Böhm, 2011)	1	74	0	1.6	N/A	596	0	T2DM (Case Report)
(Bolognesi, Tsialtas, Bolognesi, & Giumelli, 2011)	1	70	0	1.88	N/A	520	0	T2DM (Case Report)
(Shipman, Narichania, & Sorajja, 2017)	1	82	0	34.41	N/A	518	0	T2DM (Case Report)
(Thiruvenkatarajan, et al., 2010)	1	79	0	11.98	N/A	690	0	T2DM (Case Report)
(Kurnaz, et al., 2019)	1	14	0	22.97	N/A	470	0	T1DM (Case Report)
(Hasan, Elrishi, Kilvert, & Fox, 2010)	1	57	0	0.69	N/A	476	0	T1DM (Case Report)
(Mezquita-Raya, et al., 2018)	26	52.2	16.4	9	1.4	409	28.7	DM (Type N/A)
				<3.9	N/A	418	14.4	

3.1 Pooled Analysis

A pooled analysis was performed on all 43 studies to analyse the relationship of QTc with the glucose excursions. These 43 studies reported data from 2177 individuals including diabetes patients and healthy population. The pooled sample sizes for hypoglycaemia, hyperglycaemia and euglycemia records are 1073, 722 and 382 respectively, as given in Table 4.

Table 4. Statistics of subgroups from all 43 studies.

Group	Sample size (N)	QTc (Mean)	QTc (SD)
Hypoglycaemia	1073	440.23	32.68
Euglycemia	382	406	21.14
Hyperglycaemia	722	417.04	22.47

Figure 5 shows a scatter plot of mean QTc values plotted against mean glucose values reported in all 43 studies. Definition of hypoglycaemia varies slightly from glucose level <3 mmol/L to <3.9 mmol/L in different studies. The glucose levels were clamped to less than 3 mmol/L to induce hypoglycaemia in the experimental studies. The definition of hyperglycaemia in the reported studies is given as glucose level >9 mmol/L. Euglycemia range is defined as glucose levels more than 3.9 mmol/L and less than 9 mmol/L. All the outliers in the scatter plot shown in Figure 5 and the boxplot in Figure 6 (left) are data from case reports, where either QTc is too prolonged or glucose levels are too extreme (either high or low). Figure 6 shows a comparison of QTc levels in the three glycaemic states where the bubble plot represent mean values as the centre of the plot and the bubble size depicts standard deviation. The mean QTc interval is 440 ms in hypoglycaemia, 417 ms in hyperglycaemia and 406 ms in euglycemia. Standard deviation is 32.7 ms in hypoglycaemia, 22.5 ms in hyperglycaemia and 21.1 ms in euglycemia. The mean difference between QTc interval in hypoglycaemia and normal glucose levels (euglycemia) is 34.23 ms (±30.08 ms). While the mean difference in hyperglycaemia and euglycemia is 11.04 ms (±22.01 ms). The effect size calculated as Cohen's d for both hypo and hyper glycemia compared to euglycemia is 1.14 (1.01-1.26; 95%CI) and 0.50 (0.38-0.63; 95%CI), respectively.

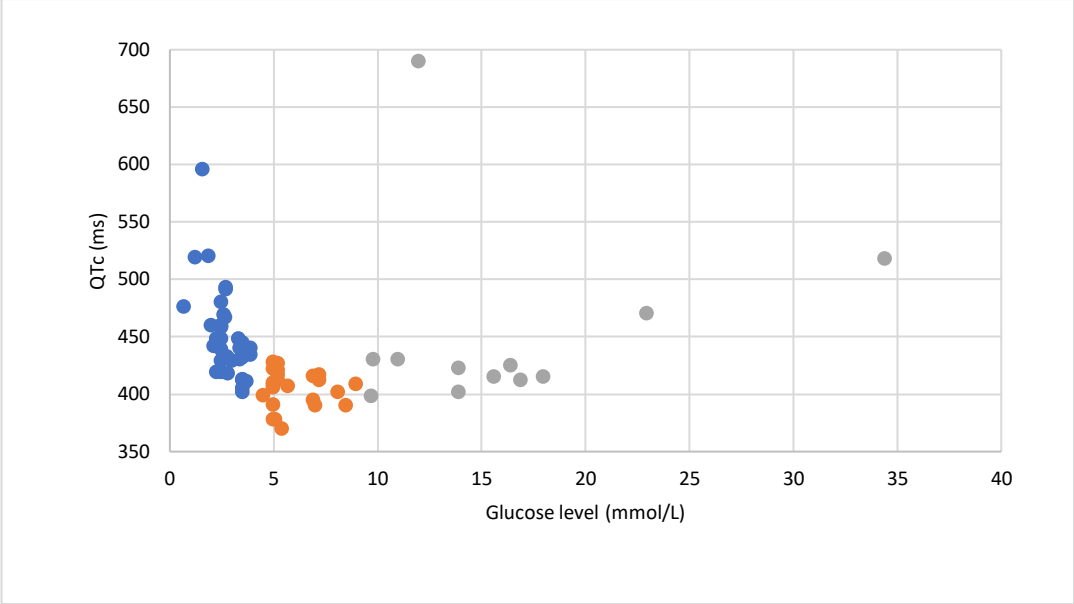

Figure 5. Scatter plot of all mean values of QTc and Glucose level reported in the 43 studies.

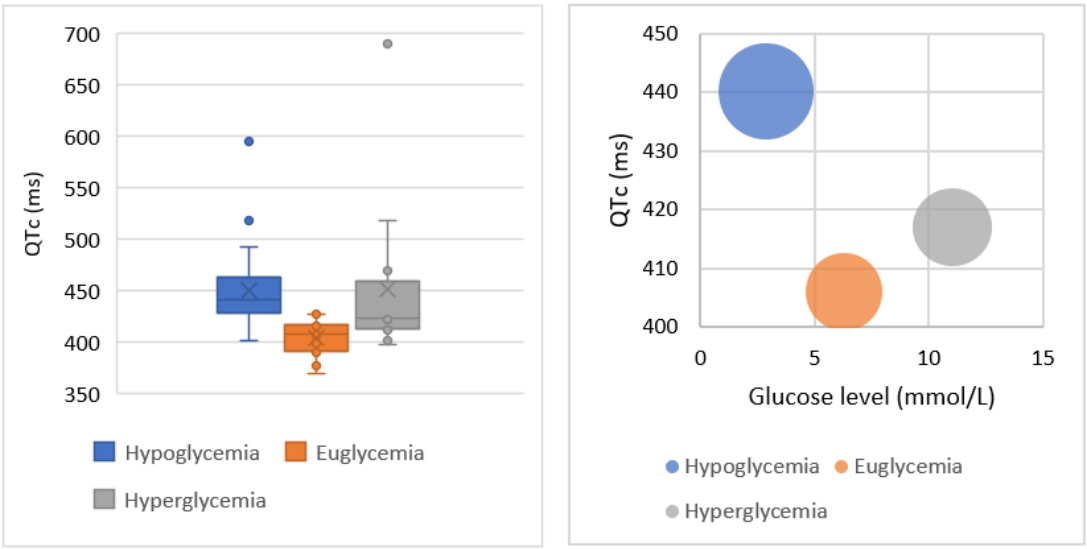

Figure 6. Comparison of QTc in Hyper, Hypo and Euglycemia conditions for all data from 43 studies. The boxplot on left side and bubble plot on the right side show relative changes in QTc.

3.1.1. Pooled t-test

A t-test was performed on the pooled data to make three comparisons: 1) QTc interval in hypoglycaemia is significantly different than in euglycemia; 2) QTc interval in hyperglycaemia is significantly different than in euglycemia; QTc interval in hypoglycaemia is significantly different than in the hyperglycaemia. Table 5 lists the t-test results of the three comparisons made for significance of the difference in the QTc intervals of three groups. It is evident that the QTc of the three groups are significantly different from each other and the strongest difference is found in the case of hypoglycaemia compared to normal glucose levels (euglycemia).

Table 5. t-test results of 3 comparisons made between the QTc interval of 3 groups.

Test Group Pair	Mean difference (ms)	95% Confidence Interval (ms)		p-value
Hypoglycaemia - Euglycemia	**34.23**	**30.71**	**37.75**	**<0.0001**
Hyperglycaemia - Euglycemia	**11.04**	**8.30**	**13.78**	**<0.0001**
Hypoglycaemia - Hyperglycaemia	**23.19**	**20.45**	**25.93**	**<0.0001**

3.2 Analysis by Types of Studies

Following subsections present detailed analysis by the types of studies and the subgroups of healthy and diabetes patients.

3.2.1 Experimental Studies

In the experimental studies participants were put on glucose clamp to induce hyperglycaemia, hypoglycaemia or euglycemia. Following definition for glucose clamps have been used in these studies:

- Hyperglycaemia: blood glucose > 9 mmol/L
- Hypoglycaemia: blood glucose < 3.5 mmol/L
- Euglycemia: blood glucose > 5 and <9mmol/L

A total of 9 studies reported hypoglycaemic clamps and 3 studies reported hyperglycaemic clamps in healthy participant studies. While 7 studies reported hypoglycaemic clamps and 3 studies reported hyperglycaemic clamps in diabetes patient. A pooled analysis of the studies reporting QTc variation in response to glucose clamps showed a strong positive effect in both hypoglycaemia and hyperglycaemia compared to normal glucose levels. Hypoglycaemia has a strong effect compared to hyperglycaemia in both healthy volunteers and diabetes patients. Figure 7 show standardised mean difference (Cohen's d) between glucose excursions and normal glucose levels in healthy participants and Figure 8 shows the standardised mean difference in diabetes patients.

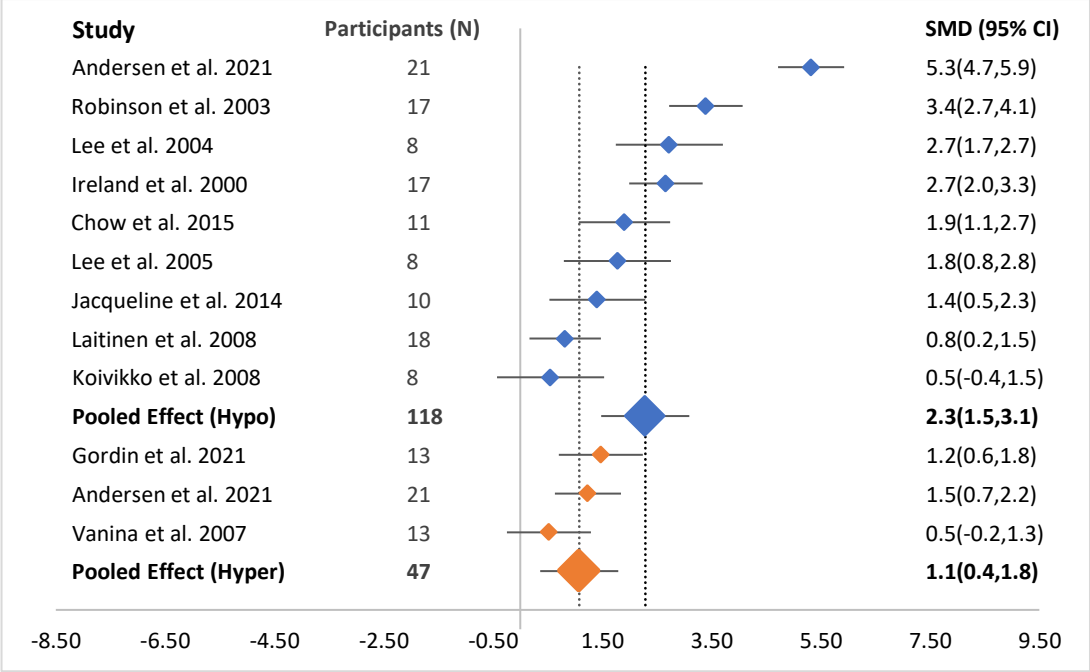

Figure 7. Standardised Mean Difference (Cohen's d) of corrected QT interval (QTc) between normoglycaemia and hypoglycaemia (blue), and normoglycaemia and hyperglycaemia (orange) in healthy volunteers.

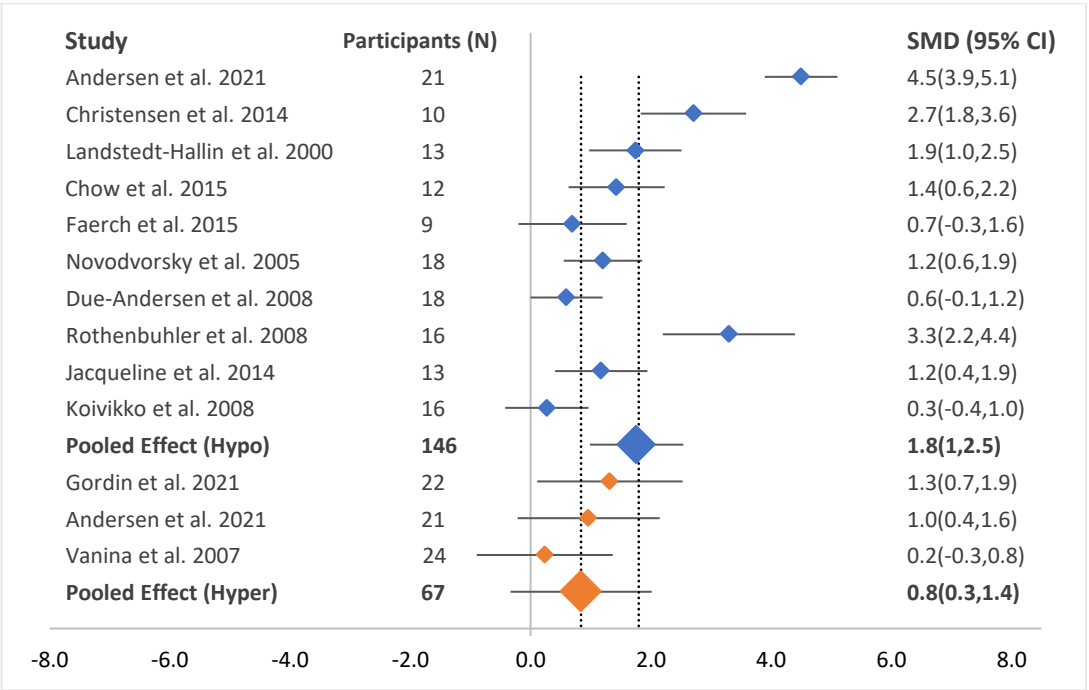

Figure 8. Standardised Mean Difference (Cohen's d) of corrected QT interval (QTc) between normoglycaemia and hypoglycaemia (blue), and normoglycaemia and hyperglycaemia (orange) in diabetes patients.

The standardized mean difference between hypoglycaemia and euglycemia in healthy participants is 2.3 (95% CI: 1.5 – 3.1) which is larger than the difference between

hyperglycaemia and euglycemia in healthy participants estimated as 1.1 (95% CI: 0.4-1.8). Interestingly, the effect size is smaller in diabetes patients compared to same groups in healthy volunteers (1.86 vs 2.3). This can be due to an improved tolerance against glucose excursions in diabetes patients compared to healthy individuals.

3.2.2 Case Reports

In the eight case reports, five patients attended emergency with severe case of hypoglycaemia and three with hyperglycaemia. In all cases QTc interval was prolonged (QTc>460ms).

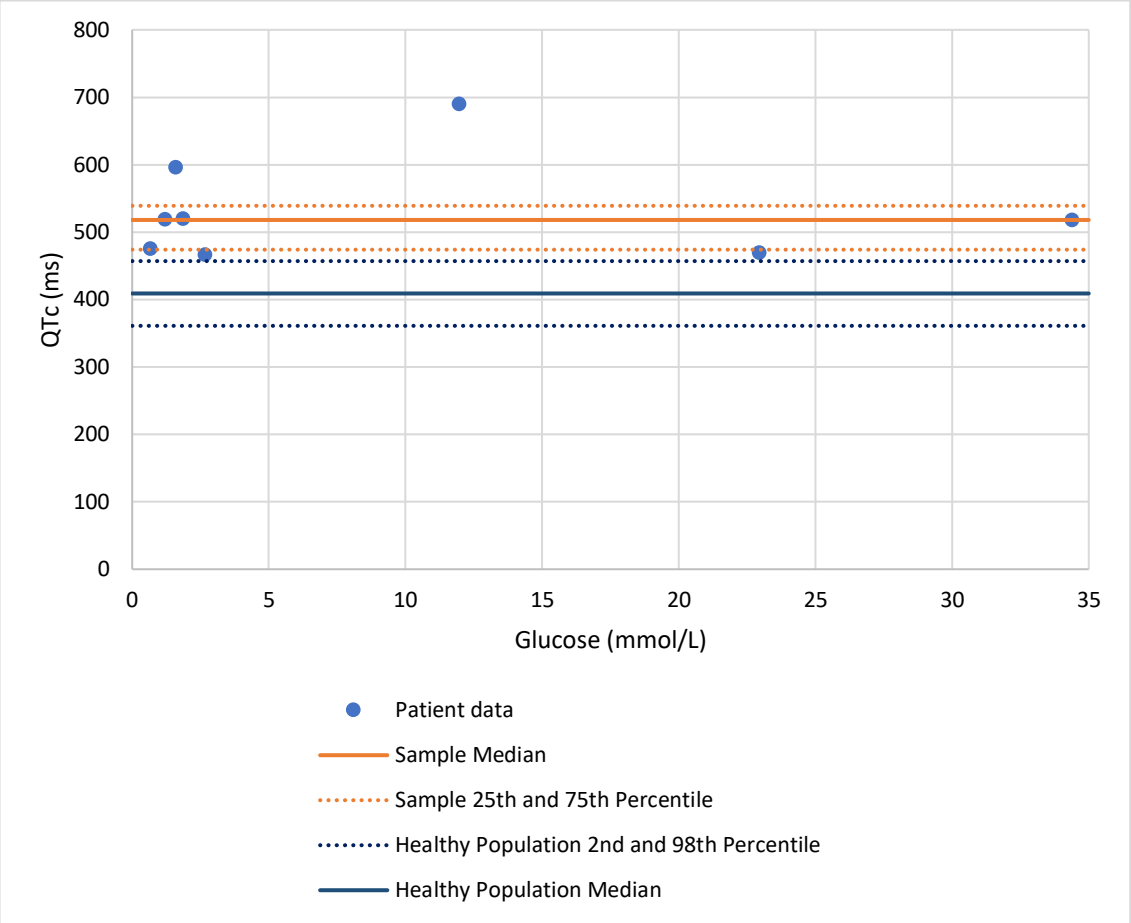

Figure 9. Scatter plot and median-range statistics of the case reports. For a comparison with healthy population, median-range data from a large study (Mason, et al., 2007) reporting QTc in healthy population is used.

There is no correlation found in QTc and Glucose levels, suggesting that QTc was equally affected by hyper and hypo glycaemia. Figure 9 shows two combined plots: a scatter plot of QTc interval against the glucose levels; median and range (25th and 75th percentile) values of the data from case reports compared with median and range (2nd and 98th percentile) values of large healthy population data from (Mason, et al., 2007). The mean QTc interval values in the case reports and the healthy population are 518

ms and 409 ms respectively, with a mean difference of 109 ms. It must be noted that these are cases of extremely abnormal glucose levels.

3.2.3 Observational Studies

In 18 observational studies, 13 studies reported QTc and corresponding glucose data for episodes of hypoglycaemia and normal glucose levels for diabetes patients (4 T2DM and 9 T1DM). Figure 10 shows standardised mean difference (Cohen's d) of the summary data reported in these 13 studies. The data points denoted by green square markers show T2DM studies and the data points in blue diamond markers show T1DM studies. The overall pooled effect is shown by orange circle. The effect of acute hypoglycaemia on QTc is almost similar in both type of diabetes with a slightly large effect in T2DM (0.64 vs 0.54). The overall effect in all patients is significant with standardised mean difference of 0.58 (95% CI: 0.01-1.18). However, this difference is smaller than that observed in experimental studies where the hypoglycaemia was induced by a glucose clamp.

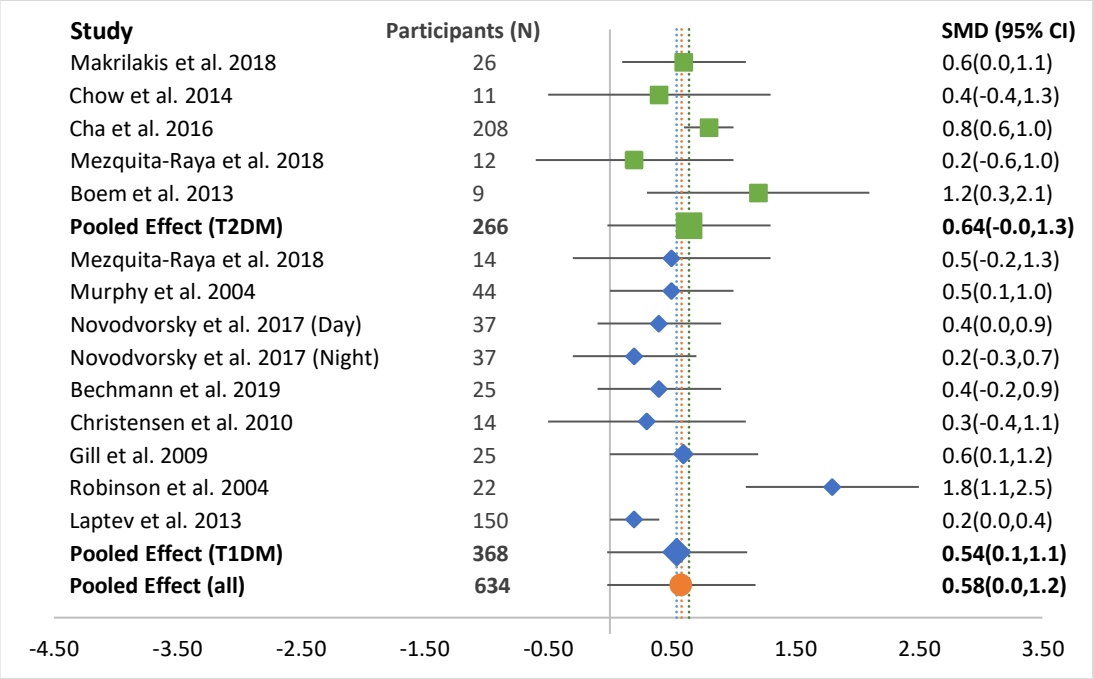

Figure 10. Standardised Mean Difference (Cohen's d) of observational studies reporting data for diabetes patients: green squares represent T2DM studies; blue diamonds represent T1DM studies; orange circle represent combined effect in all patients.

In addition to the 13 observational studies analysed for pooled effect in Figure 10 where full data were available, five observational studies were reviewed for a relative

change in QTc. In these five studies, the baseline QTc and corresponding glucose values were reported for a total of 566 patients. The mean QTc value from each study is plotted against the mean glucose value in Figure 11. The shaded regions show glucose and QTc range for healthy (green region) and unhealth (red region) people. These data confirms the results found in other studies that both hypo and hyperglycaemic condition increase the QTc interval.

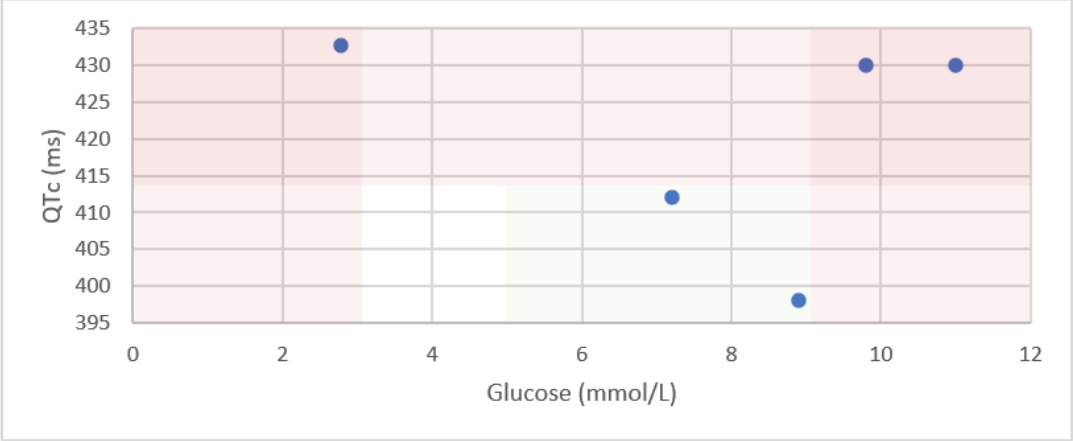

Figure 11. Scatter plot of data from 5 observational studies that reported only the baseline mean and standard deviation of the data. Region shaded green shows QTc and glucose values of healthy population. Red shaded regions show abnormal QTc and glucose values.

4. Discussion and Conclusions

In this thesis, a systematic review and meta-analysis was performed to study association of QTc interval with glycaemic excursions (extremely high or low values of glucose level in blood). A total of 3039 research papers were identified in search from three major databases: PubMed, Embase and the Cochrane library. After removing duplicates, 2599 abstract were reviewed for inclusion in full-paper reviews. After the abstract and title reviews, 250 papers were selected for full-paper review and 43 were included in meta-analysis. These 43 papers report 17 experimental studies where a glucose clamp was used to induce glycaemic excursions, 18 observational studies, and 8 case reports. The summary level data from these 43 studies were standardised to mean and standard deviation for meta-analysis. The analysis includes estimation of effect size where euglycemic data is treated as control and hyper/hypoglycaemic data is treated as intervention group, and a t-test was performed to assess significance of differences in the groups.

In the pooled analysis of all data from 43 studies (N=2177), the mean QTc interval in euglycemia group is 406 ms, which is similar to the mean QTc interval of 409 ms reported in a large population (N=79,43) study (Mason, et al., 2007). Both hypoglycaemia and hyperglycaemia have a significant (p<0.0001) effect on QTc interval with an increase of 34.23ms (95% CI: 30.71-37.75) in the case of hypoglycaemia and 11.04ms (95% CI: 8.30-13.78) in the case of hyperglycaemia. Hypoglycaemia appears to have a stronger effect than hyperglycaemia thereby potentially posing a higher risk to patients.

Similar trends of stronger effect of hypoglycaemia were found in subtypes of the studies reviewed in this thesis. In general, the effect of glucose excursions on QTc interval is higher in experimental studies compared to observational studies. The effect size measured using standardized mean difference (Cohen's d) is also higher in healthy population compared to diabetes patients in the experimental studies. This can be associated with higher tolerance of glucose variations in diabetes patients.

In experimental studies, the mean standardised difference is 2.3 (95% CI: 1.5-3.1) in hypoglycaemia group and 1.1 (95% CI: 0.4-1.8) in hyperglycaemia group in healthy

individuals, and 1.8 (95% CI: 1.0-2.5) and 0.8 (95% CI: 0.3-1.4) in diabetes patients, respectively.

In the observational studies, the mean standardised difference is 0.58 (95% CI: 0.01-1.18) in diabetes patients. As all the observational studies reported data for hypoglycaemia compared to euglycemia, the effect is calculated considering euglycemia as control group and hypoglycaemia as intervention group. The effect is relatively small compared to experimental studies. One important difference between the data in experimental studies and observational studies is that in the case of experimental studies both glycaemic states were more controlled and regulated. While in the observational studies, the glucose levels had higher natural variability.

The case reports present data for 2 T1DM and 6 T2DM patients attending emergency with extremely low or high glucose levels. The QTc interval was prolonged (>460 ms) in all cases and had no correlation with quantitative glucose values.

To conclude, QTc is prolonged in both hypo and hyperglycaemia in diabetes patients as well as healthy population. The effect of glucose excursions on QTc interval is significant (p<0.0001) in all cases and stronger in hypoglycaemia compared to hyperglycaemia. It is notable that the relative stronger effect in hypoglycaemia case compared to hyperglycaemia is at variance with most previous studies which reported that the hyperglycaemia has stronger effect compared to hypoglycaemia.

On the basis of the results of this systematic review and meta-analysis, it is recommended that QT interval should be monitored as a primary tool for prevention, especially in diabetes patients who are at high risk of CVD and torsade de points, and those taking medication with risk of QT prolongation.

Future work may investigate the relative risk of severe outcomes due to prolonged QTc and assess the risk for mean QTc interval increase found in this review.

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