The effects of a combined aerobic and resistance exercise programme on physiological parameters and metabolic control in type 1 and 2 diabetes

By

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Statement

Unless otherwise indicated by acknowledgment or reference to published literature, the presented work in this thesis is the author's own and has not been submitted for a degree at another institution.

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Abbreviations

Abbreviations	Definition
°C	Degrees Centigrade
1RM	One-Repetition Maximum
ACSM	American College of Sports Medicine
ADA	American Diabetes Association
ADI	ADInstruments Analysis System
AE	Aerobic Exercise
ANOVA	Analysis of variance
BF	Body Fat
BG	Blood Glucose
BMI	Body Mass Index
BP	Blood Pressure
CHO	Carbohydrate
CSII	Continuous Subcutaneous Insulin Infusion
CVD	Cardio Vascular Disease
DAFNE	Dose Adjustment for Normal Eating
DEPL	Diabetes and Exercise Physiology lab
DESMOND	Diabetes Education and Self-Management for On-going and Newly Diagnosed
DKA	Diabetic ketoacidosis
DMU	De Montfort University
EDTA	Ethylene diaminetetraacetic Acid
ELISA	Enzyme-linked immunosorbent assay
FPP	Finger Pricking Procedure
GLUT	Glucose Transporter
GLUT4	Glucose Transporter Type 4
GP	General Practitioner

HbA1c	Hemoglobin A1C (Glycated hemoglobin)
HDL	High-Density Lipoprotein Cholesterol
HR	Heart Rate
HRR	Heart Rate Reserve
HR_{max}	Maximum Heart rate
IL-6	Interleukin-6
IR	Insulin Resistance
LDL	Low-Density Lipoprotein Cholesterol
MDI	Multi Daily Injections
ND	Non Diabetic
NHS	National Health Service (UK)
RE	Resistance Exercise
RER	Respiratory Exchange Ratio
RM	Repetition Maximum
RPE	Ratings of Perceived Exertion
RPM	Revolutions Per Minute
SD	Standard Deviation
SEM	Standard Error of Mean
SPSS	Statistical Package for Social Science
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
T2I	Type 2 Diabetes Insulin user
T2T	Type 2 Diabetes Oral Hypoglycaemic user
TC	Total Cholesterol
TG	Triglyceride
TNF-α	Tumor Necrosis Factor α
VCO_2	Carbon Dioxide Production
VO_2	Oxygen consumption
µL	Microliter

Volunteers statements about the study

"***Thank you so much Ahmed. Throughout my time as a volunteer I learnt more than just the standard exercises shown, It was an educational experience. The team were amazing, friendly and always had time for your questions. I would always go back if they needed me again***".

T1D volunteer

"Wanted to say big thanks for your help and support over the last 8 weeks. You have all changed my life for the better and would not forget you all, especially Ahmed".

T2D volunteer

Abstract

Diabetes is a common chronic disease that affects almost all countries in the world and has continued to increase at an alarming rate in the last decades. It kills a person every seven seconds. Recent thinking treats both types of diabetes as inflammatory diseases. The aim of the thesis was to obtain a better understanding of the relationship between exercise and the management of diabetes by conducting surveys and experimental work. It investigates the effects of exercise on the physiology and metabolic control in Type 1 (T1D) and Type 2 diabetes (T2D), using non-diabetic (ND) people as a control.

The management and treatment of T1D and T2D volunteers were first assessed in surveys and the novelty was second to expose both to exercise. In the latter, volunteers were compared biochemically including for inflammatory responses to their illness and to practical exercise.

Four studies were undertaken in this thesis involving a mixed approach: questionnaire based studies (first and second surveys) and experimental based studies (first and second exercise studies). The first survey study was about insulin users with opinions gathered from both T1D and T2D (T2I) respondents (n=707). In this survey diabetic people were asked about the condition and coping strategies for the difficulties using insulin in daily life. The first survey does touch on exercise but only as part of the larger picture. The second survey study (n=240) evolved from the first one and was again about opinions but in this case oral anti-hyperglycaemics were included in the management of T2D respondents (T2T). This survey focused more strongly on the role of exercise. The surveys were conducted by post, email and online while detailed statistical analysis followed.

Two exercise studies with the same volunteers (n=25; ND=7, T1D=7, T2T=7, T2I=4) were then carried out based on some findings of the surveys. These studies explored the effects of a combination of aerobic (AE) and resistance exercise (RE) components for a six week period on diabetes. The methodology of the first exercise study

concentrated on the physiological variables, involving the use of exercise and measurement equipment to monitor for expired gases and anthropometric changes. Substrate oxidation, blood profiles for lipid, blood glucose (BG) and glycated haemoglobin (HbA1c) were also assessed. The second exercise study builds on this with specific inflammatory marker profiles such as tumour necrosis alpha (TNF-α), interleukin-6 (IL-6), leptin and resistin on ND, T1D and T2D volunteers over the same time period as in the first exercise study.

The first survey study showed that many respondents (13-47%) lacked adequate professional information about the various separate aspects of their insulin-treated illness. For example, 38% of T1D and 28% of T2I reported that they did not have enough information regarding raised cholesterol levels. The results for diabetes complications revealed that T2I had greater complications compared to T1D (for example angina 18.5% for T2I compared to 4.6% for T1D), although the groups could not be matched for age, reasons for responding to the survey, duration of illness or severity of illness when starting insulin.

The second survey revealed that insulin users often had an HbA1c that did not meet best practice expectations of 6.5% - 7.5% (48 -58 mmol/mol). It also showed that those who did exercise regularly were more likely to have acceptable HbA1c values (5-7% or 31-53mmol/mol), than those who did not. This is especially the case for the type 2 groups (eg for T2T 46% exercising compared to 31% non-exercising) who were less likely (19% respondents compared to 25%) to have HbA1c over 8% or 64 mmol/mol.

It was of interest to know the risks, barriers and likely recommendations for the two groups. For example, fewer T2I people test BG frequently (12.5% compared to T1D 62%, testing four or more times daily), even when they are insulin basal bolus users, which could foster hypoglycaemic events during exercise. The findings of the first and second surveys showed that managing diabetes in the 21st century remains difficult for many people, despite the availability of diagnostic, monitoring and medication improvements. This leads to anxiety and illness over the short and long term.

In the first exercise study, it was clear that for this combined exercise regimen, the chronic effects were notable. The most significant finding was that the effect of 6 weeks was the drop in HbA1c in all groups ND from 5.4-5.2% *or 36-33mmol/mol* ($p < 0.01$), T1D 7.0 to 6.7% *or 53-50mmol/mol* ($p < 0.01$), T2T 7.6 to 7.2% *or 60-55mmol/mol* ($p < 0.05$), T2I 7.3 to 6.8 *or 56-51mmol/mol* ($p < 0.05$). This is equivalent to raising insulin or other medication and while clearly very beneficial, especially as occurring as a result of moderate exercise over only 6 weeks.

Lipid factors showed improvements, not all significantly but these were likely to be influenced by support medication such as statins. However, the heart rate (HR) and blood pressure (BP) reduced at rest for all groups over the six weeks. The respiratory exchange ratio (RER), a measure of substrates oxidation showed that the carbohydrate metabolism was steady. The muscular strength and the subjective assessment improved after the exercise period.

The second exercise study showed the interleukin 6 levels fell with the chronic effects of combined exercise ND (3.97-2.7pg/ml), T1D (2.15-1.02 pg/ml), T2T (3.67-2.72pg/ml) and T2I (3.66-1.17pg/ml) as did TNFα and other cytokine levels which may thus be cardioprotective. This suggests that exercise could be part of the anti-inflammatory treatment of T1D and T2D.

To conclude, the findings of the two survey studies showed that the management of diabetes is difficult for many diabetics. Furthermore, the exercise studies demonstrated that a regular combined (RE and AE) exercise trial at moderate intensity for six week could be physiologically beneficial for diabetics. The underlying mechanism for this could be improvements in glycaemic control, lipid profile, cardiovascular fitness level and strength, as well as the inflammatory features of both T1D and T2D.

List of publications

1. **Insulin pump users would not rule out using an implantable artificial pancreas.**

Taylor, M. Joan ; Gregory, R. ; Mitchell, H. ; Alblihed, Mohamd Abdulrahman **; Alsabih**, **A.** ; Tomlins, P. ; Sahota, T. S. (2014) Insulin pump users would not rule out using an implantable artificial pancreas. *Practical Diabetes*, 31 (1), pp. 18-23.

2. **Management of Diabetes, Hypoglycaemia and Hyperglycaemia by Type 1 and Type 2 Insulin Users.**

Taylor, M. Joan ; Gregory, R. ; Mitchell, H. ; **Alsabih, A**.; Alblihed, Mohamd Abdulrahman ; Tomlins, P. ; Sahota, T. S. (2015) Management of Diabetes, Hypoglycaemia and Hyperglycaemia by Type 1 and Type 2 Insulin Users. *International Journal of Diabetes Research* 4 (1).

List of posters

1. **Effect of a Combined Aerobic and Resistance Exercise Programme in Type 1 and 2 Diabetes**

Alsabih, A, Sahota, T.S. and Taylor, M.J. (2015) Effect of a Combined Aerobic and Resistance Exercise Programme in Type 1 and 2 Diabetes. Poster presented by A. Alsabih at 8th Saudi Student Conference, 31 January-2 February 2015, London, UK.

2. **Experiences and attitudes of people with T1 and T2 diabetes to exercise**

Alsabih, A., Taylor, M.J. and Sahota, T.S. (2014) Experiences and attitudes of people with T1 and T2 diabetes to exercise. Poster presented by A. Alsabih at 7th Saudi Student Conference, 1 -2 February 2014, Edinburgh, UK.

3. **Experiences and attitudes of people with T1 and T2 diabetes to exercise**

Alsabih, A., Taylor, M.J. and Sahota, T.S. (2013) Experiences and attitudes of people with T1 and T2 diabetes to exercise. Poster presented at Insulin Club Meeting, from basic science to clinical practice conference, Berlin, Germany, 31 Oct - 2 Nov 2013.

4. Effect of a Combined Aerobic and Resistance Exercise Programme in Type 1 and 2 Diabetes

Alsabih, A, Sahota, T.S. and Taylor, M.J. (2012) Effect of a Combined Aerobic and Resistance Exercise Programme in Type 1 and 2 Diabetes. Poster presented by A. Alsabih at 6th Saudi Student Conference, 11 - 14 October 2012, London, UK.

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Chapter 1: Introduction and literature review

1.1 Introduction

The aim of this chapter is to provide a scientific literature review to the research studies within this work as well as to find out the theoretical basis for research studies on T1D and T2D. This chapter begins with an overview of diabetes description, prevalence, classification, glucose and insulin metabolism, insulin resistance, diabetes diagnosis and complications. Following this is a description of T1D and T2D management and treatments will be discussed. Physiological and metabolic response to exercise as well as the effects of aerobic and resistance exercise (AE and RE) on T1D and T2D will also be explored. Finally the aims and objectives of this thesis were highlighted.

1.2 Description and prevalence of diabetes mellitus

Diabetes is a global health problem and most common chronic disease that affects almost all countries in the world. It has become a widespread epidemic and continues to increase at alarming rate in the last decades (Guariguata, Whiting et al. 2014). Diabetes occurs when the pancreatic β-cells do not release sufficient amount of the hormone insulin or the body cell cannot utilise insulin effectively (T2D) or by a damage of the pancreatic β-cells by the immune system which lead to T1D. The International Diabetes Federation (IDF) estimated the total number of people with diabetes worldwide was 387 million in 2014 (Figure 1) rising to 592 million in the next 25 years (International Diabetes Federation, 2014, Guariguata, Whiting et al. 2014). T2D accounts for 85% to 95% of all diabetes in high-income countries and may account for an even higher percentage in low- and middle income countries. The prevalence of diabetes in adults (20-79 years old) in the UK is 5.4% and much higher with 20.52% in the Kingdom of Saudi Arabia (KSA). Recently publications about diabetes stated that in the UK (24.5 T1D cases per 1000) and in KSA (31 cases of T1D per 1000) has one of the highest world's rate of T1D in children aged 14 and below (5^{th} and 3^{rd} highest, respectively in the world), (International Diabetes Federation, 2014). These findings for

both types of diabetes T1D and T2D show how this chronic disease is a global huge health challenge. It also, provides an idea about the potential size of the diabetes epidemic facing these countries as well as the whole world. The cost of Diabetes and its complications is very expensive. About 11% of the total healthcare budget worldwide was spent on diabetes (USD 612 billion) in 2014 and this may increase in the future (International Diabetes Federation, 2014).

The majority (80%) of diabetes patient live in low- and middle- income countries (International Diabetes Federation, 2014). According to Diabetes UK records in 2012 more than £10 billion was spent by the NHS on treating diabetes (Diabetes UK, 2012). This was 10% of the NHS budget in 2010-2011 with total NHS expenditure of approximately £103 billion. After calculation, it is a cost of about £208 million per week, £30 million per day, £1.2 million per hour, £20,000 per minute.

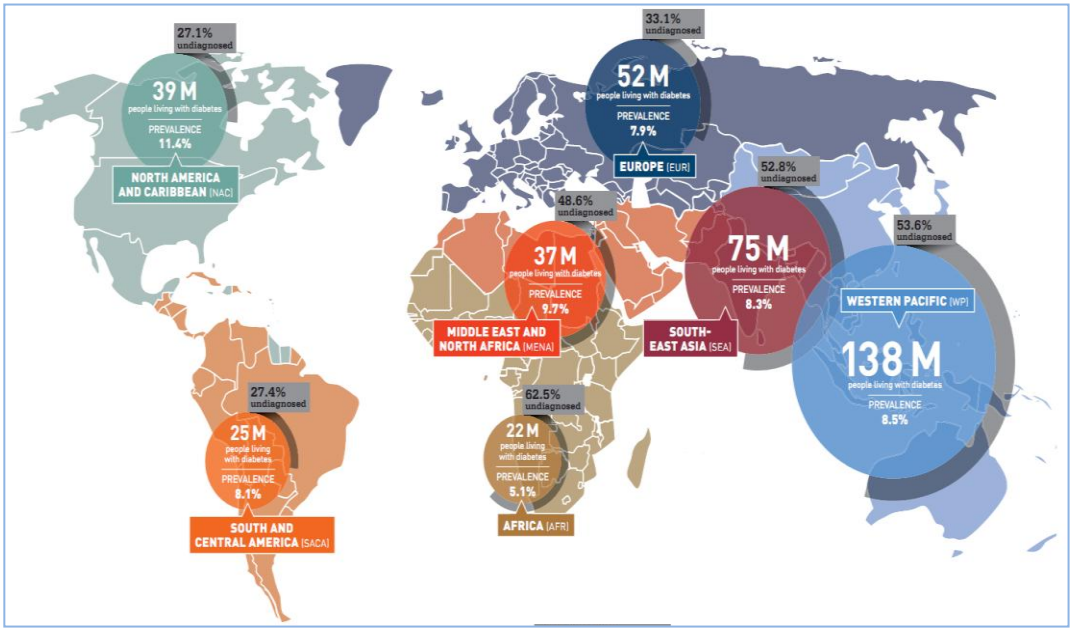

Figure 1: Global diabetes prevalence (International Diabetes Federation, 2014).

1.3 Classification of diabetes

1.3.1 Type 1 diabetes (T1D)

T1D Previously named 'insulin dependent diabetes mellitus', because most of the pancreatic β-cells have destructed which results in absolute chronic deficiency of insulin secretion (Figure 2). Therefore, immediate and urgent administration of insulin therapy is required to prevent diabetic ketoacidosis (DKA) which can lead to coma and death. T1D can be defined as an autoimmune disease where the body's own natural defences progressively attack and destroy the cells that responsible to release insulin which are islets of Langerhans β-cells in the pancreas. Multiple autoimmune attack triggers the pathophysiology of T1D (Regnéll, Lernmark 2013, Hermann, Krikovszky et al. 2005). About 80% of β-cells destruction occurs before T1D become clinically diagnosed. Destruction of the β-cells might be pathogenically relevant to circulating autoantibodies against islet of Langerhans cells which precede the clinical onset of disease (Kawasaki 2014, Regnéll, Lernmark 2013, Shriver 2011). Normally, T1D affects children and adolescent only, although it can happen at any age and might be genetically inherited. It is usually developed in children and teenagers and persists during whole life. T1D patients would need both insulin treatment and extensive life time balance between nutritional consumption and insulin dose (Krochik, Botto et al. 2015) .

1.3.2 Type 2 diabetes (T2D)

T2D previously called 'non-insulin dependent diabetes mellitus' and can be defined as a chronic disease whereby the body is unable to effectively use glucose as a fuel due to relative insulin deficiency caused by insulin resistance and progressive beta cell failure. T2D is a heterogeneous disorder in which multiple pathophysiologic defects result in an imbalance between the rate of glucose production (which is increased) and its disposal (which is decreased) resulting in hyperglycaemia (Figure 2).

Among the defects is insulin resistance, leading to decreased glucose uptake by peripheral tissues (predominantly the muscles) and an increase in hepatic glucose

production (gluconeogenesis) (Meah, Juneja 2015). Thus both impaired pancreatic β cell function and insulin resistance further deteriorate physiological consequences of T2D. Muscle and adipocytes show impaired insulin-stimulated glucose uptake with reduced inhibition of liver glucose production. This condition of tissue specific pathophysiology contributes to increase fasting BG and the lack of ability to effectively dispose glucose from the blood stream in the post-prandial state (Frayn 2003).

T2D develops slowly (mostly in older, obese people), and it has a long preclinical phase and about of 30- 50% or 174.8 million of all diabetes cases in adults are estimated to be undiagnosed for many years (Stevens, Khunti et al. 2015, Guariguata, Whiting et al. 2014). People who are overweight or obese are more likely to have insulin resistance, (where the body does not respond correctly to insulin) because fat interferes with the body's ability to use insulin. Most of T2D have a family history of the disease or disorders and conditions commonly related with diabetes such as high lipid profile, hypertension (high blood pressure), sedentary life style, smoking and obesity (Wang, Bordi et al. 2015, Frontoni, Solini et al. 2014, Chen, Pei et al. 2015).

Acute and chronic states of hyperglycaemia, if left untreated, could lead to a myriad of debilitating long-term complications (Beagley, Guariguata et al. 2014). Heart attacks and strokes are 2- to 3- fold higher in people with diabetes, along with increased risks for microvascualr diseases such as retinopathy, nephropathy and neuropathy. Life expectancy can be shortened by as much as 10-15 years as a result of premature and accelerated atherosclerosis, and the attendant medical complications (Laditka, Laditka 2014).

1.3.3 Gestational diabetes (GD) and other types

GD is defined as glucose intolerance with onset or first recognition during pregnancy in a previously undiagnosed female and takes place mainly because body β-cells is not able to provide sufficient insulin to interact with the additional requirements of pregnancy which leads to abnormal high BG levels. Its prevalence varies from 4.6% to 25% depending on the diagnostic criteria used and the study population (Goldstein, Gibson-Helm et al. 2015). GD is normally transitory and vanishes after delivery the

baby. Women who are overweight or obese are at a higher risk of GD and approximately 7% are at risk to develop T2D later in their lives (Goldstein, Gibson-Helm et al. 2015). Children born to mothers with GD also have a higher risk of suffering from obesity and T2D in later life (International Diabetes Federation, 2014). There are other minority diabetic conditions such as latent autoimmune diabetes of adults (LADA) and maturity onset diabetes of the young (MODY), (Siddiqui, Musambil et al. 2015).

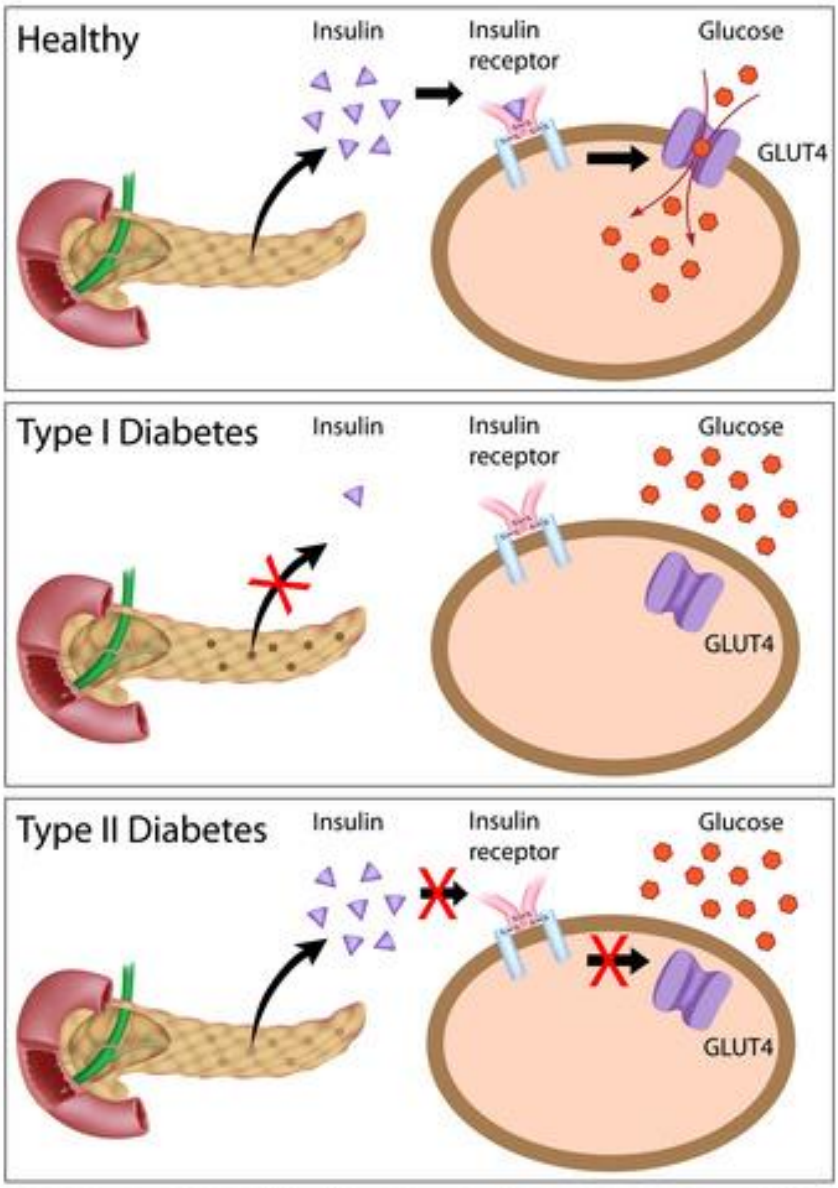

Figure 2: Overview of glucose homoeostasis in healthy, T1D and T2D diabetes (Source: http://familylifehealth.com/health/chronic-conditions/diabetes)

1.4 Glucose and Insulin

1.4.1 Glucose and insulin metabolism

Glucose is the primary source of energy for the body tissue cells to perform the normal physiological body functions ATP. Glucose taken up by the β-cells, utilised in the body tissue through different biochemical mechanisms (broken down into intermediates that fuel oxidative metabolism inside the mitochondria) to produce the primary energy-carrying molecule adenosine triphosphate (ATP) which is the body ultimate source of energy (Groschner, Alam et al. 2014). Glucose is carried into most cells by specific proteins or glucose transporters (GLUT) that cover the cell membrane and permit the connecting and transferring of glucose across the hydrophobic lipid layer (Scheepers, Joost et al. 2004). In the periphery through a number of intracellular signalling pathways, some of which are complex, insulin promotes glucose uptake in muscle and fat cells and inhibits lipogenesis and lipolysis in adipocytes (Frayn 2003). Normally BG utilised by the body tissue and used for energy, otherwise it is converted to glycogen and stored by the liver if it is not required directly (Glycogenesis). It is very important to maintain BG levels within the normal range and avoid any increase in the BG level (hyperglycaemia) or the opposite action low BG level (hypoglycaemia) which progressively may results in diabetes complications.

1.4.1.1 Regulation of blood glucose and insulin

Glucose is the main energy source for the tissue cells. It also acts as a precursor to various metabolites in nearly all tissues. There are two hormones released by the pancreatic cells mainly regulate BG level in the blood circulation; insulin which reduces blood BG level and glucagon is the hormone responsible for decrease blood BG level. Plasma blood glucose levels are typically managed within a limited range of (3.5-5.5 mmol/L) through the insulin-glucose-glucagon regulatory system. Therefore BG levels are controlled through process of the negative biochemical feedback system ('closed-loop') which manages constantly and immediately can give a proper response to the BG levels. Normal glucose management is controlled by means of the antagonistic process of the two pancreatic hormones, insulin and glucagon. Under normal

physiological conditions, BG level continues to rise in response to macronutrients (carbohydrate, fat and protein) intake. β-cells will respond to the increase of BG concentration and release corresponding amounts of insulin to meet the metabolic demand. Insulin acts on different body tissue cells to accelerate facilitated diffusion of glucose into cells especially skeletal muscles and adipose tissues. Then boost up conversion of BG into glycogen (glycogenesis) and supresses hepatic glucose production (gluconeogenesis and glycogenolysis) (Fu, Gilbert et al. 2013). As a result of these various mechanisms, blood BG levels falls to a normal range (Figure 3).

The cascade of insulin action in vivo includes many steps through a number of intracellular signalling pathways (Figure 4). This is including transendothelial transport of hormone, binding to the insulin receptors, and activation of tyrosine kinase, followed by movement of GLUT4 transporters from cytoplasm inside the cell into the plasma membrane, which allows BG enter the cells to utilised or stored (Yoon, Dang et al. 2014).

Low BG level (hypoglycaemia) enhance pancreatic α-cells to secrete glucagon which acts on hepatocytes (liver cells) to facilitate breaking down glycogen molecules into glucose and to promote formation of glucose from lactic acid. Hepatocytes then release glucose into the circulation more rapidly and BG increases to the normoglyceamic state (Figure 3) (Fu, Gilbert et al. 2013, Saltiel, Kahn 2001).

Adipose tissue cells are essential in metabolic regulation, releasing free fatty acid (FFA) that decrease BG uptake in muscle cells, insulin secretion from the β-cells, and increase gluconeogenesis from the hepatocytes (Boden 2003). Adipose tissue cells can also secrete 'adipokines' such as leptin, adiponectin and TNF, which regulate food intake, energy expenditure and insulin sensitivity (Fu, Gilbert et al. 2013).

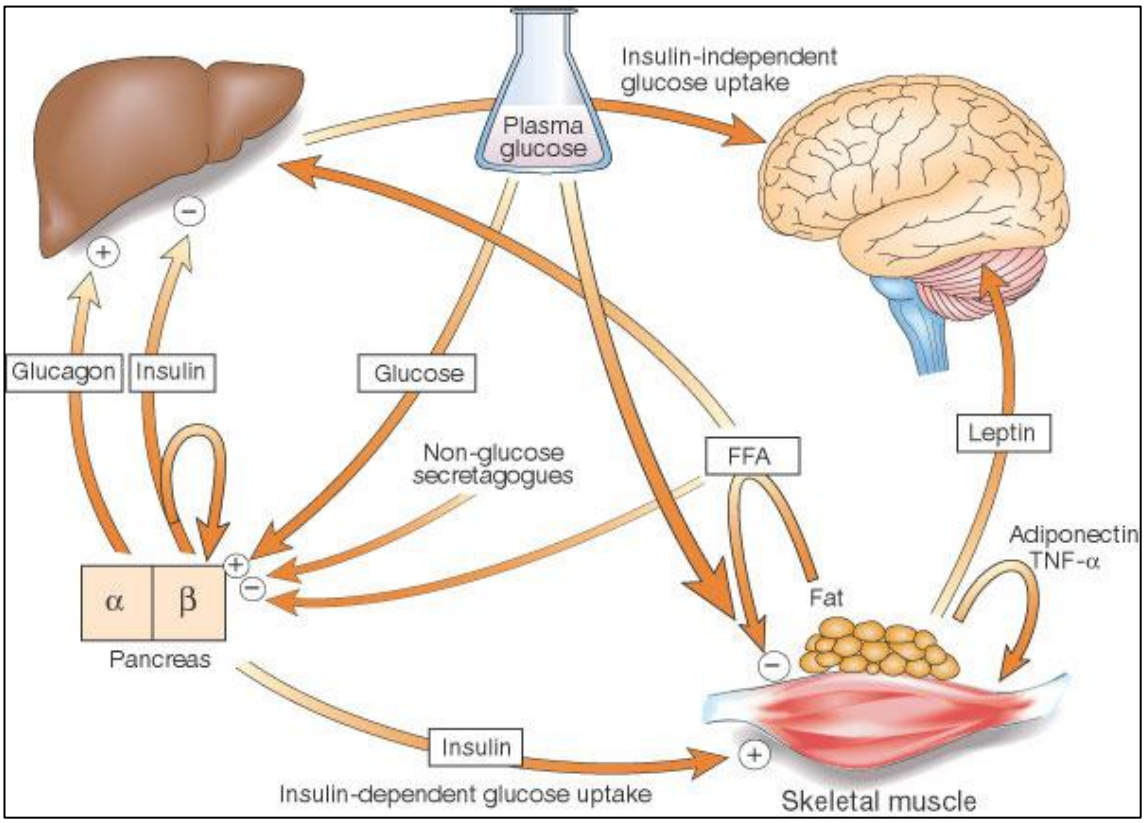

Figure 3: Overview of glucose homoeostasis under normal physiological condition (Saltiel, Kahn 2001).

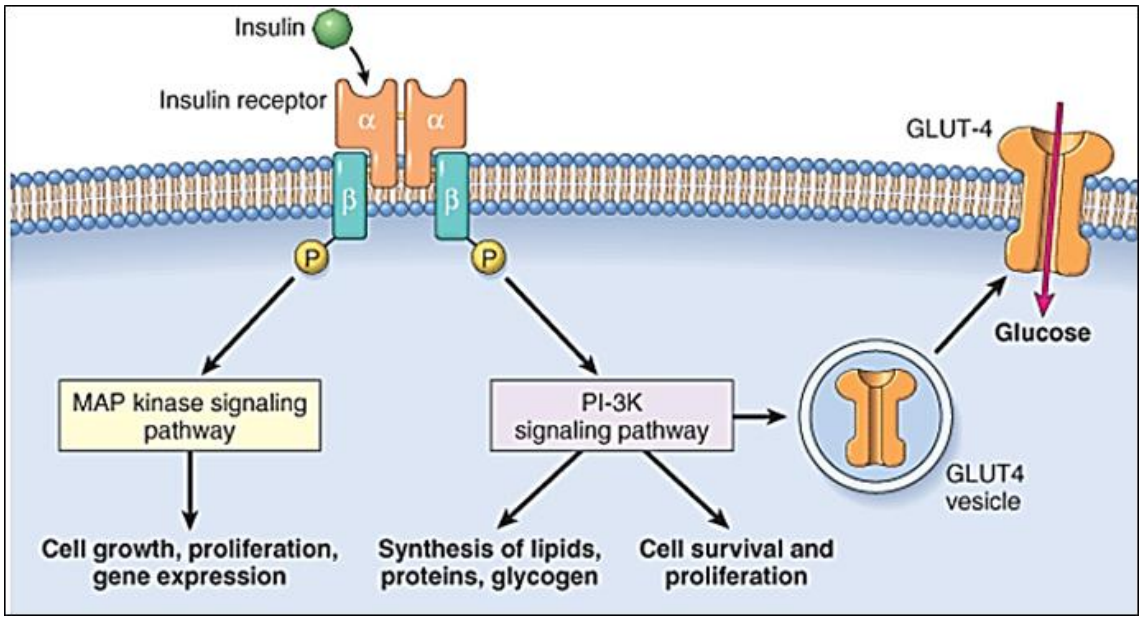

Figure 4: The mechanism of action of insulin (Chhabra 2014).

1.4.2 Insulin

Insulin is a peptide hormone that is secreted by the β-cells and permits cellular glucose uptake and regulates levels of glucose in the blood stream. Insulin involves in different biochemical mechanisms and performs its function by controlling the metabolism of lipids, carbohydrate and protein and encouraging cell division (Preza, Pinon et al. 2013, Strachan, Frier 2013).

1.4.3 Type of insulin

Patients with T1D cannot survive without administration of insulin as well as T2D to whom insulin is administered much later in their treatment. Table 1 describes key features from all the commercially available insulin most widely in use today.

1.4.4 Pathology of glucose and insulin metabolism

1.4.4.1 Insulin resistance

Insulin resistant (IR) is a pathological condition and one of the main metabolic sign of T2D and it can be defined as reduced response to a physiological amount of insulin when the body cells receptors fail to respond to the regular amounts of circulating insulin. There are two possible reasons for IR condition, first one it might be defect in the receptors may prevent insulin from binding or there are no enough receptors for insulin to attach. Secondly, insulin may attach to the receptors, but the tissue cells do not recognise the signal to oxidise the BG (Liu, Park et al. 2015).

IR is known as an impaired sensitivity to glucose removal by insulin-mediated signalling pathway resulting in systemic hyperglycaemia. It is commonly affect T2D, however, over the last ten years it has been shown that IR plays a key role in the development of T1D (Krochik, Botto et al. 2015). As insulin has pleiotropic functions, IR is closely linked with other metabolic symptoms such as hypertension and hyperlipidaemia, unhealthy life-style and endocrine abnormalities (Krochik, Botto et al. 2015, Goyal, Singh et al. 2014). Obesity is the most common cause of IR in humans with or without

hyperglycaemia (Wang, Chang et al. 2013). An important potential mechanism of IR in obesity has been the observation that adipose tissue cells may produce and secrete hormones or cytokines that affect metabolism and insulin sensitivity, such as leptin which may play a role in the modulation of IR following weight loss (Wang, Chang et al. 2013). In addition, prolong exposure of β-cells to insulin and glucose leads to desensitisation and reduced insulin sensitivity and progression to β-cells damage (Fu, Gilbert et al. 2013).

1.5 Signs and symptoms of T1D and T2D

The typical symptoms and signs of T1D are usually include polyuria (frequent urination, especially at night), extreme tiredness, polydipsia (excessive thirst), hyperglycaemia, blurred vision, and normally recent unexplained loss of weight along with at least two of the following characteristic features: rapid onset of symptoms over days or weeks, glucosuria or blood glucose markedly raised, ketones in the urine or blood, ketoacidosis or family history of T1D (International Diabetes Federation, 2014).

The symptoms in T2D almost the same but milder than T1D and usually remain unrecognized at the beginning with often complications developing before diagnosis. Signs of IR or conditions associated with IR such as acanthosis nigricans (brown to black, poorly defined, hyperpigmentation marks of the skin), hypertension and dyslipidaemia. Excessive thirst, polyuria, polydipsia are characteristic symptoms for T2D (Hays, Galassetti et al. 2008, International Diabetes Federation, 2014).

1.6 Diagnosis of T1D and T2D

Based on the American Diabetes Association (ADA) and IDF guidelines there are four key tests used for the diagnosis of diabetes and they are as follows: first test is glycosylated haemoglobin test (HbA1c), with level of ≥6.5%. Second one is fasting plasma glucose (FPG) of 7 mmol/L (126mg/dL), patient should fast for at least 8 hours before this test. Third one is oral glucose tolerance test (OGTT) with BG value of ≥11.1 mmol/L (200 mg/dL), after two hours of having a 75mg dose of glucose. Last test is random plasma glucose (RPG) of ≥ 11.1 mmol/L (200 mg/dL) in a patient with classic

symptoms of hyperglycaemia or hyperglycaemic crisis. To confirm the diagnosis in the absence of unequivocal hyperglycaemia, tests 1 – 3 should be performed again in another day (International Diabetes Federation, 2014, ADA 2014). People who have a fasting BG level between 6.1 and 6.9 mmol/L (100 and 124.2 mg/dL) are described as having an impaired fasting glucose (IFG) and may need an OGTT to confirm the diagnosis of diabetes or not. The ADA also recommended an HbA1c of 39−46 mmol/mol (5.7-6.4%), FPG 5.6 mmol/L (100 mg/dL) to 6.9 mmol/L (125 mg/dL) IFG or 2-h PG (plasma glucose) in the 75-g OGTT 7.8 mmol/L (140 mg/dL) to 11.0 mmol/L (199 mg/dL) (IGT) indicates a high risk of diabetes (pre-diabetes).

1.7 Treatments and management of diabetes

1.7.1 Exercise, lifestyle and diet

Sedentary lifestyle is one of the most important risk factors for T2D. Studies in prediabetic and diabetic subjects have demonstrated benefits of physical activity in the prevention and management of T2D. The mechanisms by which exercise produces positive results in patients with diabetes include improvement in insulin sensitivity and glucose disposal in the skeletal muscle, expression of nitric oxide synthase in the endothelial cells, improvement in obesity, and body fitness (Hall, McDonald et al. 2013, Maahs, Taplin et al. 2009, Snowling, Hopkins 2006).

Exercise interventions that produce fat losses should produce improvements in glyceamic control or insulin sensitivity, especially if the fat loss is from visceral deposits. Even if fat loss is not present, reductions in HbA1c may be observed as a result of the cumulative chronic effects of the individual exercise programme (Church, Blair et al. 2010).

In the UK there have been two education programmes which are nationally developed in order to support people with diabetes to gain the skills and right attitude to manage their disorder. Certainly one is made for T1D, a programme known as the Dose Adjustment for Normal Eating (DAFNE) had been developed to help people to regulate their insulin injection therapy to match their lifestyles (Leelarathna, Ward et al. 2011). DAFNE programme is a method of controlling T1D and provides people with the

knowledge that is necessary to calculate the carbohydrate in every food and then to inject the corrected dose of insulin. Some studies show significant reductions in total, quick acting and basal insulin doses in patients undergoing DAFNE training (Leelarathna, Ward et al. 2011) The other one is designed for T2D patients and is known as The Diabetes Education and Self-Management for On-going and Newly Diagnosed (DESMOND) and not essentially focused on insulin. DESMOND is a NHS education training course to provide T2D patient with the essential knowledge about diabetes and how to manage it to achieve their targets and to be aware of the health risks and consequence complications. DESMOND and other education programmes such as a low-intensive lifestyle education programme (DiAlert) lead to improvements in the metabolic control and body composition in T2D (Heideman, de Wit et al. 2012, Srinivasan, Davies 2014).

An epidemiologic analysis conducted by the United Kingdom Prospective Diabetes Study (UKPDS) Group estimated that for every 1% decrease in mean HbA1c, a marker of long-term glycaemic control, the incidence of clinical complications decreased significantly over the entire range of HbA1c levels represented in the study (<6% - >10%), the risk for microvascular complications was reduced by 37% for each 1% reduction in HbA1c, the risk for any clinical event or death associated with diabetes was reduced by 21%, and the risk for myocardial infarction was reduced by 14% for all relative hazards (Stratton, Adler et al. 2000).

To achieve normoglycaemic state, T1D needs intensive diabetes management and the care of T1D patient either child or adult should be under specialists supervision team qualified in the care of diabetes such as dietician, diabetes nurse and diabetologist (Care 2011). T1D children are different from T1D adults in many respects such as ability to provide self-care, insulin sensitivity, and unique neurological weakness to hypoglycaemia and DKA (Care 2011).

1.7.2 Oral medication

The first therapeutic approach and management of T2D usually start with changes lifestyle by increasing physical activity and exercise as well as eating healthy diet with low saturated fat and cholesterol, and reduce calorie intake as recommended by health service carers to manage BG level close to the normal ranges. However, as data from the UKPDS demonstrate, only a small minority of patients are able to reach or maintain the currently accepted glycaemic targets without pharmacologic intervention (Stratton, Adler et al. 2000).

If diet and exercise alone are not sufficient to improve or maintain glucose control within 3 months, the next step is to add an oral hypoglycaemic agent. Several classes of oral hypoglycaemic agents are approved by the United States Food and Drug Administration as treatment for T2D. Sulfonylureas (Glimepiride® and Gilclazide ®) bind to K^+ channels on the β-cells membrane, leading to increased insulin release in elevated BG. Biguanides (Metformin®) inhibit hepatic gluconeogenesis while increasing hepatic and muscular sensitivity to insulin and act primarily on liver. The sulfonylureas and metformin® are most effective for decreasing HbA1c (decrease 1.3%-2.0%). Rosiglitazone® or Pioglitazone® (thiazolidinediones) act on muscle and fat tissue and decrease HbA1c by 1.0% -1.3%. Acarbose® or Miglitol® (Alpha-glucosidase inhibitors) interfere with carbohydrate digestion, delaying and reducing gastrointestinal absorption of dietary glucose (Srinivasan, Davies 2014).

1.7.3 Insulin

T1D patients need a lifelong administration of exogenous insulin because their pancreatic β-cells had destroyed which lead an absolute deficiency of insulin. Typical treatment for T1D is extensive insulin therapy. In contrast to people with T1D, the majority of those with T2D usually do not have need of daily doses of insulin to survive. Many of T2D able to manage their condition by a healthy diet and increased physical activity or oral agents as mentioned earlier.

For those who are unable to regulate their BG levels and the oral hypoglycaemic is not effective they may be prescribed insulin (Nyenwe, Jerkins et al. 2011).

Table 1: Insulin types, onset of action and peak.

Insulin type	Name of insulin	Manufacturer	Source	Vial, cartridge or prefilled pen	Onset of action*	Peak*
Rapid-acting analogue	Humalog	Lilly	analogue	cartridge, vial & prefilled pen	< 15 min	15-60 min
	Novorapid (Novolog	Novo Nordisk	analogue	vial	< 15 min	15-60 min
Long-acting analogue	Glargine (Lantus)	Aventis	analogue	cartridge, vial & prefilled pen	< 60 min	No peak as such
	Detemir (Levemir)	Novo Nordisk	analogue	cartridge	< 60 min	No peak as such
Short-acting	Actrapid	Novo Nordisk	human	cartridge, vial & prefilled pen	< 30 min	1 – 3 hours
	Humulin S	Lilly	human	vial & cartridge	< 30 min	1 – 3 hours
	Hypurin	CP Pharmaceuticals	Beef/pork	vial & cartridge	< 60 min	2 – 5 hours
	Insuman Rapid	Aventis Pharma	human	cartridge, vial & prefilled pen	< 30 min	1 – 3 hours
Medium & long-acting	Humulin I	Lilly	human	cartridge, vial & prefilled pen	< 120 min	2-12 hours
	Insulatard	Novo Nordisk	human/pork	cartridge, vial & prefilled pen	< 120 min	6-12 hours
	Hypurin Bovine Isophane	CP Pharmaceuticals	human/beef/pork	vial & cartridge	< 120 min	6-12 hours
	Hypurin	CP Pharmaceuticals	Beef/pork	Vial & cartridge	< 120 min	6-12 hours
	Insuman Basal	Aventis Pharma	human	Vial, cartridge & prefilled pen	< 120 min	2-12 hours

* The above information from http://www.diabetes.co.uk/insulin.

Basal bolus methodology consists of a basal dose which is a calculated background of long acting insulin together with a short acting bolus or boost of insulin which is administered at mealtimes. This variable dosing allows the patient a much more normal diet. More importantly this must be done in conjunction with frequent BG testing to prevent excursions from normoglycaemia. It is often the case that most diabetes patients find regular injections and finger prick testing uncomfortable and invasive and this could be alleviated to some degree by the use of continuous glucose monitors for BG testing and insulin pumps for infusion (DCCT, EDIC 2014).

1.7.4 Insulin Pump

There is a cannula which usually inserted abdomen subcutaneous, continuous subcutaneous insulin infusion (CSII). The main advantage of insulin pump therapy over multiple daily insulin injections (MDI) is its ability to significantly reducing the risk of hyperglycaemia and hypoglycaemia. It has been observed that insulin pump users have fewer events of post-exercise hyperglycaemia as compared with MDI users (Yardley, Iscoe et al. 2013). Furthermore, T1D sufferers who use insulin pump, children and adults, reported lowering of HbA1c (Battelino, Phillip et al. 2011).

1.7.5 Artificial Pancreas

This is an insulin dispensing device that responds to the body to deliver variable doses as an intelligent response to the blood glucose. Instead of two to four injections into the skin at intervals throughout the day, this is a continuous supply, but one that adapts to the changing blood levels and should give better outcomes as a result. The intention is that it will be totally implantable and nothing would therefore be visible from the outside. It is not ready yet for human trials but already known to work to improve overall glycaemic control but not postprandial surges (Taylor, Gregory et al. 2014).

1.8 Complications of T1D and T2D Diabetes

About five millions of diabetes patients have died in 2014 because of diabetes complications which mean that every 7 seconds one person dies from diabetes and its complications (International Diabetes Federation, 2014, Guariguata, Whiting et al. 2014).

T1D requires both insulin therapy and careful lifelong control of the balance between dietary intake and insulin dose. Without insulin replacement, people developing T1D risk surviving and with which they can participate normally in the usual daily activities, but still are at risk of associated complications. T1D and T2D individuals are at risk of the following complications: metabolic complications such as hyperglycaemic ketoacidosis, hypoglycaemia, and dyslipidaemia. Hypoglycaemia is a condition when is the BG level fall to < 3.5 mmol/L due to the effect of different reasons such as fasting, exercise and over insulin dose (Forbes, Cooper 2013).

Macrovascular complications (chronic complications) such as cardiovascular vascular diseases (CVD), coronary artery disease (CAD). Microvascular complications such as retinopathy (eye impairment), nephropathy (kidney impairment), sensory, motor, and autonomic neuropathy (nerve impairment). Moreover, psychological complications such as depression and anxiety might present in T1D and T2D. In addition, other complications associated with non-adherence to recommended management in children and young adults due to family conflict or risky behaviour. Pregnant women have increased risks of complications, such as: hypertension and pre-eclampsia, foetal and neonatal complications such as congenital malformations (a physical defect present in a baby at birth) and macrosomia (large baby at birth) (Mitanchez 2010).

1.9 Impact of Exercise on healthy and diabetes people

1.9.1 Diabetes, lipid profile and risk factors

Diabetes is associated with a high risk of CVD, CHD and other heart disease mortality (Chen, Pei et al. 2015, Li, Xiao et al. 2014, Jaiswal, Schinske et al. 2014). It has been known for decades that exercise and physical activity are one of the main cornerstones along with medication and diet to treat and manage diabetes and high lipid profiles (Yavari, Najafipoor et al. 2012, Sigal, Kenny et al. 2006). Dietary intervention, and changes in sedentary lifestyle by increasing physical activity contribute to the prevention and management of T2D and lead to significant benefit in risk factors that are known to be associated with development of CVD in patients with T2D such as HbA1c, Body Mass Index (BMI), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and lipid profile: Total Cholesterol (TC), Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL) and Triglyceride (TG) (Chen, Pei et al. 2015, Li, Xiao et al. 2014). BMI measurement of less than 18.5 suggests underweight and between 18.5 to 24.9 is healthy weight. However from 25 to 29.9 indicates that the individual is overweight and 30 or more is obese. High BMI is an indicator of obesity and it is associated with T2D (Li, Xiao et al. 2014).

Presence of lipid disorders can be found in both T1D and T2D and it is associated with the development of T2D (Billimek, Malik et al. 2015, Jaiswal, Schinske et al. 2014, Verges 2009, Hjerrild, Gravholt 2006). Therefore, it is crucial to investigate lipid abnormalities and to control lipids profile in people with T1D and T2D to reduce the risk of CVD and other diabetes complications such as Hyperglycaemia, micro- and macrovascular complications (Jaiswal, Schinske et al. 2014, Maahs, Ogden et al. 2010). An improvement in glycaemia is suggested as an initial treatment for dyslipidaemia when caring for patients with T1D and T2D. Nevertheless, lipid-lowering medicine can also be administered if lipid goals are not achieved (Jaiswal, Schinske et al. 2014, Brunzell, Davidson et al. 2008, Buse, Ginsberg et al. 2007).

Elevated HbA1c level has been considered as a risk factor for CHD and CVD in patients with diabetes (Haring, Baumeister et al. 2014, Selvin, Coresh et al. 2005, Selvin,

Marinopoulos et al. 2004). Furthermore, it is also has been observed that there is a direct correlation between raised HbA1c concentration and the severity of CAD and CVD in people with diabetes (Hong, Li et al. 2014, Jaiswal, Schinske et al. 2014).

A significant correlation between HbA1c and lipid profile in T1D and T2D has been reported by several researchers (Jaiswal, Schinske et al. 2014, Yan, Liu et al. 2012, Faulkner, Chao et al. 2006). Raised lipid levels decrease insulin-stimulated glucose disposal in the skeletal muscle, probably because of fatty acid–mediated inhibition of insulin signalling (Szendroedi, Frossard et al. 2012). Reduced insulin sensitivity is linked with abnormal lipid profile in people who have T1D either as adults or in their youth (Maahs, Nadeau et al. 2011) as well as in T2D (Jaiswal, Schinske et al. 2014). High TG and lipid profile levels are correlated with CVD in T1D and T2D (Maahs, Eckel 2015, Mäkinen, Soininen et al. 2013, Maahs, Ogden et al. 2010).

1.9.2 Aerobic and resistance exercise

Aerobic exercise (AE) is any exercise that depends on oxygen for energy such as walking, running and swimming, and increases heart rate (HR) up for a prolonged period of time and large muscle groups are included. Resistance exercise (RE) is anaerobic exercise, such as weight lifting, strength exercise using machines or even using body weight. Normally, RE performed in short bouts with rest periods between each set and is anaerobic, meaning that oxygen is not used for providing energy, however, the source energy from ATP, creatine phosphate and muscle glycogen (Lucotti, Monti et al. 2011). Both of these approaches lead to health benefits for ND and people with diabetes (T1D and T2D). AE, RE or combined exercise programme is recommended in the management of T1D and T2D, and has physiological benefits including improved physical work capacity, body composition, blood pressure, blood lipid profile (Chen, Pei et al. 2015) and HbA1c (Yardley, Kenny et al. 2013). It is associated with less risk of diabetes complications and mortality in individuals with diabetes (Hordern, Dunstan et al. 2012).

1.9.3 Substrates oxidation measurements and the principles of Indirect Calorimetry

Indirect calorimetry is a method to non-invasively measure metabolic rate and allows calculation of substrate utilisation under different conditions (Frayn 1983). The basic principles of this technique are based on the measurement of the oxygen consumption and carbon dioxide production at the level of the lungs, nitrogen excretion and the knowledge of the stoichiometry of carbohydrate, protein and fat oxidation.

Respiratory exchange ratio (RER) is the ratio of the volume of carbon dioxide (VCO_2) released to the volume of oxygen (VO_2) taken up into the lungs at the same time. Respiratory exchange ratio normal ranges are between 0.7 and 1.0 and this factor is used as an indicator of substrate oxidation, where 1.0 indicates total carbohydrate oxidation, while 0.7 refers to total fat oxidation (Ferrannini 1988). Frayn (1983) chose glucose and palmitoyl-stearoyl-oleoyle-glycerol (PSOG) to represent carbohydrate and fat oxidation, respectively. The stoichiometry of glucose and PSOG is as follows:

Glucose ($C_6H_{12}O_6$) + 6 O_2 $\rightarrow$ 6 H_2O + 6 CO_2

PSOG ($C_{55}H_{104}O_6$) + 78 O_2 $\rightarrow$ 52 H_2O + 55 CO_2

From the above equations, oxidation of 1 mol of glucose, requires an uptake of 6 mol of oxygen and a release of 6 mol of carbon dioxide, thus, RER will be 6/6 =1.0. Also, the oxidation of 1 mol of PSOG requires an uptake of 78 mol of oxygen and a release of 55 mol of carbon dioxide, thus, RER will be 0.70.

There are different techniques used in indirect calorimetry to measure fuel oxidation, the Douglas bag method and breath-by-breath system (Jeukendrup, Wallis 2005). In this method the volunteer is required to wear a nose clip and breathe through a mouth piece into tube connected to a chamber and gas analyser. Expired air can be analysed to calculate the fraction of oxygen and carbon dioxide by passing the expired air into a gas analyser. The indirect calorimetry methods are considered as an attractive way to conduct research due to the non-invasive nature and the quick response time (Jequier, Acheson et al. 1987).

In order for RER to be used to estimate substrate oxidation during exercise, the subject must have reached the steady state, which means that physiological function remains relatively stable (Jequier, Acheson et al. 1987). This is important because it is only during steady state exercise that the ratio of VCO_2 to VO2 reflects the metabolic gas exchange in the body tissues (Jeukendrup & Wallis, 2005).

Basically, during low to moderate exercise intensities this does not present a problem, because the lactate concentration in the circulation during low to moderate intensity exercise may be matched or slightly higher than the baseline value, but it is still in steady rate (Jeukendrup & Wallis, 2005). Therefore, lactate production in the muscles is mostly in equilibrium with lactate elimination, due to oxidation and conversion to glucose in the liver (Jeukendrup & Wallis, 2005).

However, during high intensity exercise, where lactate acid production can be greater than oxidation, lactate will accumulate in the muscle (Jeukendrup & Wallis, 2005), resulting in hydrogen ions release and increased in plasma. These ions are may buffered by bicarbonate [HCO_3^-], and finally extra non-metabolic CO_2 will be excreted on the breath (Frayn, 1983). Thus, during heavy exercise when lactate excretion is high, estimation of substrate utilisation by indirect calorimetry technique may be flawed (Frayn, 1983).

1.9.4 Normal glycaemic response to exercise

The glycaemic response to exercise is dependent on the intensity and duration of exercise. BG concentration does not change very much in the short-term when participating in moderate exercise, however when high intensity exercise is performed plasma BG concentrations will initially rise and then fall as exercise continues will the symptoms of hypoglycaemia being rare. An increase in hepatic glucose output maintains BG homeostasis by balancing increases in BG uptake by working muscles. The balance must be maintained between reducing insulin concentrations and/or increasing glucagon concentrations which become necessary for plasma BG homeostasis. When changes in insulin and glucagon are prevented BG concentrations

fall. Any deviation from euglycaemia can result in a mismatch between hepatic glucose production and peripheral glucose use (Frayn 2003).

The role of the liver for maintaining glucose homeostasis is pivotal as it is able to store large amounts of glycogen as well release glucose by glycogenolysis. Additionally, lactate, glycerol and amino acids can be converted to glucose by gluconeogenesis within the liver. During exercise the rate of muscle glucose uptake is linked to hepatic glucose produced and with prolonged exercise an increasing contribution is derived from gluconeogenesis. When participating in high intensity exercise hepatic glucose production increases and is often higher than the glucose used, this can be attributed to a rise in catecholamines rather than to changes in insulin and glucagon levels. This marked increase in catecholamines results in increased muscle glycogenolysis and increased glucose-6-phosphate (McArdle, Katch et al. 2006).

1.9.5 Effect of different intensities and duration of exercise on ND, T1D and T2D

According to two widely-cited studies by (Romijn, Coyle et al. 1993, Romijn, Coyle et al. 2000) fat oxidation increases with increasing exercise duration. Romijn *et al* (1993) studied exercise intensity and substrate utilisation during prolonged exercise using indirect calorimetry and isotopes (tracer techniques). They examined trained subjects, five males in the first study and eight females in the second. Subjects exercised at 25%, 65%, and 85% of maximum volume oxygen consumption ($\dot{V}O_2$ max). They found that the rate of fat oxidation increased from low-intensity exercise (25% of $\dot{V}O_2$ max) to moderate-intensity (65% of $\dot{V}O_2$ max), and then reduced at high-intensity (85% of $\dot{V}O_2$ max). Fat oxidation rates increased from rest to low- to moderate-intensity exercise and plasma fatty acid was the main substrate utilised for energy. However, when the exercise intensity exceeded 75-85% of $\dot{V}O_2$ max, carbohydrate oxidation became the major source of energy provision and fat oxidation was suppressed; this suppression is probably the result of the stimulation of glycolysis and glycogenolysis during high-intensity exercise (Jeukendrup 2003).

1.9.6 Effect of resistance and aerobic exercise on T1D and T2D

A significant reduction of 0.3 to 0.5% HbA1c levels achieved by combination exercise programme (AE + RE) might be expected to produce a 5% to 7% reduction in CVD risk and a 12% reduction in risk of microvascular complications (Church 2011). The improvements of glycaemic control without weight gain has been associated with lipids control and this include TG, TC and LDL (Purnell, Hokanson et al. 1998). AE, RE or combined exercise programme is recommended in the management of T1D and T2D, and has physiological benefits including improved physical work capacity, body composition, blood pressure, blood lipid profile (Chen, Pei et al. 2015) and HbA1c (Yardley, Kenny et al. 2013). It is associated with less risk of diabetes complications and mortality in individuals with diabetes (Hordern, Dunstan et al. 2012).

Small-scale studies have revealed that RE decreased HbA1c in patients with T1D (Yardley, Kenny et al. 2013) and T2D, it has been reported that HbA1c was significantly improved after 4 months of AE or RE (Bacchi, Negri et al. 2012). Furthermore, other study reported a statistically significant impact of exercise (AE, RE and combined training) on the management of glucose HbA1c (Shriver 2011).

1.9.7 Immune-inflammatory markers

Interleukin-6 (IL-6) plays a role in obesity and insulin resistance and is widely expressed in adipose tissue as well as obesity in humans. IL-6 interrupts insulin signalling mediating insulin resistance which facilitates obesity (Senn, Klover et al. 2003). It has been reported that IL-6 deficient mice show an onset in obesity on maturity, hepatic inflammation and insulin resistance which can be reversed on IL-6 administration (Matthews, Allen et al. 2010, Wallenius, Wallenius et al. 2002). This administration of IL-6 enhances energy expenditure and decreases obesity by influencing obesity and insulin sensitivity through a central nervous system mechanism.

Tumor necrosis factor-α TNFα a pro-inflammatory cytokine has increased in obese humans and rodents suggesting that it contributes to insulin resistance. TNF-α levels in the circulation correlate positively with insulin resistance, and neutralisation of TNF-α improves the insulin sensitivity in rodents, although clinical effects of TNF-α

neutralisation in humans are debatable (Hotamisligil 2007, Hotamisligil, Shargill et al. 1993).

Leptin is a hormone that has been recognised as a mediator of long-term regulation of energy balance it acts by suppressing food intake and thereby inducing weight loss. Consumption of fat and fructose do not initiate insulin secretion, results in lower circulating leptin levels, a consequence which may lead to overeating and weight gain in individuals or populations consuming diets high in energy derived from these macronutrients. Leptin levels in circulation have been shown to increase in obese rodents and humans suggesting that obese subjects display leptin resistance. This resistance is mediated by impaired leptin transport in blood brain barrier (Kievit, Howard et al. 2006) and activates monocytes and macrophages to produce pro-inflammatory IL-6, TNF-α. Leptin production is usually regulated by insulin-induced changes of adipocyte metabolism.

Resistin is a hormone identified as one of the markers of atherosclerosis and is one of the important predicting factors of CVD (Kadoglou, Perrea et al. 2007) as a promoter of insulin resistance (Steppan, Bailey et al. 2001). The increase in the level of resistin mostly happens in inflammatory conditions and it is shown that resistin stimulates the synthesis and the release of pre-inflammatory cytokines such as TNFα (Silswal, Singh et al. 2005). However resistin's function in humans unclear, as levels in blood circulation do not correlate with obesity and insulin resistance. The major sources of resistin in humans are monocytes and macrophages and inflammatory cytokines such as IL-1β, IL-6, TNF-α, and LPS induce the resistin are widely expressed in these macrophages (Silswal, Singh et al. 2005).

In obese rodents and humans the liver and muscle have been shown to produce mild inflammatory responses without significant numerical changes in immune cells. Adipose tissue depots become vulnerable to mediate significant immune cells infiltration and inflammation contributing to insulin resistance and systemic

inflammation (Odegaard, Chawla 2013). Adipose tissue provides the majority of excess nutrient storage for TG as well as producing adipokines (Waki, Tontonoz 2007). Leptin and adiponectin are generated from adipose tissue to regulate feeding behaviour and pro- and anti-inflammatory adipokines to modulate inflammatory responses.

Adipocytes are the most abundant cell population of adipose tissue and act as an energy storage secreting hormones and many bioactive substances (adipocytokines) such as IL-6, TNFα , resistin and leptin that are required for normal body function and are found at altered levels in metabolic disease (Poulos, Hausman et al. 2010, Galic, Oakhill et al. 2010). Thus an increase in nutritional intake results in adipocytes hypertrophy and hyperplasia which provoke cellular stress which in turn initiates oxidative stress and inflammatory responses in adipose tissue. These inflammatory responses in adipose tissues become self-generating and lead to an increase in pro-inflammatory cytokines such as TNFα, IL-6, IL-1β, at a systemic level and are the causes of insulin resistance. Along with inflammatory adipokine production in adipose tissues, obesity-related hyperlipidemia, hyperglycaemia, hypoxia and oxidative stress which induces insulin resistance in peripheral tissues resulting in activation of inflammatory signalling cascades in adipose tissues (Labouesse, Gertz et al. 2014).

1.9.8 Exercise (AE and RE) and immune-inflammatory markers

AE and RE (acute and chronic) have different impacts on inflammatory adipocytokines (Cullen, Thomas et al. 2015, Moran, Barwell et al. 2011, Goldhammer, Tanchilevitch et al. 2005). It is well-known that a single bout of strenuous or moderate exercise acutely increases systemic IL-6 levels, as well as concentrations of other cytokines such as TNFα (Christiansen, Bruun J. et al. 2013, Pedersen, Steensberg et al. 2001). In acute exercise, IL-6 is released by muscles and the level of IL-6 may increase significantly (Christiansen, Bruun J. et al. 2013, Petersen, Pedersen 2005). Chronic exercise for different duration and intensities has reduced the basal level of TNFα, IL-6, resistin and leptin (Reihmane, Dela 2014, Rashidlamir, Saadatnia 2012, Moran, Barwell et al. 2011).

It has been determined that regular physical activity and exercise decrease the levels of inflammatory markers and decrease the risk of CHD (Beavers, Hsu et al. 2010). The results of different researches investigated the effects of regular exercise in diabetes TD1, T2D as well as ND have reported significantly decreases in the levels of TNF-α, IL-6, IL-1β and C-reactive protein (CRP) (Rosa, Heydari et al. 2011, Christiansen, Paulsen et al. 2010, Nicklas, Hsu et al. 2008, Kadoglou, Perrea et al. 2007, Kohut, McCann et al. 2006). There is a relationship between higher levels of physical activity/physical fitness and lower levels of these inflammatory markers (Akbarpour 2013). It has been established that IL-6 can be released locally from contracting skeletal muscle tissue and that the net release from the muscle can account for the exercise-induced rise in arterial concentration of IL-6 (Cullen, Thomas et al. 2015).

Moderate exercise can stimulate the immune system; however, high or extreme exercise might suppress it (Liesen, Baum 1997, Fitzgerald 1988). Evidence suggests that exercise intensity and duration as well as the form of contraction (e.g. eccentric or concentric) and muscle damage all influence IL-6 response to acute exercise (Reihmane, Dela 2014). Furthermore, previous study has demonstrated that resistin and IL-6 concentrations have reduced significantly after 12 weeks of AE in T2T (Kadoglou, Perrea et al. 2007).

In addition, a research study has investigated the effects of 12-week of RE, AE, or combination exercise programme at moderate intensity showed a reduction in TNFα and IL-6 in healthy volunteers with obesity or overweight. They found that TNF-α levels were significantly decreased at week 12 compared to baseline by 20.8 % in AE group, 26.9 % in RE group, and 32.6 % in the combination group. Thus, combination exercise may help to reduce the risk of common chronic diseases such as diabetes, CHD and CVD (Ho, Dhaliwal et al. 2013). Furthermore, another study on patients with CAD, reported that a 12 weeks of AE at 70‑80% of individual maximal HR has reduced significantly baseline levels of inflammatory cytokines such as CRP, and IL-6 from 2.50 ±1.50 to 1.44±0.57 pg/ml (Goldhammer, Tanchilevitch et al. 2005). Moreover, an investigation into the effect of 12 weeks of AE on inflammatory markers of CHD in

obese men found decreases in the levels of CRP, IL-6, leptin and BF% and an increase in the level of adiponectin in the experimental group relative to the control group. In addition, the level of TNFα in the experimental group decreased by 2.86% and 23.76% after 6 and 12-week AE, respectively, although this change was not statistically significant (Akbarpour 2013).

Exercise has been shown to lower levels of inflammatory markers. However, results are inconsistent, indicating different modes, durations and intensities of exercise may have different effects on inflammatory cytokines. Exercise may lower the risk for CHD, CVD and diabetes by mitigating inflammation (Reihmane, Dela 2014, Christiansen, Bruun J. et al. 2013, Christiansen, Paulsen et al. 2010).

1.10 Aims and Objectives

Chapter 3 (first survey):

- Determine both positive and negative experiences of T1D and T2D patients currently using insulin by injection.
- To compare T1D and T2D insulin users regarding the diagnosis, management, treatments and complications.

Chapter 4 (second survey):

- To assess views and attitudes of people with diabetes to diet and exercise and compare between T1D and T2D.
- To compare the type and intensity of exercise that T1D and T2D normally perform.
- To consider factors such as diet, insulin dose and BG management in non-exercise and exercise days for T1D and T2D.
- To assess barriers and coping strategies when exercising safely for diabetes patients.
- This survey's results may support and feedback to the practical part of the study.

Chapter 5 and 6 (first and second exercise studies):

- To compare and contribute research toward the effects of exercises in T1D and T2D with ND using same exercise intervention.
- To study the effect of exercise on HbA1c, BG, lipid profile (TC, LDL, HDL and TG), insulin, other physiological and immunological parameters (TNF-α, IL-6, leptin and resistin) on ND, T1D and T2D volunteers.

- To investigate the effects of acute and chronic combined exercise programme (AE and RE).
- To improve insulin dosing and exercise regimes to prevent hypoglycaemic and hyperglycaemic episodes in T1D and T2D undertaking exercise.

Chapter 2: Materials and methods

2.1 Overview

This chapter describes the methods used for the analysis of the first survey (T1D and T2I users diabetes management survey) and the second survey with (T1D and T2D Diet and Exercise survey), as well as the practical studies involved in this thesis. It describes the methods employed in enrolling participants for the surveys, volunteers for the exercise trials and the measurement of the anthropometric, metabolic and physiological variables required in the study protocol.

A combined (RE and AE) exercise session involved the following: stretching and warm up on the ergometer bike followed by RE working upper and lower muscle groups. After rest, cycling as AE was conducted, the session ended with cooling down and stretching. Exercise trials included two combined exercise sessions a week for a six-week period (twelve sessions).

BG levels were monitored before, during and after each exercise session. Lipid profile (TC, HDL, LDL and TG), metabolic and many of physiological parameters as well as immune-inflammatory markers (IL- 6, TNFα, leptin and resistin) have been measured at different time points throughout the exercise trials. All studies were reviewed and approved by the Faculty of Health and Life Sciences Ethics Committee at De Montfort University, Leicester, UK.

2.2 T1D and T2D Surveys:

2.2.1 First survey: T1D and T2I users diabetes management survey

The first survey produced by the research group questioned T1D and T2I users (707 participants) about their attitudes and experiences with their approach to glucose management, their appreciation of its importance and their understanding of the practical difficulties of achieving desired glycaemic control. Responses were sought about their diagnosis, their medical check-ups as well other areas of their diabetes management such as diet, hypo- and hyperglycaemia awareness and other medical

conditions. This survey had 77 open and closed ended questions. Data from questions which were open were analysed but not included in this thesis as they ask for specific information relating to the views and attitudes of T1D and T2I injectors towards an implantable artificial pancreas. The first survey provided a good approach on how to design and analyse patient surveys in order to develop a second survey about diabetes, which focused more on how people who have T1D and T2D respond and deal with diet and exercise.

2.2.2 Second survey: T1D and T2D diet and exercise survey

A second survey discussed T1D and T2D experiences with various aspects of their diabetes and their attitudes toward exercise and diet (240 participants). This survey had 78 open and closed ended questions and included four sections: background information, diabetes diagnosis and management, hypoglycaemia and hyperglycaemia as well as exercise and diet (Appendix 1).

2.2.3 Surveys validity

In order to validate the surveys in this thesis, face validity was used. Initial drafts of the surveys were forwarded to a team of experts and scientists such as a Diabeteologist, Pharmacologist, Physiologist as well as some diabetes volunteers who read and critiqued the questions and replied with feedback to the researcher.

2.2.4 Surveys distribution

The surveys were produced in English and launched on Survey Monkey® website and distributed to T1D and T2D diabetes patients through various channels such as local newspapers (Leicester Mercury) and diabetes websites as well as through social network sites such as Twitter® and Facebook®. The surveys were distributed by the research group at the Diabetes Clinic (Leicester Royal Infirmary), Balance magazine, newspaper, Diabetes UK and several diabetes forums. Moreover, diabetes exhibitions and some community events in England, such as Diabetes UK and NHS exhibitions and conferences, were used to distribute these surveys. In addition, an internal e-mail and

advert were sent to all De Montfort University (DMU) staff and students as well as a panel and webpage were created on the DMU student portal.

2.2.5 Analysis of surveys responses

The responses from Survey Monkey® were downloaded in Microsoft Excel 2010® and then coded and modified before inputting into Statistical Package for the Social Sciences (SPSS) (version 22 "IBM", Chicago, IL, US). All the responses from different questions in SPSS were then labelled and coded, for example all the questions with yes and no answers were coded as number 1 for (Yes) response and number 2 for (No) response. All postal responses were entered manually using the same coding directly into SPSS®. All data was analysed using SPSS and Microsoft Excel 2010®. All data were filtered and missing data were excluded from the analyses and only valid percentages were considered. Some of the open-ended questions were filtered and then grouped in the appropriate responses if possible. Descriptive statistics, frequencies and percentages were calculated to examine the different questions and variables in the survey. Responses and variables were compared using chi-square test. For normally distributed data paired t-test was used while for non-normal distributed data the Wilcoxon test was used to determine significance. Cross tabulations were used to investigate the relationship between T1D, T2T and T2I. Data values are reported as mean ± SD unless otherwise stated. The level of statistical significance was set at $P < 0.05$.

2.3 Exercise studies design and participants

2.3.1 Diabetes and Exercise Physiology lab (DEPL)

The Diabetes and Exercise Physiology Lab (DEPL) was established at the commencement of the exercise trials. The research team found a suitable laboratory location with convenient and easy access, good ventilation and temperature control (Figure.5).

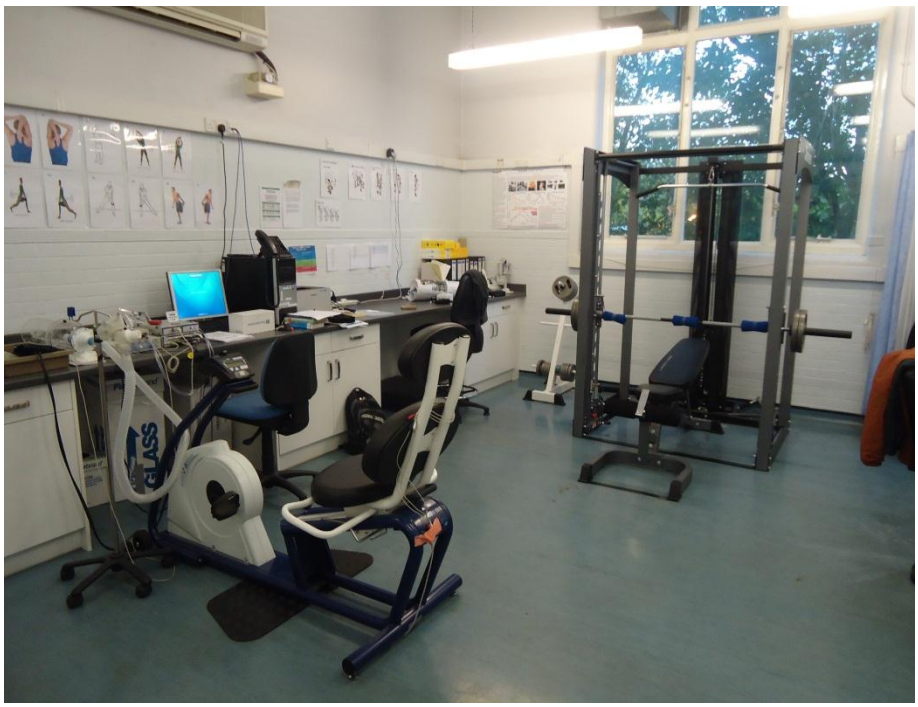

Figure 5: Diabetes and exercise physiology lab (DEPL).

At this early stage of the project, necessary advice was taken from the Sport Exercise Department at Loughborough University. The research group demonstrated the proposed exercise trial and sought technical guidance from Exercise Physiologists, Diabetologist, Physiologists, Pharmacologists and a Sports Medicine Consultant in the planning and regular review stages.

2.3.2 Phlebotomy, first aid and defibrillation training

In order to commence the exercise trials with the volunteers, the researcher had to be well trained and aware of all risks that might occur during the trials such as hypoglycaemia. Therefore, the researcher attended and passed a Phlebotomy course with full training at the Clinical Department, Royal Infirmary Hospital in Leicester. Furthermore, The Advanced First Aid at Work course provided by the East Midlands Ambulance Service NHS, Leicester and a defibrillation course provided by HeartSine Technologies was also attended and passed.

2.3.3 Equipment and procedures

Equipment and procedures used for exercise trials are as follows:

2.3.4 Multi-use gym machine

Volunteers were instructed on how to use a multi-use gym machine (Body Craft Jones Maxrack 3D Machine) for all the RE (Figure 6.)

Figure 6: Multi-use gym machine.

2.3.5 Ergometer bike

Recumbent ergometer bike (Lode, Corival Recumbent, US) was used for warm-up and for the AE component exercise sessions. Workload and resistance were monitored via the bike's digital display (Figure 7.)

Figure 7: Recumbent ergometer bike.

2.3.6 Power lab system ADInstruments machine (ADI)

ADI Analysis System (PL3516/P ADInstruments, 16 channels, Australia) is a power lab system (Figure 8). This system included : gas analyser (Carbon dioxide CO_2 and Oxygen O_2), gas mixing chamber with a 4.7 L capacity for collecting, mixing and sampling expired respiratory gases, long smooth tubing for connection to the gas mixing chamber and face mask. ADI generates an immediate visual representation of performance associated with various metabolic variables for example oxygen consumption (VO_2), carbon dioxide production (VCO_2), respiratory exchange ratio (RER), heart rate (HR), bike revolutions per minute (RPM) and breath flow and temperature of respired air. The ADI software enabled the measurement of RER at rest and during the cycling.

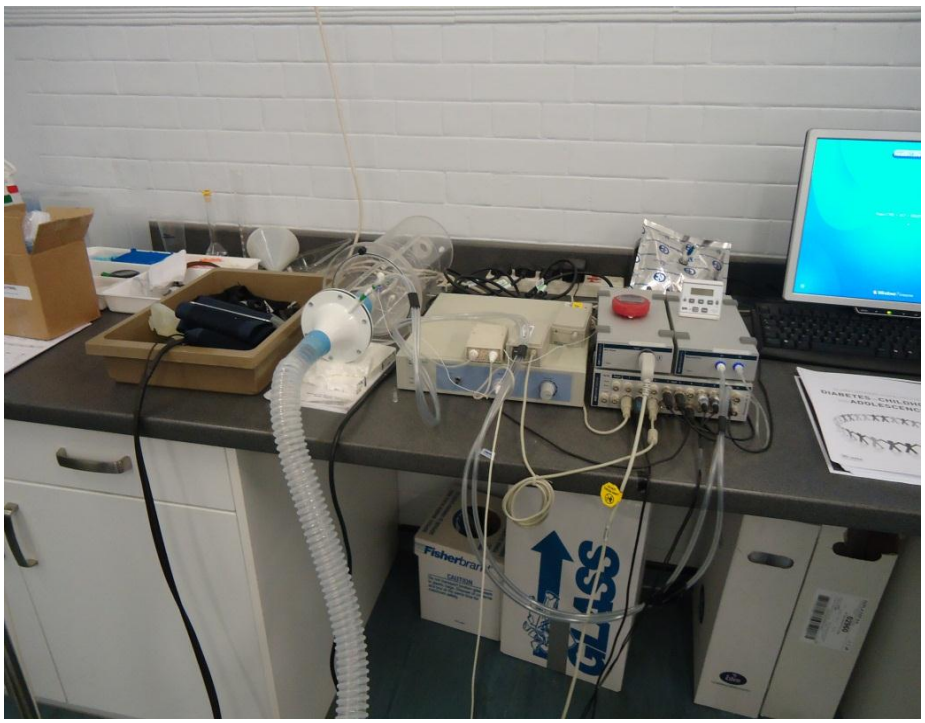

Figure 8: ADI power lab system.

2.3.7 Calibrating, filtering and sterilising the ADInstruments analyser

The calibration of machines is very important in obtaining accurate and consistent results; therefore, the ADI power lab system used and described in section 2.3.6 was calibrated before use with reference gases from BOC Ltd, Surrey, UK. A rubber tube connected the reference gas bag with the gas analyser, and a calibration gas containing 16% oxygen, 4% carbon dioxide was passed through the gas analyser. This calibration was repeated every few hours to minimise the errors. To prevent moisture damage to the sensors and to remove any possible damaging particulates, an in-line filter (0.45µ hydrophobic membrane) was changed every 2–3 weeks.

A face mask, nose clips (Speedo® Universal, UK) and drying tube were cleaned and sterilised before and after each exercise session. This was done by unclipping these components from the ADI hardware and immersing them in sterilising fluid (Chlor-Clean, Guest Medical, UK) for a minimum of 2 hours prior to re-use.

2.3.8 Heart rate (HR)

The volunteer's HR was monitored at rest and continuously during the combined exercise trial by short-range telemetry (Polar S610i, Polar Electro, Finland) using a chest heart rate monitor and watch (Polar, FT1-TRA/BLK, Finland).

2.3.9 Rate of perceived exertion (RPE)

Rate of perceived of exertion values were obtained from the subjects using the Borg scale (1973) during the resistance and aerobic exercise. The Borg scale ranged from 6 as 'minimum,' and 7 as 'very, very light' to 19 as 'very, very hard' and 20 as 'maximum' (Borg, 1973). This scale was shown to the volunteer, so he was be able to point at how hard or easy the exercise he performed was.

2.3.10 Finger pricking procedure (FPP)

FPP was used to obtain blood samples, which was as follows: A finger was sterilised with alcohol swab (Reliance Medical, UK) and allowed to dry for 10-15 seconds. A spot on a finger was chosen and pricked with a lancet device (Microlet 2, Bayer Contour, US) to obtain the required quantity of capillary blood for the test.

2.3.11 Glycated haemoglobin ($HbA1_C$) analyser

HbA1c was measured by Quo-Test A1c reagent kit (Figure 9), which had been already tested for reasonable precision and accuracy. Using FPP, a blood sample of 4µl was loaded into Quo-Test cartridge. The cartridge was placed into the analyser and the result was displayed on the digital display and a printout of the result was taken within five minutes.

2.3.12 Blood glucose monitor

Blood glucose was measured specifically 4 times for each volunteer: at rest before exercise, after RE exercise, after 10 min of aerobic exercise and at the end of each trial. BG was measured using a blood glucose kit (Contour, BAYER, Switzerland) (Figure 9). A blood drop of ~1µl was obtained using FPP, and then placed within the dedicated well

in the test strip which absorbed enough blood to perform the test, a result was achieved within seconds.

2.3.13 Blood pressure monitor

BP was taken at different time points during exercise trials using an upper arm blood pressure monitor (Omron M10-IT, Omron Healthcare Co., Ltd, Japan), (Figure 9) . BP was taken with the volunteer sitting in a chair; the BP cuff was placed on the upper arm ensuring that the cuff was at the same level as the heart. The volunteer were asked to sit upright and not to move and talk while their BP was measured.

2.3.14 Measurement of lipids profile

TC, HDL, LDL, and TG were measured by a CardioChek® analyser (PA Bundle, Health Check Systems, Germany), (Figure 9). 15 µL of whole blood was obtained using FPP. A plastic blood pipette was used to collect exact amount of blood required for the test and it was placed on a test strip (PA Lipid Panel, Health Check Systems, Germany) which was present in the CardioChek analyser.

Figure 9: BG and BP monitors, HbA1c and lipids analysers.

2.3.15 Collection, separation and analysis of venous blood samples

Volunteers were asked to sit on a comfortable chair in order to collect venous blood samples. An alcohol swab and a disposable latex-free tourniquet (Fisher Thermo Scientific- Cat no. 22-040-225) were used to avoid any infection or contamination. Venous blood samples from the Antecubital Fossa were collected using a S-Monovette (Monovette, SARSTEDT) blood collection system needle and 10 ml tube (BD, Plymouth, UK) containing EDTA (ethylenediaminetetraacetic acid) anticoagulant.

In order to separate blood plasma, labelled samples were centrifuged at 3000 rpm for 15 min at 4°C using a centrifuge (Fisher Thermo Scientific, UK). Plasma was then dispensed into labelled 1.5 ml Eppendorf tubes (Eppendorf, Germany) and stored in a -80°C freezer until analysis which was within 6 weeks.

In order to assess the immunological response to an acute exercise as described later in section 2.5.2 on the first exercise session three venous blood samples using the above procedure were collected. These were taken before any exercise was performed, after the RE component of the combined exercise programme and finally after the AE component (cycling).

The chronic response to exercise over the 12 sessions was assessed by collecting venous blood samples in the following sessions: 1^{st}, 2^{nd}, 4^{th}, 6^{th}, 8^{th}, 10^{th} and 12^{th}.

2.3.16 ELISA kit and plate reader

Insulin and C-peptide were determined using a commercially-available enzyme-linked immunosorbent assay (ELISA) with <0.01 cross reactivity with pro-insulin (Mercodia AB, Uppsala, Sweden). Microplate Reader with Manta Software, (Labtech LT-4000, Ireland) and a plate shaker (IKA® MTS 2/4 digital, Germany) was used to read and analyse the tests. Mercodia Insulin and C-peptide ELISA is a solid phase two-site enzyme immunoassay. It is based on a direct Sandwich technique in which two monoclonal antibodies are directed against separate antigenic determinants on the insulin or C-peptide molecule. The insulin assay procedure was as follows:

All reagents and samples were brought to room temperature before use and a calibrator curve was made for each assay run. Enzyme conjugate solution, wash buffer solution, sufficient microplate wells to accommodate calibrators and samples in duplicate were prepared. The experiment started with pipetting 25 µL of each Calibrator and sample into appropriate wells. After that, 100 µL of enzyme conjugate solution was added to each well and Incubated on a plate shaker (700-900 rpm) for 1 hour at room temperature (18–25°C). Then microplate wells reaction volume was discarded by inverting the microplate over a sink. 350 µL wash buffer solution was added to each well then discarded by inverting the microplate over a sink. The microplate then was tapped firmly several times against absorbent paper to remove excess liquid. This washing step was repeated 5 times.

After washing, 200 µL of Substrate 3,3',5,5'-tetramethylbenzidine (TMB) was added to each well then incubated for 15 minutes at room temperature (18–25°C). After the incubation 50 µL Stop Solution was added to each well. The plate was then placed on a shaker for approximately 5 seconds to ensure mixing. As a final step the plate was read at an optical density of 450 nm and insulin concentration calculated.

C-peptide kit procedure was same as the insulin except the following: after pipetting 25 µL each of calibrators and the samples, a 50 µL of Assay Buffer was added to each well and it had another washing step after the second incubation step which was for 1 hour. The enzyme conjugate was adding after the first wash step and Substrate TMB was added after the second wash (Figure 10).

Figure 10: ELISA technique.

2.3.17 Blood gas and electrolytes analyser

A Radiometer (ABL800 FLEX analyser, Denmark) was used to measure pH, blood gases (pCO_2 and pO_2) and electrolytes such as sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), and chloride (Cl^-) (Figure 11). For measurement of blood gases, arterial blood was required which was taken from the ear lobe of the volunteer into a plastic capillary tube (85 µL, *safe*Clinitubes, Denmark) with anticoagulant (sodium heparin) and placed into the Radiometer machine for testing.

Figure 11: Radiometer, blood gas and electrolytes analyser.

2.3.18 Multiplexing ELISA

The Evidence Investigator (Randox, UK) which is a Multiplexing ELISA technology was used to measure immune- inflammatory markers such as Interleukin-6 (IL- 6), Tumour Necrosis Factor α (TNFα), resistin and leptin (Figure 12).

Figure 12: The Evidence Investigator, Randox machine.

2.3.19 Body composition and anthropometric measurements

In the first session before exercise commenced, base line anthropometric measurements and other different physiological variables were recorded in the DEPL. Volunteer body mass was measured in (kg) to the nearest 0.10 kg using a digital weighing machine (SECA) while subjects were wearing light clothing. The volunteer stood without wearing shoes on a wall-mounted stadiometer to measure height to the nearest 0.1 cm. According to volunteer age, height and gender, body fat (%BF), and body water (%BW) percentages were analysed by a bioelectrical technique using SECA scale as follows: the volunteer stepped on to the scale which sends a small, harmless electrical current through the volunteer's body to measure %BF and %BW. Hip and waist were measured in centimetres by measuring tape. The waist-to-hip ratio (WHR) was determined by measuring the waist circumference at the narrowest region between the costal margin and iliac crest and then dividing this measurement by the hip circumference measured at its greatest gluteal protuberance. BMI was calculated as weight (kg)/height $(m)^2$.

2.3.20 Fridge, water cooler and temperature monitor

A suitable fridge and water cooler were used to provide cold water and Lucozade glucose drinks to the volunteer if needed. Lab temperature was adjusted at 20°C and monitored by a weather station (Oregon Scientific, Hong Kong) and the room's climate control system.

2.4 Selection criteria for volunteers

The target population for this study were T1D, T2T, T2I and ND males volunteers aged between 18–55 years who were not physically active or taking part in any regular exercise programmes and met the inclusion criteria (Section 2.4.1). A total of sixty volunteers who responded to the study advertisement and expressed an interest in participating.

Twenty-eight volunteers were deemed unsuitable for inclusion because they did not meet the inclusion criteria due to different reasons such as medical problems, age, were female or they were participating in regular exercise. Seven subjects were excluded due to failure to return for follow-up sessions.

The final study population consisted of 25 male volunteers divided in to following groups: ND control =7, T1D = 7, T2T = 7 and T2I = 4.

2.4.1 Exclusion criteria

Exclusion criteria for excluding the subjects were as follows:

had any of the following: heart disease, liver disease, kidney disease, high blood pressure, rheumatic, heart murmur, HIV positive or aids, any allergy, hepatitis, asthma, tuberculosis (TB), stroke, epilepsy, any injury in head, hand or other injury and tumour (cancer) history.

- were currently using glucocorticoids or beta blockers.
- had an active infection.
- anticipated a significant change in exercise regimen after admission.
- had another medical condition or were using medication that in the judgment of the researcher could affect completion of the exercise trial.
- had blood pressure greater than 160/95 mm Hg.
- had participated in regular exercise two or more times weekly for 20 minutes or longer per session or any resistance training during the previous 6 months .
- showed restriction in physical activity because of disease.
- had recent blood loss or hemolytic anaemia.
- were terminally or mentally ill.
- had any recent surgery.

2.4.2 Volunteers' recruitment

A variety of media were utilised to publicise the study. Initial recruitment was generated from an advertisement in DMU, further exposure occurred through an article in the Leicester Mercury® which coincided with a press release from Western Park Gazette®. Recruitment posters were displayed around the main campus, and associated campuses across Leicester as well as outside other places of worship such as Mosques, Churches and Gurdwaras. A display panel on the DMU electronic student portal was used to further promote recruitment.

A number of General Practitioners (GP) who provide primary care for patients with T1D and T2D diabetes through the Leicester Diabetes Service agreed to display recruitment posters in their surgery waiting rooms. Potential volunteers could access information about the study through a dedicated webpage sited on the University website. In addition to this, volunteers were able to provide basic contact details and note their interest by emails to the principal investigators. Information on the study was disseminated by word-of-mouth, by both the research group and volunteers themselves, and was responsible for a small proportion of the total number of subjects recruited.

Participants included in the study met the following criteria: they were aged at admission time between 18 and 55 years old either healthy or diagnosed with T1D or T2D. Their HbA1c was ≤10.0% (86 mmol/mol) and they were not participating in any form of training, vigorous physical activity or formal exercise for 2 weeks before the commencing the study. They had normal thyroid function with no medication, anti-inflammatory agents, steroids, antioxidants or vitamin supplements before, during, or after study entry. No recent history of infectious, inflammatory or immune diseases. Volunteers were recruited locally from Leicester area. Interested volunteers were initially contacted by telephone and email to provide informations and to arrange a formal screening visit to the DEPL in the Faculty of Health and Life Sciences at DMU.

2.4.3 Ethical approval and risk assessment

Ethical approval of the exercise trials plan and procedures was granted by DMU Ethics Committee (Appendix 2). Some of the key documents and forms produced and submitted to the Ethics Committee to obtain the ethical approval are discussed below.

2.4.4 Volunteer information sheet (VIS)

The VIS (Appendix 3) explained the purpose and aims of the study for the interested volunteers. It contains information about what would happens to the volunteer if they decide to take part, an explanation of the experimental trials, expenses and payments, possible benefits or risks of participating in the exercise interventions, confidentiality, withdrawal time and who had reviewed the study.

2.4.5 Standard operating procedure (SOP)

The SOP (Appendix 4) provides details about preliminary and main experimental procedures and any tests used in the exercise programmes.

2.4.6 Risk assessment form

This document is an assessment of any possible hazards which might affect the volunteers and researchers during all the exercise trials.

2.4.7 Consent form

This form (Appendix 5) sought permission from the volunteers to take part in the study and to confirm that the volunteer had read the VIS and understood all the details about the exercise trials. The document made volunteers aware that they were free to withdraw at any time.

2.4.8 Volunteers health screen

This document (Appendix 6) focused on information regarding the volunteers health and medical history. The health screen form was used to make sure that volunteers participating in the exercise trials were in good health and had no significant medical

problems or complications in the past or at present. All volunteers were asked to check with their GP before getting involved in this study to make sure that it was ideal for them to take part. Every volunteer had been given an information sheet describing all the trials and tests involved in the study to give it to their GP, and a GP approval letter was also sought, though was not compulsory.

2.4.9 Volunteer record sheet

After the subject agreed to participate in the exercise trials and had signed the consent form, a record sheet (Appendix 7) was given to be completed by the volunteer. This record sheet includes: volunteer name, contact details, type of diabetes or non-diabetes, GP contact details, history of acute diabetic complications including number of hypoglycaemia and hyperglycaemia episodes and other medical conditions.

2.4.10 Confidentiality

In order to protect confidentiality, each participant's identity was coded and stored by identification number. Access to this data and all other corresponding information was restricted and stored securely. Upon completion of enrolment into the study, signed informed consents and individual data were collected, coded, sorted by identification number, and kept in a locked file cabinet at the DEPL in the School of Pharmacy.

2.5 Preliminary testing

2.5.1 Screen DEPL visit

Before enrolling in the study, all interested volunteers attended a screening visit to discuss and complete questionnaires regarding their health, family history and current physical activity levels. They were provided with VIS, given an oral presentation which explained the study and were then encouraged to give feedback and ask questions. Subjects were asked to fill out a questionnaire for a physical activity (Appendix 8) and health history screen (Appendix 6). The health history screen was designed to determine whether the subjects were taking any medicine or had any previous sickness or injuries that might affect their exercise performance.

Informed consent was obtained in duplicate. One copy was given to the volunteer for reference; one copy was retained as part of an individualised case record for the volunteer. Any subject met the inclusion criteria and agreed to participate in the study; a second appointment was booked for him in the DEPL for the familiarisation of RE and AE exercise.

2.5.1.1 Familiarisation of resistance and aerobic exercise

All participants were asked for a second visit to familiarise themselves with the laboratory and exercise equipment, testing procedures and exercise protocol. In this visit, a demonstration on how to lift the weights safely with the multigym machine was demonstrated as well as how to use and cycle on the recumbent bike. In addition, each subject was asked to do one set of 10 repetitions for each resistance exercise to ensure that the subject become familiar with RE.

2.5.1.2 Determination of one repetition maximum (1RM) for RE

One repetition maximum (1RM) is the highest amount of weight that can be lifted in a single repetition for resistance training and is used to determine intensity levels. As this may not be a safe protocol, especially for people with diabetes if tried at once, strategies have been designed to obtain an approximate value based on a weight and the number of repetitions the subject can perform to exhaustion for that exercise. There are particular methods of calculation 1RM. In this work the 1RM value was determined according to the (Brzycki 2000) formula (1RM=100×repweight/ (102.78 - (2.78×reps)) where repweight is the workload value of repetitions performed and reps is the number of repetitions performed. Prior to performing a 1RM, a warm-up was a compulsory step. The machine and the weights were optimised for each subject according to the target weight which was 50-60% of 1RM.

2.5.1.3 Determination of intensity level for AE

Volunteers were required to perform each exercise at 50- 60% of their estimated heart rate reserve (HRR). In order to record heart rate at rest the subjects were given heart rate monitors to take two readings when they are at complete rest (sitting or lying

down) in the late evening and two readings first thing in the morning when they wake up. After reviewing of literature, the Karvonen formula method (Equation.1) was used to determine HR reserve (Goldberg, Elliot et al. 1988; Shnayderman and Katz-Leurer 2013) as follows:

Karvonen formula: [(220-age)-(resting HR) × intensity] + resting HR

For Example: if a volunteer aged 30 and the mean of his heart rate at rest is 65 bpm, his maximum heart rate would be 220 - 30 = 190 bpm. Heart rate reserve = maximum HR- HR at rest (bpm), 190 – 65 = 125 bpm. Based on Karvonen formula calculations methods, the target HR for the cycling in the exercise trials would be: (125 × 0.5 + 65 = 127.5 bpm)

2.5.2 Main exercise trials

A combined exercise session involved stretches and warm up on the cycle ergometer for 10 min followed by 35 min of RE at 50-60% of 1RM then 5min of rest and after that 20 min of AE (cycling) at 50-60% of HRR and finished by 10 min cooling down.

Volunteers arrived at DEPL, asked to rest for 10 min before any measurements were taken. After resting, the HR chest monitor was attached to volunteer's chest to record HR readings during the session. A venous blood sample (as described in section 2.3.15) and the first readings of BG and BP were taken before volunteers stretched lower and upper muscle groups left and right for a total of 5 min. Stretching included loosening front and back upper arms, chest, shoulders, middle back, lower arms, wrists, hands, fingers, back, tops of shoulders, neck, triceps, hamstrings, as well as hip flexor stretches and chest stretches for the pectoral muscles.

After stretching, volunteers warmed up 10 min on the recumbent bike. Warm-up is an essential part of exercise sessions and designed to prepare the body for exercise, increase body temperature and reduce the potential for post-exercise injury or pain, especially muscle stiffness. Immediately, after warming up volunteers started the RE which last for 35 mins on the multi-gym machine. The RE performed included five different exercises working upper and lower muscle groups: squat, incline bench press,

lateral pull-down, bicep curls, and triceps (Figure 13). Volunteers performed three sets of ten repetitions of each type of exercise with one minute of rest before the start of the next exercise. After each set, RPE and the HR data were recorded.

After RE, the volunteer had a 5 min rest, a second venous blood sample was collected, BG and BP were taken, and then both the subject and the bike were attached to ADI power lab analysis System.

Physiological signals were converted from analog to digital during aerobic exercise by a PowerLab data acquisition unit LabChart (LabChart v6.1.3, ADInstruments, springs, Colorado) modules provided acquisition and analysis features specific to specialised applications.

Volunteers were attached to the ADI via a breathing mask (breath-by-breath) system, Polar chest heart-rate monitor and Polar Receiver Interface Cable. Volunteers were asked to cycle for 20 min of moderate intensity at 50 to 60% of (HRmax) on a recumbent ergometer (Figure 14). After 10 min and at the end of the cycling, BG was monitored and volunteers were asked to rate their RPE (Figure 15).

Finally, all volunteers were asked to cool down by stretching the lower and upper muscle groups as described previously in this section. After that, a third blood sample was collected and final readings of BP and BG were taken. In the event of low BG after final exercise, volunteer was asked to stay in the exercise lab and not to leave for final observation for 45min to 2 hours.

During each exercise session, the measurements sheet (Appendix 9) was filled out. This sheet was designed to make sure every step was in the correct order and to follow up volunteer performance as well as to record all the different physiological variables measured during the exercise session. This exercise programme involved 2 sessions (48 hours apart) for a total of 150 min each week for a 6-week period.

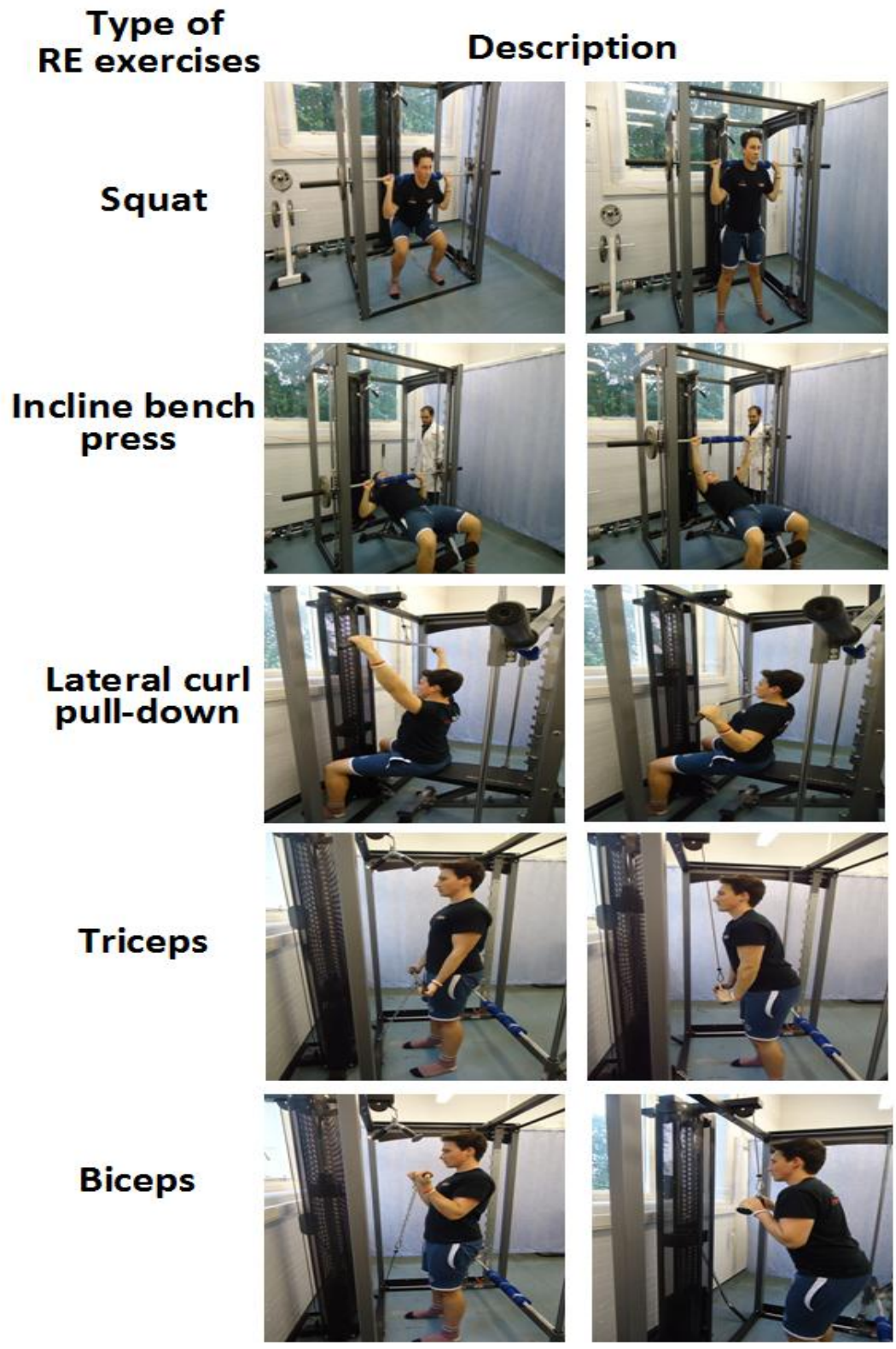

Figure 13: A volunteer performing resistance exercises.

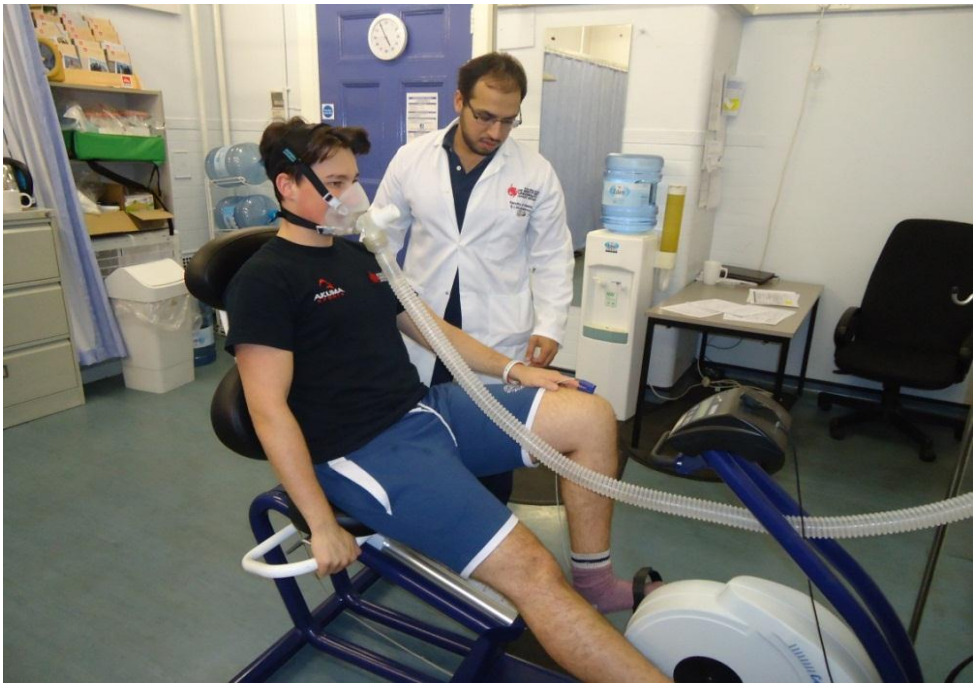

Figure 14: A volunteer cycling on the recumbent ergometer bike.

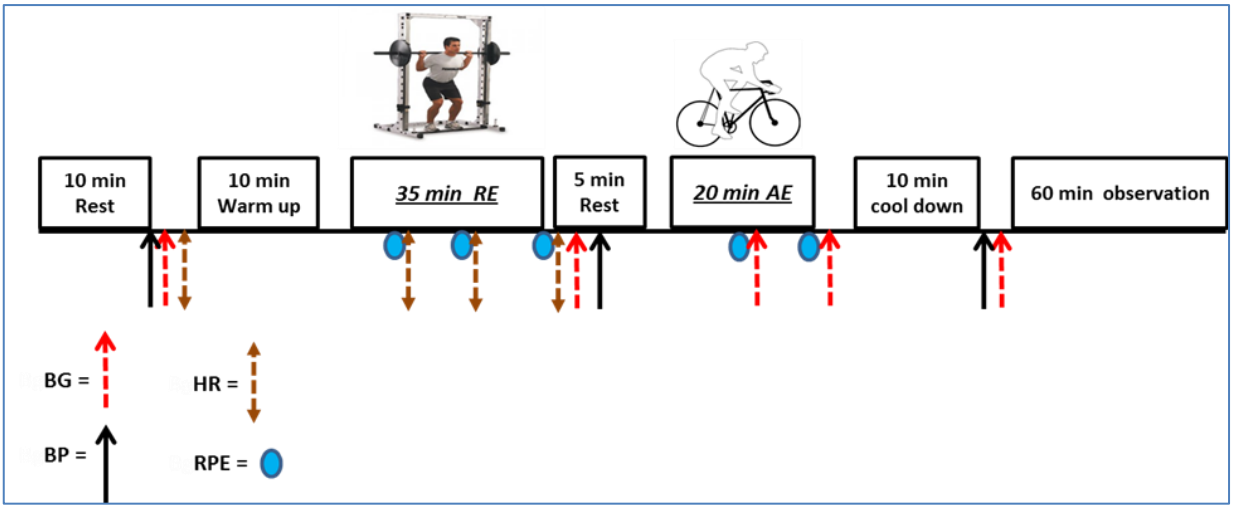

Figure 15: Schematic representation of the study protocol.

2.5.2.1 Lipids, blood gases and electrolytes sampling timepoints

Lipids (HDL, LDL, TC, TG), blood gases (PCO_2, PO_2), electrolytes (Na^+, K^+, Ca^{2+}, Cl^-) were measured three times: before the exercise programme at the first session, after session 6 and at the end after session 12.

2.5.2.2 Timepoints of anthropometric measurements

Weight, %BF, %BW and BMI data were measured at three time points: before the exercise programme at the first session, after session 6 and at the end after session 12. Waist and hip measurements were taken at two time points, before exercise at the first session and at the end after session 12.

2.5.2.3 BG and HbA1c sampling timepoints

BG was measured specifically 4 times for each volunteer in each exercise session: at rest before exercise, after RE exercise, after 10 min of cycling and at the end of each session. HbA1c level was measured at session 1 and after session 12.

2.5.2.4 Insulin and immune- inflammatory markers sampling timepoints

Using ELISA, plasma samples were analysed for, Insulin, C-peptide, and Inflammatory markers (IL- 6, TNFα, resistin and leptin,) after the following sessions: 1^{st}, 2^{nd}, 4^{th}, 6^{th}, 8^{th}, 10^{th} and 12^{th}.

2.5.2.5 Assessment of caloric intake

It was important that all volunteers weighed and recorded everything that they ate and drank for the day prior to each experimental exercise session. Food inventory sheets were provided to volunteers (Appendix 10). Volunteers were asked to try to keep the same food regimen for the 24 hours before each exercise session and to refrain from alcohol and smoking 24 hours before an exercise session.

2.5.2.6 Statistical Analysis

All data were analysed using (SPSS) and Microsoft Excel 2010®. Throughout the trials, differences in blood physiological parameters concentrations, BMI , weight, %BW,

%BF, electrolytes and immune-inflammatory markers were compared using a one-way (trial vs. time) analysis of variance (ANOVA) with repeated measures, followed by Tukey's post hoc test; for comparison of the mean of waist, hip and HbA1c values of different parameters, a paired t-test was used. Data values are reported as mean ± SD unless otherwise stated. The level of statistical significance was set at $P < 0.05$.

Chapter 3: Management of diabetes, hypoglycaemia and hyperglycaemia by T1D and T2I

3.1 Introduction

About 387 million people have various common forms of diabetes, including lifestyle associated T2D (90% of the total) (International Diabetes Federation, 2014, Malkova, Evans et al. 2000), with T1D, gestational (Manetta, Brun et al. 2002) and other minority diabetic conditions such as latent autoimmune diabetes of adults (LADA) and maturity onset diabetes of the young (MODY) account for the rest. It is expected that this number may rise by about 50% in the next 15 years, with about 10% of the world's population experiencing one form or the other of diabetes (Manji, Shikora et al. 1990).

In T1D, the most effective treatment for controlling changing BG levels remains the introduction of insulin, with the inclusion of statins and anti-hypertensives which aid in protecting against biochemical abnormalities occurring in the cardiovascular system. In T2D sulphonylureas (for example Gliclazide®) and other oral anti diabetic agents such as Metformin® are often combined with dietary control as a preventive therapy for metabolic derangement. The introduction of insulin is often started at a later stage of T2D treatment (often after a heart attack has occurred) and most medical professionals believe that its usage should occur much sooner (Marra, Scalfi et al. 1998).

The loss of protein function that occurs in tissue (Marwick, Hordern et al. 2009) as a result of changes in body chemistry from diabetes usually occur from high BG concentrations where glycation to amine groups in proteins results in structural protein and enzyme changes both temporarily and permanently (Marzolini, Oh et al. 2008, McArdle, Katch et al. 2006). Other biochemical dysfunctions and compensatory anomalies occur in concert. These result in metabolic imbalances in lipids and carbohydrates that support the development of complications which can begin to develop in both types of diabetes when not controlled effectively (Melanson, Sharp et al. 2002). The main complications which are expensive to treat are renal, infection-related and wound-healing difficulties,

ophthalmic, dental, neurological and cardiovascular.

For T1D and T2I diabetes patients the most effective treatment for maintaining satisfactory HbA1c levels comes from regimens such as basal bolus which are intensively controlled with regular BG testing in combination with insulin doses .

Basal bolus methodology consists of a basal dose which is a calculated background of long acting insulin together with a short acting bolus or boost of insulin which is administered at mealtimes. This variable dosing allows the patient a much more normal diet. More importantly this must be done in conjunction with frequent BG testing to prevent excursions from normoglycaemia. It is often the case that most diabetes patients find regular injections and finger prick testing uncomfortable and invasive and this could be alleviated to some degree by the use of continuous glucose monitors for BG testing and insulin pumps for infusion. The use of insulin pumps is more common in the USA for this reason, and the UK and other countries often lack behind in investment in core areas of treatment such out-patient and community support staff, such as diabetes specialist nurses (DSNs).

The financial burden in the UK amounts to £1 million per hour (Melanson, Sharp et al. 2002, Meltzer, Leiter et al. 1998) which could be reduced by an improvement in the uptake of intensive control. Evidence across the world for children and adults shows that they fail to achieve optimum HbA1c (Merry, McConell 2009). A fall in HbA1c from 7.9 to 7.0 (63 to 53mmol/mol) lowers microvascular risk by 25% which is critical because poorly controlled T1D can reduce lifespan by 20 years (Merry, McConell 2009).

In this work data presented from responses to a questionnaire distributed to T1D and T2I insulin users relating to their diagnosis, management, treatment and complications as a result of their diabetes.

3.2 Survey design, distribution and response collection

A survey of patients with T1D and T2I diabetes who were insulin users was carried out. The questionnaires were produced in English and distributed to T1D and T2I insulin users through various channels. Advertisements were placed in various local and national media (such as newspapers) within the UK, and in publications from various diabetes charities such as Diabetes UK. An interactive web-based version of the survey (Survey Monkey®) was also available via a dedicated website for participants who wanted to submit responses via the internet. The UK Diabetes Network and other diabetes websites also distributed copies to members on their databases. Finally we used social networking sites such Twitter® and Facebook® to publicise the survey (Refer to section 2.2).

A total of 707 participants answered 77 questions relating to their approach to glucose management, their appreciation of its importance and their understanding of the practical difficulties of achieving desired control. Responses were sought about their attitudes since diagnosis, their medical check-ups as well other areas of their management such as diet, hypo- and hyperglycaemia and other medical conditions.

3.3 Analysis of responses

All data were analysed using (SPSS) and Microsoft Excel 2010®. Refer to section 2.2.5.

3.4 Results

3.4.1 Background information, diagnosis and check-ups

From the 707 completed surveys, 95% of responses were from the UK where the survey was widely distributed and advertised with 91.1% of responses from British respondents of white ethnicity. The remaining responses were gathered from the USA. All respondents were insulin users with 71% having T1D diabetes and 29% having T2I diabetes. 42.2% of T1D respondents were male compared with 56.9% of T2I. Respondents were asked how old they were when they left full-time education with 19.7% T1D and 44.3% T2I being 16 years or younger. However, 67.1% of T1D were

most likely in or had a higher education (e.g. university), compared to 46% of T2I.

The most difficult aspect of the diabetes management for respondents was found to be exercising (36.6% for T2I and 34% for T1D). Other difficulties were identified as diet, testing BG and injecting insulin. About 19.4% of T1D and T2I did not report anything difficult about their diabetes. 58.5% of the respondents thought that their diabetes was very well controlled.

Respondents were asked where they went for their diabetes check-up, the majority (93%) were seen at their doctor's surgery or in a hospital clinic. Respondents were also asked to describe the amount of written and verbal information they received when they were first diagnosed with diabetes. For verbal, 3% of T1D and 7.3% of T2I did not receive any information, 27.1% of T1D, 31.7% of T2I received too little information and 44.6% of T1D, 52.2% of T2I received the right amount of information. However, for written help, 8.8% of T1D and 14.6% of T2I did not receive any (such as leaflets or information booklets), 25.3% of T1D, 22.4% of T2I too little information and the right amount of information was received by 32.5% of T1D, 40.5% of T2I. Of these, 2.8% of T1D and 2.0% of T2I had not had a diabetes check-up in the last 12 months, 30.9% of T1D, 24% of T2I had one, 40% of T1D, 49.5% of T2I had two and 26.2% of T1D, 24.5% of T2I had had three or more check-ups.

3.4.2 Management and diet

In the last 12 months, 69% of T1D and T2I had an opportunity most of the time to discuss their ideas about the best way to manage their diabetes with their medical advisors. However, a high proportion, 38.8% of T1D and 37.9% of T2I had no chance or rarely discussed possible different medications. In addition to this, 41.5% of T1D and 35.1% of T2I had rarely or never had personal advice about the kinds of food to eat and 43.5% of T1D, 37% of T2I received similarly little personal advice about their levels of physical activity.

More than half of the respondents (50.7% T1D and 56.7% T2I) reported that they always or mostly had a plan to manage their diabetes over the next 12 months with their medical advisors. The majority of all respondents (95%) had had a HbA1c test, blood pressure measurement and their weight checked by a doctor or nurse in the previous 12 months as part of their treatment. Also in the past 12 months over 72.3% of T1D and T2I respondents had their cholesterol, eyes and bare feet examined. 36.3% of T1D and 26.3% of T2I had also talked to a dietician in the previous 12 months about their dietary management. When T1D and T2I respondents were asked if they had stayed in hospital overnight as a patient in the last 12 months, 19% of T1D and T2I reported that they had. Of those respondents 65.2% of T1D and 56.4% of T2I had stayed for 1 – 3 nights, with 43.7% of T1D and 17.9 of T2I reporting that the reason was diabetes related.

Table 2: Types of insulin used by T1D and T2I respondents.

Type of insulin	T1D	T2I
Actrapid®	1.4%	0.5%
Humalog®	4.8%	4.8%
Humulin I®	2.8%	2.9%
Humulin M®	0.4%	2.9%
Humulin S®	0.6%	0.5%
Hypurin®	0.6%	1.5%
Insulotard®	4.8%	5.4%
Mixtard®	1%	3.4%
Novorapid®	7.1%	4.8%
Novomix®	3.6%	13.6%
Other	3.4%	22.4%
Combination of insulins selected		
Lantus®/Levemir® + Novorapid®	54.5%	24.0%
Lantus®/Levemir® + Humalog®	17.7%	9.3%
Lantus®/Levemir® + Actrapid®	3%	0.5%
Lantus®/Levemir® + Humulin I®	0.6%	0.5%
Lantus®/Levemir® + Mixtard®	1%	0%
Lantus®/Levemir® + Insulotard®	0.6%	0.5%
Lantus®/Levemir® + Novomix®	0%	0.5%
Lantus®/Levemir® +Other	0.2%	0.5%
Lantus®/Levemir® + Humulin S®	0.6%	0.5%

Table 2 shows the types of insulin used by T1D and T2I respondents. It should be noted that respondents were asked to tick all insulins they used and all respondents that injected Lantus® or Levemir® also used a short acting insulin such as Novorapid® (54.5% for T1D and 24% for T2I), Humalog® (17.7% for T1D and 9.3% for T2I) and Actrapid® (3% for T1D and 0.5% for T2I). 13.6% of T2I respondents also used Novomix®

and 22.9% used other insulins not listed in the survey responses and shown in Table 2. Most of T1D 77.6% and more than half of T2I 53.6% started using insulin longer than 5 years ago.

86.4% of T1D and 39.5% of T2I gave themselves 4 or more daily injections. 42.1% T2I gave themselves 2 injections compared with only 8.4% of T1D. 21.2% of T1D and 36.7% of T2I have been using the same number of injections since they started taking insulin and 45.1% of T1D compared with 21.3% of T2I have using the same regimen for 5 years or longer. 72.3% of T1D and 82% of T2I described the total amount of insulin they used for the previous 24 hours as more than 30 units.

The majority of T1D (65%) and 22.6% of T2I tested their blood glucose 4 or more times a day. About half of T2I (49.2%) tested it once to three times a day compared to 27.6% of T1D. Respondents in this survey used the results of their BG tests to check or alter the amount of insulin they take (87.5% of T1D and 57.1% of T2I). A further 72.7% of T1D, 48.8% of T2I used BG tests to warn them about impending hypoglycaemic episodes. More than 79% of T1D and T2I respondents knew their HbA1c result and what that result meant.

Table 3: How much information do you feel you have been given about the following aspects of your diabetes care?

	Too much information		Right amount of information		Not enough information	
	T1D	**T2I**	**T1D**	**T2I**	**T1D**	**T2I**
How to manage your diabetes when you are ill, e.g. having flu.	0.0%	0.0%	71.1%	51.7%	24.3%	42.0%
Getting to and keeping to a certain weight	0.8%	1%	53.6%	59.5%	39%	32.7%
What to expect if your blood glucose drops too low or becomes high.	2.2%	0.5%	84.9%	74.6%	8.2%	19.5%
The reasons for taking prescribed medicines to manage your diabetes.	2.0%	1%	80.9%	76.6%	9.6%	15.1%
The long term health effects of your diabetes.	7.8%	3.9%	69.9%	69.8%	17.5%	21%
The importance of raised cholesterol levels for people with diabetes	1.4%	0.5%	55.4%	66.3%	38.2%	27.8%
The importance of high blood pressure in people with diabetes	0.8%	1.5%	59.4%	67.8%	34.5%	24.9%
The importance of regular eye checks for people with diabetes	2.6%	1.5%	87.8%	88.3%	5.2%	5.4%
The importance of checking and looking after your feet	1.6%	2%	77.7%	80%	16.3%	13.7%
How drinking alcohol can affect your diabetes	1.8%	2.9%	66.7%	66.8%	25.3%	21.5%
How smoking can affect people with diabetes	2.4%	2.4%	72.3%	70.7%	17.5%	17.1%
The effects of stress on your diabetes	0.8%	0.0%	39.2%	40.5%	54.4%	53.2%
The effects of tiredness on your diabetes	0.0%	0.0%	27.5%	37.1%	67.1%	57.6%

Table 3 outlines the amount of information respondents were given relating to the management of their diabetes.

In terms of a healthy lifestyle and calorie balance, 71% of T1D and 58.1% of T2I found eating the right foods to help them manage their diabetes was easy, however, 29% of T1D and 41.9% of T2I found it difficult. More than 81% of T1D and T2I had been given dietary advice to help control their diabetes with 30.3% of T1D and 30.1% of T2I describing their daily calories consumed as between 1500 – 2000. 36.8% of T1D and 28.4% of T2I did not know their daily calorific consumption. 79.8% of T1D and only 32.2% of T2I respondents have been given information to help them to count carbohydrates. 68% of T1D compared with only 19.3% of T2I counted carbohydrates regularly in order to help them to control their diabetes. In addition, more than half of T1D (50.8%) and only minority (7.5%) of T2I used DAFNE to calculate or count carbohydrates.

When questioned about exercise habits, 44.2% with T1D and 37.1% of those with T2I did between 1 and 3 hours of exercise per week, 32.1% of T1D and 24.4% of T2I participated in more than 3 hours of exercise. However, 11.1% of T1D and 17.8% of T2I did not do any exercise. Only 30.1% of T1D and 17.6% of T2I found BG results helpful in deciding how much physical activity they should do.

With regards to respondents general health, 65.6% of T1D and 58.2% of T2I described their health since discovering they had diabetes as good, but 16.5% of T1D and 31.1% of T2I said their health remained poor since diagnosis of their diabetes. More than half of the respondents described diabetes as affecting their day-to-day activities and only 5.6% of T1D and 8.2% of T2I found it did not affect their activities at all.

3.4.3 Hypoglycaemia

The vast majority of respondents had experienced hypoglycaemia at some time since diagnosis (98.9% T1D and 86.1% T2I), however, the majority of these respondents did not experience black out, convulsions/fit and coma when this occurred. Nevertheless, they experienced the following symptoms: paleness (45% of T1D and 22.4% of T2I),

trembling (64.7% of T1D and 56.1% of T2I) , sweating (76.9% of T1D and 62% of T2I), feeling of weakness (76.3% of T1D and 65.4% of T2I), rapid heartbeat (37.6% of T1D and 22.4% of T2I), hunger (49.2% of T1D and 25.9% of T2I), agitation/irritability (69.5% of T1D and 34.6% of T2I), poor concentration (68.9% of T1D and 46.3% of T2I), blurred vision (43% of T1D and 23.4% of T2I) and loss of coherence (45.2% of T1D and 21.5% of T2I). In general, the survey found that people with T1D diabetes have experienced these symptoms more than T2I.

About 67% of T1D and T2I felt hypoglycaemic symptoms when their BG level was between 3 and 4 mmol/L. However, 6.3% of T1D and 19.9% of T2I felt similar symptoms between 4 and 5 mmol/L while 26.4% of T1D and 13.7% of T2I only felt symptoms below 3 mmol/L. 21.6% of T1D and 11% of T2I stated that hypoglycaemia affected their day-to-day activities quite a lot or great deal. However, 77.5% of T1D and 89% of T2I described little or no effect. Most of the respondents in this survey (93.2% of T1D and 76.1% of T2I) responded to a low BG by taking a sugary food or drink immediately.

About 14.3% of T1D and 8.4% of T2I had decided whether or not to drive, either on occasion or permanently due to problems with low BG. 29.6% of T1D and 20.1% of T2I had had “severe” hypoglycaemic episodes during the past 12 months with 52.4% of T1D and 61.8% of T2I having severe symptoms once or twice. 25.2% of T1D and 17.6% of T2I had it three to five times and 22.4% of T1D and 20.6% of T2I had it six times or more. During a12 month period, 16.3% of T1D and 6.5% of T2I had passed out or had a seizure because of low blood sugar and required help from others. Most of them (73.3% of T1D and 81.8% of T2I) had this once or two times, 12% of T1D and 9.1% of T2I had it three to five times and 14.7% of T1D and 9.1% of T2I had it six times or more. When respondents were asked when their last “severe” low blood sugar episode happened, 55.3% of T1D and 43.2% of T2I reported that it happened longer than 6 months ago and 24.8% of T1D and 33.3% of T2I said that they had it within the last month. 4.5% of T1D and 4.6% of T2I reported they had to go to hospital because of their hypoglycaemic episode.

3.4.4 Hyperglycaemia

When respondents were asked if their BG had ever been above 20mmol/L, 84.2% of T1D and 57.5% of T2I replied positively. About 63.2% of T1D and 46.7% of T2I said they could sense when their BG was above 13mmol/L without testing. Interestingly, however, 31% of T1D and 33.8% of T2I had found their BG 13mmol/L or above once or twice a week. 59.2% of T1D and 33.1% of T2I had more than twice a week. Only a third, (33.1%) of T2I and 9.8% of T1D had never reported a BG as high as 13mmol/L or above, but despite the tendency to hyperglycaemia, 93.2% of T1D and 97.1% of T2I had never been in a coma because of high BG. When respondents were asked what triggered their high blood sugar (13mmol/L or above), 36.5% of T1D and 16.6% of T2I said it was due to a missed insulin injection. 27.1% of T1D and 25.9% of T2I mentioned the trigger was an illness or due to physiological stress such as infection.

3.4.5 Other medical conditions and complications

28.3% of those with T1D and 26.7% of T2I were hospitalised several times. Table 4 shows a summary of responses from both T1D and T2I respondents relating to other medical conditions diagnosed or symptoms tested for. 57.6% of T2I and 32.7%T1D had been told that they had high blood pressure (BP) and 34.6% of T2I and 17.3% of T1D monitored their BP at home. When asked about BP medication, 60% of T2I and a quarter of T1D said that they took it. When respondents were questioned about other complications, 10.2% and 18.5% of T2I had had a heart attack or chest pain/pressure (angina), respectively, only 2% and 4.6% of T1D had these complications. Stroke was suspected or experienced by 12.2% of T2I and 3.4% of T1D.

Table 4: Medical conditions or symptoms experienced by respondents.

	T1D	T2I
Have you ever seen a specialist eye doctor (ophthalmologist)?	64.5%	61%
Has your eyesight suffered as a consequence of your diabetes?	36.3%	37.6%
Have you been diagnosed with retinopathy (decrease in visual acuity)?	20.7%	22.0%
Have you been diagnosed with diabetic macular oedema (blurred vision)?	3.2%	4.9%
Have you ever been told that you have protein in your urine?	30.3%	36.6%
Do you have your blood creatinine checked?	48.8%	45.9%
Do you have diabetic kidney disease?	3.8%	4.9%
Do you require dialysis?	1.0%	1.0%
Have you had a kidney transplant?	1.0%	0%
Is your usual blood pressure normal?	74.3%	50.2%
Have you ever been told you have high blood pressure	32.7%	57.6%
Do you monitor your own blood pressure (BP) at home?	17.3%	34.6%
Do you take medication for high blood pressure?	24.1%	60.0%
Are you on lipid lowering medication (for high cholesterol or triglycerides)?	32.1%	58.5%
Have you ever had a heart attack?	2.0%	10.2%
Do you ever have chest pain or pressure (angina)?	4.6%	18.5%
Have you ever had a cardiac catheterisation?	2.6%	6.8%
Have you ever had heart bypass surgery (coronary artery bypass)?	1.2%	7.3%
Have you ever had a balloon angioplasty or a coronary stent placed?	1.6%	5.9%
Have you ever had, or suspected that you had a stroke?	3.4%	12.2%
Other symptoms experienced		
Numbness or tingling of extremities	31.7%	55.6%
Burning or pain in feet	14.9%	35.1%
Decreased sensation to a body part	10.8%	27.3%
Foot deformity	1.4%	7.8%
Loss of sensation to a body part or area	7.0%	20.0%
Diagnosed with diabetic neuropathy	8.0%	22.9%
Foot ulcers	2.4%	7.3%

3.5 Discussion

In the UK the prevalence of T2D in comparison to T1D is approximately 9 to 1 respectively (Melanson, Sharp et al. 2002). The causes of T2D are often attributed to patients being overweight or obese and the first line of treatment are usually oral medications (Sulfonylureas® and Metformin®) and lifestyle changes such as more frequent exercise and improvements in dietary control. Once these changes have been implemented and the patient still maintains abnormal BG and HbA1c readings suggesting that they no longer maintain normoglycaemia as a result of factors such loss of insulin receptor sensitivity and beta cell deterioration, insulin is introduced. Symptoms of T2D diabetes usually present in people who are over 25 years of age although the highest prevalence are in patients over 60 years of age (Meyer, Gassler et al. 2007). This study provides a comparison by means of a questionnaire between insulin users with T1D and T2D diabetes to assess how they have essentially managed and treated their diabetes.

Most of the responses gathered in this survey were from patients with T1D diabetes which usually presents in people under the age of 40 with the majority of cases occur in juveniles. As these patients are generally younger than most T2I patients and they have to inject insulin daily in order to survive, they may respond more enthusiastically to questionnaires. There was a greater proportion of T1D than T2I respondents having received a higher education and this may underpin a keenness for learning more about their condition and engaging in research initiatives. It may be important when recruiting for surveys to think about the font size and other aspects of visual clarity, so that those with poor or ageing eyesight are not excluded.

In 2007 the largest survey ever conducted by the Healthcare Commission's National Patient Experience Survey Programme (Meyer, Gassler et al. 2007), which included 152 Primary Care Trusts (PCT) across England collected responses from 68501 questionnaires (a response rate of 55%), where 87% of the respondents were T2D and 13% T1D. Of those respondents 96% T1D and 17% T2D (25% of the total 68501

respondents) were insulin users in the same way as those participating in this survey. They found that 73% of all respondents received the right amount of verbal information, compared with 57% of all respondents when it came to written information at the time of diagnosis. They also found that those patients diagnosed with diabetes in the last five years were more likely to receive the right amount of written and verbal information. Although the Healthcare Commission's findings (Meyer, Gassler et al. 2007) were from all respondents in the survey (so include T2T as well as others) their results suggest that there is a lack of information provided across the whole spectrum of people diagnosed with diabetes in terms of information to allow self-management effectively. The results in this work show that the provision for verbal information at the time of diagnosis was similar or better than for written information to the Healthcare Commission's (Meyer, Gassler et al. 2007), 70% of T1D and 61% T2I received at least the right amount of verbal information and 65.9% T1D and 61% received at least the right amount of written information at diagnosis. These results show that well targeted information in both forms seems a prerequisite for managing patients on insulin.

Respondents were asked where they went for their diabetes check-up, 22.6% of T1D and 52.1% T2I were seen in their doctor's surgery, 70.2% of T1D and 41.7% were seen at a hospital clinic. The Healthcare Commission survey (Meyer, Gassler et al. 2007) found that 85% of T2I diabetes patients had their check-up at their doctors surgery, with only 13% attending a hospital clinic, whereas those with T1D diabetes had a check-up in a hospital clinic (63%) and 32% at their GP's surgery. These findings would incorporate T2T diabetes patients who were controlling their diabetes by tablet so were not so perhaps did not need more specialised diabetes clinics. However, the T2I patients in this survey were insulin users similar to those that are T1D yet 52.1% (T2I) versus 22.6% T1D were still seen by their GP suggesting that despite injecting insulin they were not checked in hospital clinics.

The results from this survey correlate well with those found in the Healthcare Commission's report (Meyer, Gassler et al. 2007) which showed that in the 12 months prior to answering their questionnaire 98% of the respondents had had their blood pressure measured, 91% HbA1c and weight, 89% cholesterol, 87% a urine test for protein, 83% their bare feet examined and finally only 23% reported seeing a dietician within the last 12 months. In the UK these tests form the basis of the National Institute for Health and Clinical Excellence (NICE) guidelines for the nine care processes which diabetes patients should undergo, yet the National Diabetes Audit results for 2009/10 (Morais, Campbell et al. 2011) showed that throughout the UK, two-thirds of adults with T1D diabetes, and half of people with T2I diabetes fail to get these annual tests and investigations that are recommended in the national standards (Morais, Campbell et al. 2011).

This survey found that for people with T2I diabetes the most difficult aspect of their diabetes management was found to be exercise. This was reflected in responses where 44.2% T1D and 37.1% T2I participated between one and three hours of exercise per week and 11.1% of T1D and 17.8% T2I respondents did not perform any exercise. T2I diabetes is often associated with lifestyle and in most cases can be related to lack of exercise and obesity. It was noticeable that the number of responses didn't participate in any exercise was greater from people with T2I diabetes. This may have been influenced by the age of the T2I respondents who present diabetes symptoms in later life and they may also have other medical conditions which prevent participation in exercise.

Diet was also identified by respondents as a source of difficulty for their diabetes with 29% of T1D finding difficult to find the right foods to manage their diabetes compared with 41.9% T2I. This is despite 51% T1D using an educational DAFNE programme and over 81% of all respondents receiving some dietary advice since diagnosis from their medical advisors. (Monteiro, Mondini et al. 1995) found that patients with T1D using MDI therapy often underestimated their carbohydrate intake by 20% and this was usually a result of anticipated exercise or fear of hypoglycaemia as a result of their

injected insulin. Paradoxically, T1D patients who don't have access to well-structured education may be systematically over-insulinised. Both these findings add to the growing body of evidence for the benefits of the DAFNE programme (Miyashita, Burns et al. 2008, Montain, Hopper et al. 1991). A judicious and targeted insulin therapy following DAFNE training in T1D has been found to allow patients to achieve better glycaemic targets with less insulin. Despite this only 7.2% of T2I respondents were using DAFNE and 50.8% of these T2I respondents counted their carbohydrates, suggesting that structured education programmes such as DAFNE for T2I insulin users were much less frequently used.

The frequency of BG testing was higher in T1D insulin users with 65% T1D testing 4 or more times which correlates with 86.4% of T1D injecting insulin 4 or more times suggesting that respondents may have been injecting prior to calorie intake with a short-acting insulin such as Novorapid® or Humalog®. Table 2 showed that most T1D and T2I respondents were using Lantus®/Levemir® and in order to see if these respondents were on a basal bolus insulin regimen a cross tabulation of the data was performed with the short-acting insulin Novorapid®, Humalog® and Actrapid®. The data in Table 2 revealed all the insulin respondents were using so more than one option may have been ticked and for T1D respondents there were responses received which included more than two insulins but these were less than 1% of total T1D responses and have therefore not been separated out in Table 2.

The data in Table 2 suggests that most T1D respondents (75%) were using the long acting insulin (Lantus® or Levemir®) in combination with short-acting insulin such as Novorapid®, Humalog® and Actrapid® and as such were using a basal bolus system. This was not the case for T2I respondents (34%) were using the same basal bolus system and 35% using Novomix® and other insulins not listed in the survey. In order to use a basal bolus insulin regimen the patient would have to test their BG prior to calorie intake and bolus accordingly which provides a more intensive BG control and would prevent hypo- and hyperglycaemia. (Millar, Stephens 1993) found that T2I

patients using a basal bolus system have found that the number of injections per day and more frequent hypoglycaemic episodes difficult and report that after 24 weeks T2I patients switching from basal-bolus insulin regimens to biphasic insulin aspart 30 (Novomix®), glycaemic control and health related quality of life were significantly improved, and hypoglycaemia was significantly reduced. This may account for the higher number of T2I respondents using Novomix® in this survey.

Differences in the testing of BG were found for T2I insulin users in this work compared to those of the Healthcare Commission (Meyer, Gassler et al. 2007) where 31% with T1D diabetes tested 4 or more with only 3% of T2I. Similarly, only 4% with T1D never monitored their BG compared with 29% T2I. This could be attributed to the greater number of participants taking part in the Healthcare Commission survey which was able to capture data over a broader range of patients with diabetes who may have been treating there diabetes with oral medications.

Both T1D and T2I patients had experienced hypoglycaemia indicating that their current treatment by insulin injection allowed them drift lower than normoglycaemia. Although most of these respondents did not exhibit serious symptoms such as black out or coma they did experience more typical conditions such as trembling and weakness. Agitation and poor concentration were felt by more T1D respondents. Most T1D and T2I respondents felt these symptoms when their BG was between 3-4mmol/L. Defining BG values for hypoglycaemia remains difficult with surgeons and forensic pathologists defining spontaneous pathological hypoglycaemia requiring investigation and treatment at BG < 2.2 mmol/L, to avoid defining healthy people as hypoglycaemic (Nielsen, Hafdahl et al. 2006). At the other extreme, ADA defined BG concentrations of < 3.9 mmol/L as hypoglycaemia, based on the reduction in endogenous insulin and increase in pancreatic glucagon which can be demonstrated at this level. However, defining hypoglycaemia < 3.9 mmol/L could lead to overestimation of clinically significant hypoglycaemia associated with any specific diabetes therapy.

The European Medicines Agency (EMEA), (Nicklas, Rogus et al. 1997) recommends a value of < 3.0 mmol/L when assessing hypoglycaemic risk of different treatment regimens. Impaired cognitive function is seen at plasma BG concentrations of < 3.0 mmol/L and avoidance of plasma BG concentrations of < 3.0 mmol/L has been able to restore hypoglycaemia awareness to people with T1D diabetes and defective counter regulation. As insulin-deficient patients with diabetes lose their ability to modulate either insulin or glucagon in response to hypoglycaemia and depend instead on autonomic activation, subjective awareness and adrenaline to defend against severe hypoglycaemia. Risk factors for individual episodes of hypoglycaemia in patients with T2I diabetes include behavioural, physiological and therapeutic factors, the most common behavioural factor being identified as missed or irregular meals. Other lifestyle factors include alcohol, exercise and incorrect use of glucose-lowering medication (dose/timing).

Hyperglycaemia causes vascular risks such as hypertension and cerobropetal arteries increasing the chance of strokes taking place is twice as much in patients with diabetes (Ormsbee, Choi et al. 2009). The present survey shows that 63.2% of T1D respondents thought that they could sense when their BG was above 13mmol/L yet that dyslipidaemia as well as atherosclerotic changes in the heart and over 90% of T1D respondents had these above normal BG reading once or more a week. Similarly for T2I respondents 46.7% could sense an above normal BG with 68% have these high BG episodes more than once a week. 33% of T1D respondents had suffered from (DKA) and most of these had been hospitalised as a result indicating that the treatment and management of respondents was clearly not adequate to maintain BG control, similar trends were observed for T2I respondents. It is likely that the DKA episodes reported by T1D respondents will have included those that were reported at the time of diagnosis.

The Diabetes Control and Complications Trial (DCCT) showed that 1422 patients with T1D diabetes who were treated with intensive control of BG concentrations for 6.5

years had a 57% reduced risk of cardiovascular events over a means follow up period of 17 years compared with individuals on conventional treatment (Oguri, Adachi et al. 2009). These trials suggest that the balance of recurrent hypoglycaemia against the advantages of a low HbA1c value should consider factors such as the patient's age, duration of diabetes and comorbidities. The results from this survey which focus on the common needs of insulin users show that careful follow-up after diagnosis, frequent testing and education about calorie turnover from intake and exercise are required for both T1D patients but more so for T2I patients whose needs become similar to those of T1D patients once they begin to inject insulin.

Although these T2I insulin patients are often older than T1D insulin users who are often children at time of diagnosis the same resources should be made available in terms of management and treatment of their diabetes. The HbA1c value forms an important part of a diabetes patient's management and subsequent treatment and as insulin is a potent drug the possibility of hypoglycaemia is always present. Treatments should therefore include judicious and frequent testing with a basal bolus insulin regimen. For T2I patients who struggle with BG management and frequent hyperglycaemia the introduction of insulin injections should also be much earlier before cumulative effects of complications make the patient too ill to really benefit.

3.6 Conclusion

Aside from the serious personal consequences, the cost of diabetes and its complications has been variously quoted as 5-10% of the UK NHS budget (Melanson, Sharp et al. 2002), depending on the costing criteria and a recent report quotes this as equating to about £1m/h. The results from this study show that current treatment and management of diabetes care still poses difficulty for most patients and that for T1D and T2I diabetes patients further improvement is required.

Chapter 4: Experiences and attitudes of people with T1D and T2D to Exercise

4.1 Introduction

Diabetes is a major public health concern associated with increased morbidity, mortality and cost for health services. The growing incidence of diabetes has been estimated to increase by 42% by 2030 (Duarte, de Almeida et al. 2012). Balancing calorie intake with insulin demands is difficult and patients often suffer excursions from normal BG levels, for example hypoglycaemic events when calorie output has not been properly accounted for. High BG levels result from diabetic defects in the system such as insulin secretion/action, or both, and lead to serious complications. Exercise along with diet therapy, and medications (oral hyperglycaemic and insulin, refer to Section 1.7) constitute the basic treatment for diabetes mellitus and are the cornerstones for glycaemic control (Lynch, Liebman et al. 2014, Kamiya, Ohsawa et al. 1995).

Exercise, however, is recommended as an effective lifestyle management technique for the prevention of T2D and for the management of both T1D and T2D. It has physiological benefits including improved physical work capacity, body composition, blood pressure (Sukala, Page et al. 2012) blood lipid profile (Kwon, Min et al. 2010) insulin sensitivity and BG management. It is associated with reducing risk of long term complications and mortality in individuals with diabetes (Hordern, Dunstan et al. 2012).

This chapter aims to assess the views and attitudes of people with diabetes to diet and exercise. Also to compare T1D, T2T as well as T2I regarding the type and intensity of exercise they normally perform. It also aims to consider factors such as insulin dose and BG management on normal and exercise days, to appreciate barriers and coping strategies for exercising safely when they have diabetes as well as to assess T1D, T2T and T2I understanding regarding self-care recommendations related to exercise.

Some of the key findings from this survey were combined with exercise trials conducted and presented in this thesis which will be discussed in Chapter 5 and 6. This may lead to recommendations to improve the lifestyle of people with diabetes in the future. The information could also help research toward a suitable exercise regime for people with diabetes.

4.2 Survey design, distribution and response collection

From the experience gained with questionnaire design and analysis from the first survey in Chapter 3, a second survey was produced about exercise and diet for people with diabetes (T1D, T2T and T2I). This survey had 78 open and closed ended questions and discussed T1D and T2D experiences with various aspects of their diabetes and their attitudes with diet and exercise. It comprised four sections:

1. Background information: this section helped to collect respondent basic details such as, gender, age, height, weight, level of education and ethnic group.

2. Diabetes diagnosis and management: this part was about diagnosis, type of diabetes, family history, insulin, HbA1c, check-ups and complications.

3. Hypoglycaemia and hyperglycaemia: this section covered hypoglycaemia episodes and symptoms as well as hyperglycaemia episodes.

4. Exercise and diet. This was the main section in this survey and outlined T1D, T2T and T2I opinions with various aspects of their perceptions with exercise and diet. It covered items such as diet approach, daily calories, dietary advice and programmes such as DAFNE. Furthermore, it explored the attitudes of T1D, T2T and T2I towards exercise and many aspects of diabetes management and specific care (before, during or after the exercise) such as BG values, testing BG, taking carbohydrate, insulin doses. The aim of this section was to assess T1D, T2T and T2I patients understanding regarding self-management recommendations related to exercise from their GP and/or their healthcare professionals. Questions sought information about the type of exercise and intensity, frequency and duration of performed exercise, and about symptoms

possibly related to hypoglycaemia during or after exercise. For those respondents reporting they did not exercise regularly, the barriers preventing them from taking part in more exercise were asked as well as the factors influence their decision to participate in exercise (Appendix 1).

The questionnaires were produced in English and distributed to the participants through various channels such as local newspapers and websites as well as social networking sites as described in section 2.2.4.

4.3 Statistical analyses (analysis of responses)

All data were analysed using (SPSS) and Microsoft Excel 2010®. Refer to section 2.2.5

4.4 Results and discussion

The following sections describe and discuss the data collected from the survey:

4.4.1 Background information and diagnosis

A total of 240 respondents completed the questionnaire, 62.1% with T1D, and 37.9% with T2D (25.4% T2T and 12.5% T2I). Eighty-one percent of responses were from the UK where the survey was widely distributed and advertised with 82.5% of responses from respondents of white ethnicity. The remaining responses were gathered from the USA and Australia. Approximately 44% of T1D respondents were male compared with 47.5% of T2T and 60% of T2I.

Those with T1D tended to be diagnosed at an earlier age than those with T2D and those classed as having T2D were generally older. All T2I patients were over the age of 40 with 30% between 61 and 80 years and were diagnosed between 51 and 60 years of age. Most of the T2T were aged between 41 and 60 years and 75% of them were diagnosed at age between 31 and 50 years while more than half 55.4% of T1D aged between 11 and 30 years and three quarter of those were diagnosed at age between 1 and 20 years.

When asked about their education level, 75% of T2T and T2I, and 70% T1 were in or have had a higher education or educational training. None of T2I and 6.7% of T2T was

still in full time education compared to 20.9% of T1D. As T1D is often described as juvenile diabetes these results suggest that some of the respondents fall into this category. Figure 16 shows that more than half 51% of T1D had healthy weight with normal BMI range between 18.5 and 24.9 kg/m^2 compared to only 16.4% of T2T and 20% of T2I. The highest percentage of obese respondents with BMI over 30 kg/m^2 was among T2T with 59%. However, this compared with only 12.8% of T1D and 43.3% of T2I. In addition, 28.9% of T1D, 24.6% of T2T and 36.7% of T2I were overweight with BMI between 25-29.9. None of T2T and T2I was underweight with BMI under 18.5 kg/m^2, whereas 7.4% of T1D were underweight. The level of obesity and BMI ranges important risk factors and indicators of overall health and play a role in irregular glucose metabolism (Bombelli, Facchetti et al. 2011) which leads to insulin resistance and T2D (Li, Xiao et al. 2014) .

A cross tabulation of data for respondent age and BMI found that 12.9% of T2T over 40 years of age were of healthy weight compared with 20% of T2T who were overweight and 43% who were classified obese. For T2I who over 40 of age, 20% had a healthy BMI , 36% were overweight and 40% classified as obese. These results show that the majority of T2D who are treated by tablets and insulin injections struggle with their weight in later life. These findings as to be expected as T2D is a lifestyle disease with high energy intake and lack of physical activity. This supports previous researches which confirmed that being overweight and obese have close association with T2D (Wang, Li et al. 2014, Henry, Chilton et al. 2013, Lau, Teoh 2013). This is supported by Charpentier study on French patients with T2D, which revealed that 39% of the patients were obese (BMI > 30 kg/m^2), (Charpentier, Genès et al. 2003).

Three- quarters (75%) of all respondents, reported having been diagnosed by (GP) and hospital clinics, while the rest 25% were diagnosed in A&E (Accident and Emergency), by themselves or by friend and family who picked some sign of the disease and led the patient to a medical professional. Half of T2I, 54.4% of T1D and 36.1% of T2T had a family history of diabetes. Respondents were asked what was their HbA1c when they were diagnosed with diabetes, 60.8% of T1D, 23.3% of T2I and 27.1% of T2T did not

know, whereas, 17.6% of T1D, 33.3% of T2I and 22% of T2T reported that it was over 10% (86 mmol/mol). For T1D respondents this may have been because they were diagnosed in their childhood and recollection of this value was difficult or even reported to their parents.

The most challenging element of the diabetes management for participants was found to be performing exercise (41.6% for T1D, 50% for T2I and 47.7% of T2T). Other difficulties were identified as diet and testing BG. These findings are consistent with a previous study by the author and the research group found that the most difficult aspect of the diabetes management for respondents was found to be exercising (36.6% for T2I and 34% for T1D) (refer to Chapter 3).

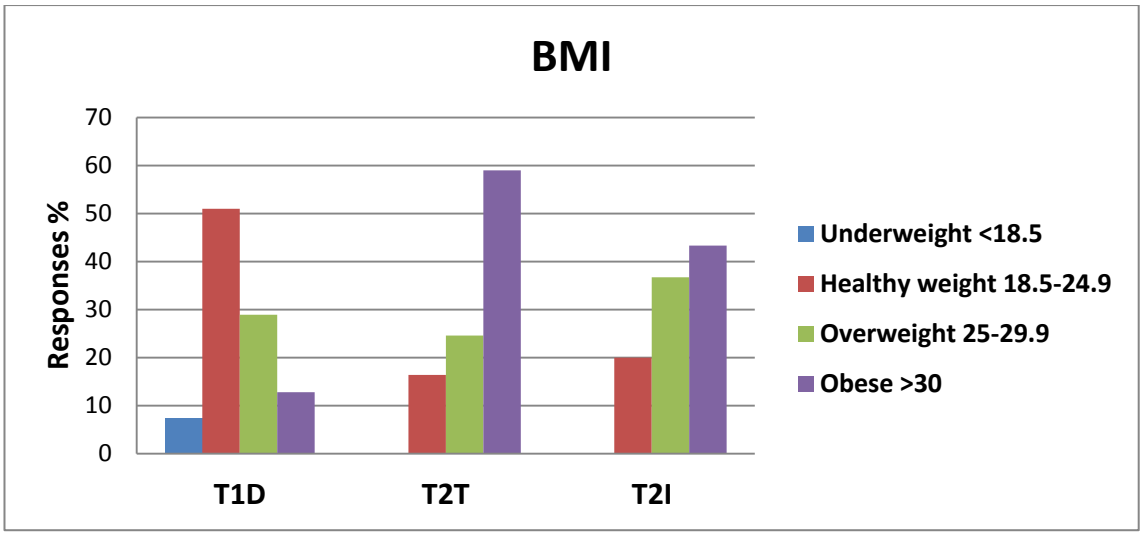

Figure 16: BMI values for T1D, T2I and T2T.

4.4.2 Check-up, management and complications

Respondents were asked how often their HbA1c was measured, 41% of T1D and T2T, and 50% of T2I reported that they had had it measured every three months. More than half (51.4%) of T1D had been HbA1c tested every six months compared to 37.3% of T2T and 39.3% of T2I. This results means that most of the respondents had achieved

(NICE) recommendation for the frequency of measurements for HbA1c which is 2 - 6 monthly depending on the level of control and /or treatment changes. It is very important in order to maintain acceptable BG level to have HbA1c measurements, because low frequency measurements of HbA1c results in poor glycaemic control in T2D (Alioune Camara 2014). Table 5 reflects the most recent medical check-up for respondents, with 61.4% of T1D, and more than half 56% of T2T and T2I having an HbA1c between 5-8%, 21.7% of T1D, 16.6% of T2I and 15.3% of T2T between 8 - 10% and 5% of T1D and T2T had an HbA1c over 10% compared to 13.3% of T2I. When asked what respondents thought their HbA1c should be, the majority of all the respondents 91.1% of T1D, 83.3% of T2T and 67.2% of T2I thought a desirable HbA1c value would be between 5-7%. All respondents thought their HbA1c should not exceed 8%, suggesting that most of them know the acceptable HbA1c value. However less than half of all the groups did not achieve this and had high HbA1c values. Moreover, 15.5% of T2T and 10% of T2I thought that HbA1c value of less than 5% was desirable, indicating that they with the minority who said did not know what it should be are not fully understand this value.

Evidence from across the world for children and adults shows that they find it difficult to achieve optimum HbA1c. A fall in HbA1c from 7.9 to 7.0 lowers microvascular risk by 25% which is critical because poorly controlled diabetes can reduce lifespan and is a major cause of mortality (Monami, Vitale et al. 2013). One study found that low and high mean HbA1c values were associated with increased all-cause mortality and cardiac events. A high HbA1c value is linked with micro and macrovasculaur complications in later life. However, intensive insulin therapy should also be considered especially among the elderly as a desired low HbA1c value can also lead to CVD. Results showed a general association with the lowest hazard ratio found to be at an HbA1c of about 7.5% (Currie, Peters et al. 2010).

Table 5: Recent HbA1c and perceived targets for T1D, T2I and T2T.

HbA1c average	Don't know	< 5%	5-6%	6.1-7%	7.1-8%	8.1-9%	9.1-10%	> 10%
T1D								
Recent HbA1c	10.8%	1.4%	10.1%	23.6%	27.7%	14.9%	6.8%	4.7%
Would like to be	6.8%	2.0%	43.5%	47.6%	**0.0%**	**0.0%**	**0.0%**	**0.0%**
T2I								
Recent HbA1c	13.3%	0.0%	23.3%	20.0%	13.3%	13.3%	3.3%	13.3%
Would like to be	6.7%	10%	60.0%	23.3%	**0.0%**	**0.0%**	**0.0%**	**0.0%**
T2T								
Recent HbA1c	18.6%	5.1%	23.7%	18.6%	13.6%	5.1%	10.2%	5.1%
Would like to be	17.2%	15.5%	51.7%	15.5%	**0.0%**	**0.0%**	**0.0%**	**0.0%**

Table 6 shows the types of insulin used by T1D and T2I respondents. It should be noted that respondents were asked to tick all insulins they used and all respondents that injected Lantus® (47.7% of T1D and 73.3% of T2I) or Levemir®(35.6% of T1D and 26.7% of T2I) also used a short acting insulin such as Novorapid® (57.7% for T1D and 73.3% for T2I), Humalog® (33.6% for T1D and 26.7% for T2I) and Actrapid® (4% for T1D and 0.5% for T2I). These findings show that 100% of the T2I are using Lantus® and Levemir® (73.3% + 26.7%) and must be using a basal bolus system. The best treatment for maintaining acceptable HbA1c values for T1D and T2I diabetes comes from frequent testing and insulin doses known as 'intensive control' (DCCT, EDIC 2014). However, some T2D have been prescribed Glargine® (Lantus®) in combination with oral hypoglycaemic such as Metformin® often quite early on their insulin therapy.

The evidence has been available for more than twenty years but the uptake is far from universal. The methodology is usually a combination of calculated background long acting (basal) and meal associated insulin boost (short-acting bolus) doses and characterised by the variation of dosing to allow a more normal diet than previously. Most of T1D and T2I, 62.2% and 70%, respectively, inject themselves 4 or more insulin injections in a normal day.

When they were asked how long they have been injecting this number of injections each day, 28% of the respondents reported that this regimen had been used ever since they started taking insulin, and 40.3% of T1D and 34.5% of T2I started using insulin longer than 5 years ago. 59% of T1D and 83.3% of T2I described the total amount of insulin they used every day and for the previous 24 hours as more than 40 units. Of these, 2.9% of T1D and 33.3% of T2I use over 100 units of insulin every day. A crosstabulation of the data shows that 46% of T2I injected more than 80 units per day and were on the overweight or obese in BMI suggesting that these respondents must suffering a loss of the insulin sensitivity.

The majority of T1D (62%), and 12.5% of T2I tested their blood glucose 4 or more times a day. Most of T2I (68.8%) tested it only two to four times a day compared to 28.4% of T1D who did likewise, 9.8% of T1D and 18.8% of T2I tested it once daily. As would expected, more than half 55.9% of T2T tested their BG once a day compared to 38.2% tested it two to four times and only 5.9% more than 4 times. T2I users who test their BG once a day must be estimating their calorie intake on several occasions on a daily basis which would suggest that their BG management is not as good as it should be. This would have an impact on their HbA1c values and suggests that they may feel higher BG values are more acceptable.

Table 6: Types of insulin used by T1D and T2I respondents.

Type of insulin	T1D	T2I
Actrapid®	4%	0%
Humalog®(Lispro)	33.6%	26.7%
Humulin I®	1.3%	0%
Humulin M3®	2%	0%
Humulin S®	1.3%	0%
Insulatard®	1.3%	3.3%
Novorapid® or Novolog®(Aspart)	57.7%	73.3%
Levemir®	35.6%	26.7%
Lantus®	47.7%	73.3%

The majority of all respondents (>89%) had had their blood pressure and weight checked by a doctor or nurse in the previous 12 months as part of their treatment. Also in the past 12 months over 70% of T1D, T2I and T2T respondents had had their cholesterol, eyes and bare feet examined (Table 7). This is important because these tests provide an early indication to possible complications which may be arising.

Table 7: Check-ups in the last 12 months.

In the last 12 months	T1D	T2I	T2T
Your blood pressure taken by a doctor/nurse	94.5%	100%	98.3%
A cholesterol test by a doctor/nurse	75.9%	96.4%	91.7%
An eye test where a photograph of the back of your eyes were taken	83.4%	92.9%	73.3%
Your bare feet were examined	75.5%	90%	70.1%
You have had your weight checked by a doctor/nurse	93.1%	89.3%	91.7%

4.4.3 Medical condition and complications

Table 8 shows a summary of responses from all respondents relating to other diagnosed medical conditions and complications. More than 60% of all respondents had a normal BP, however, 20.3% of T1D, 39.3% of T2I and 31.7% of T2T had been told that they had high BP and took medication to control it. More than third 35.7% of T2I, 41.7% of T2T and only 12.8% of T1D had high lipid profile (TC or TG) and were on lipid lowering medication. When respondents were questioned about other complications, 35.8% of T1D, 30% of T2I and 21.7% of T2T had eyesight problems. None of T2I or T2T and only 1.4% of T1D had had a heart attack. Some of the respondents (14.3% of T2I, 6.7% of T2T and 2% of T1D) had chest pain/pressure (angina). Stroke was suspected or experienced by 3.6% of T2I, 6.8% of T2T and 3.4% of T1D. A nationwide French survey by Charpentier et.al 2003, showed similar results from 4390 respondents with T2D, which showed that 15% of the patients had evidence of associated symptomatic coronary heart disease, 8% had a history of myocardial infarction, 8% had a history of angina, 4% had been hospitalised previously for cardiac insufficiency and 3% had a history of stroke (Charpentier, Genès et al. 2003).

Table 8: Other medical conditions and complications.

	T1D	T2I	T2T
Has your eyesight suffered as a consequence of your diabetes?	35.8%	30%	21.7%
Do you have diabetic kidney disease?	1.4%	13.3%	3.3%
Do you require dialysis?	2%	0%	0%
Have you had a kidney transplant?	2.7%	6.7%	0%
Is your usual blood pressure normal?	79.7%	60.7%	68.3%
Do you take any medication to control blood pressure?	20.3%	39.3%	31.7%
Are you on lipid lowering medication (for high cholesterol or triglycerides)?	12.8%	35.7%	41.7%
Have you ever had a heart attack?	1.4%	0%	0%
Do you ever have chest pain or pressure (angina)?	2%	14.3%	6.7%
Have you ever had heart bypass surgery (coronary artery bypass)?	0%	0%	0%
Have you ever had a balloon angioplasty or a coronary stent placed?	0%	14.3%	1.7%
Have you ever had, or suspected that you had a stroke?	3.4%	3.6%	6.8%

4.4.4 Hypoglycaemia and Hyperglycaemia

Not surprisingly the vast majority of T1D and T2I respondents had experienced hypoglycaemia at some time since diagnosis (95.1% T1D and 86.7% T2I) but this had affected less than half (42.4%) of T2T. Table 9 presents the symptoms the respondents had experienced with hypoglycaemia and most likely to be suffered by T1D and T2I. In contrast, as would be expected T2T respondents were least likely to have these symptoms compared with T1D and T2I, because they were using Sulphonylureas as the first line of treatment which can reduce BG level in the blood stream by higher pancreatic insulin output (Refer to Section 1.7.2). Most of these findings about hypoglycaemia from this study in agreement with previous study (Chapter 3) where 98.9% of T1D and 86.1% of T2I reported that they had encountered hypoglycaemia at several times since diagnosis.

About 62% of T1D, 54.1% of T2I 48% of T2 felt hypoglycaemic symptoms when their BG level was between 3 and 3.9 mmol/L. However, 18.7% of T1D and 16% of T2T felt similar symptoms between 4 and 5 mmol/L while 15.8% of T1D, 29.2% of T2I and 8% of T2T only felt symptoms below 3 mmol/L. A minority of T1D and T2T (15.5% and 4.2% respectively) and none of T2I stated that hypoglycaemia affected their day-to-day activities quite a lot or a great deal. Low BG is important as it has severe consequences such as seizure, coma, accidents and death. Clinically it is now appreciated that the greatest benefits on the complications of diabetes may be seen following minimisation of plasma BG and insulin excursion including low bold BG concentration providing better overall glycaemic control. However, 77.5% of T1D and 89% of T2I described little or no effect. Most of the respondents from all groups in this survey (more than 95%) responded to a low BG by taking a sugary food or drink immediately.

When the respondents were asked about driving, none of T2I or T2T and only 5% of T1D said that the problems of hypoglycaemia stopped them permanently from being able to drive. When respondents were asked during the past 12 months did they have any “severe” hypoglycaemia episodes and how often, only 12.6% of T1D had it. The majority of them (81%) said that they had it 1-2 times, 14.3% 3-5times and 4.8% 6 or

more. Very few % of T1D and 3.8% of T2T reported they had to go to hospital because of their hypoglycaemic episode in the past 12 months.

Table 9: Hypoglycaemia symptoms.

Hypoglycaemia Symptoms	T1D	T2I	T2T
Paleness	50.3%	10%	18%
Trembling	74.5%	56.7%	24.6%
Sweating	73.8%	53.3%	19.7%
A feeling of weakness/fatigue	81.9%	50%	32.8%
Rapid heartbeat	48.3	33.3%	9.8%
Hunger	61.1%	16.7%	14.8%
Agitation/irritability	51.7%	26.7%	21.3%
Poor concentration	68.5%	40%	23%
Blurred vision	35.6%	23.3%	13.1%
Loss of coherence	41.6%	13.3%	9.8%
Black out	10.7%	10%	8.2%
Convulsion/fit	4%	0%	4.9%
Coma	1.3%	3.3%	0%

When respondents were asked if their BG had ever been above 20mmol/L, 84.2% of T1D, 57.5% of T2I and a third of T2T replied with yes. When they asked how many times per week their fasting BG was 10mmol/L (180 mg/dl) or above, 27.9% of T1D, 25.9% of T2I and 20% of T2T had found their BG 10mmol/L or above once or twice a week. Forty one % of T1D and T2I, and only 12.7% had more than twice a week. About a third, (30.7%) of T1D, 33.3% of T2I and 67.3%T2T had never reported a BG as high as 10mmol/L or above. More than 91% of all the groups had never been in a coma because of high BG. Some of these high BG readings may have been the results of the dawn phenomenon. This would be especially applicable to T1D who are often young as during their growth years the productions of hormones (primarily growth hormones and cortisol) stimulate the liver to release extra glucose into the blood stream.

Respondents in this survey were asked if they have ever been in (DKA), the condition where ketones in the blood due to catabolism. The vast majority of T2I and T2T, 96.4% and 86.4% respectively, and more than half (59%) of T1D said that they did not experienced DKA. However, minority of 3.6% of T2I, 13.6% of T2T and 41% of T1D had it before.

4.4.5 Attitude to exercise and diet

4.4.5.1 Diet and healthy lifestyle

With regards to diet and healthy lifestyle, respondents were asked about drinking and smoking habits, more than 93.1% of all the groups did not smoke. However, 57.9% of T1D, 43.1% of T2T and 32.1% off T2I did drink alcohol. Respondents were asked how they would describe their current approach to diet, slightly more than half (55.3%) of all the groups mentioned that their eating habits were healthy. About third (29.6%) of T1D, quarter of T2T and 46.4% of T2I said that they sometimes try to eat healthy food. However, only few 5% of T1D and T2T had poor eating habits. Three quarter 74.1% of T1D, 37.9% of T2T and 42.9% of T2I reported that they counted carbohydrates regularly in order to help them to control their diabetes. In total, more than 85% of all the survey respondents had been given dietary advice to help control their diabetes with 30.9% describing their daily calories consumed in atypical day as between 1500 – 2000. About quarter (24.8%) of T1D, 22.2% T2I, and 17.2% of T2T did not know what their daily calories consumption was. However, in a typical day 22% of respondents consumed >2000 – 2500 calorie which is recommended dietary allowance (RDA). These findings support what have been found from first survey (Chapter.3), 30.3% of T1D and 30.1% of T2I describing their daily calories consumed as between 1500 – 2000 and 36.8% of T1D and 28.4% of T2I did not know their everyday calories .

4.4.5.2 Attitude and barriers to exercise

Over 67% of T1D and T2D respondents valued exercise and considered it important to them, with just a small minority (5% of T1D, 15% of T2T and 8% of T2I) stating that participation in sport and exercise not important. Most of the participants in this study (80.5% of T1D, 74% of T2T and T2I) undertook exercise regularly. A cross tabulation of the data found that 80% of T2D (T2T + T2I) who responded yes to regular exercise and who had a BMI which was overweight or obese (Refer to Section 1.9.1). For those who responded no to regular exercise 87.5% of T2D (T2T + T2I) were overweight or obese. These results suggest that T2D (T2T + T2I) struggle with their weight despite doing exercise. One possible reason for this may be that only 9.8% of T1D, 9.6% of T2T and 5.9% of T2I were participating in at least 150 min of exercise per week which achieve the exercise recommendations. American college of Sport and Medicine (ACSM) and American Diabetes Association (ADA) recommended people with T2D diabetes to exercise at least 150 min per week of moderate to high intensity of AE spread out within at least 3 days per week, with no more than two consecutive days between bouts of AE. In addition to AE, ACSM and ADA recommended T2D to undertake RE at moderate to high intensity (3 sets × 10 repetitions) two or three days per week (American College of Sport and Medicine, American Diabetes Association. 2010)

T2T and T2I were observed to exercise less compared with T1D group (73% and 80 .5% respectively). The results can be partly explained by these cohorts characteristics. T2T and T2I patients are usually older, have higher BMI, and lower education and often exercise for a short duration compared with the T1D group as shown previously in Section 4.4.1. Individuals with T1D are usually younger (Section 4.4.1) and, therefore, more likely to be active at work and during leisure time. About two thirds of T1D and T2T, 60% and 62%, respectively and 84% of T2I confirmed that exercise did have a positive impact on their diabetes and their life after becoming diabetic. The positive effects of exercise, included better general health (82% of T1D, 76.5% of T2I and 70.7% of T2T), low HbA1c (44.3% of T1D, 64.7% of T2I and 50% of T2T) and fewer hypoglycaemia events (44% of T1D, 50% of T2I and 16% of T2T). In contrast, only

12.1% of T1D and no T2D said that exercise had any negative impact. Less than a quarter 19.5% of T1D and 26% of T2T and T2I had some barriers preventing them from doing exercise in a regular basis. These barriers are summarised in Table 10 with lack of time being the most cited reason by 66.7% of T2T, and 50% of T1D and T2I. About half 48.6% of T1D, 27.8% of T2I and 56.5% of T2T said that lack of motivation was one of the main factors that discouraged them from doing exercise. A quarter of T1D and T2T, 24.3% and 25% respectively, and 20% of T2I did not do exercise due to health reasons, although these were not explicitly described.

Table 10: Barriers preventing from exercise.

Barriers preventing from exercise	**T1D**	**T2I**	**T2T**
Health reasons	24.3%	20%	25%
Lack of motivation	48.6%	27.8%	56.5%
Embarrassment about how you look. EG overweight or lack of fitness	17.3%	33.3%	20.5%
You doubt it will lead to weight control	8.7%	0%	6.8%
Lack of time	50%	50%	66.7%
It does not interest me	21.9%	17.6%	27.7%
It is too expensive	22.8%	27.8%	31.1%
Lack of transport	9.7%	6.3%	15.9%
Fear of injury	6.9%	5.9%	15.9%
Do not know	10.5%	12.5%	3.6%

When respondents were asked about the factors that influenced their decision to participate in exercise and sport, more than 69% mentioned the following: to keep well with diabetes, better control of their BG, better HbA1c values and to improve health and fitness levels. Two thirds of T1D, 94.7% of T2I and 87.5% of T2T said that losing weight was one of the primary factors for participating in exercise. Table 11 highlights more of these factors for all the groups.

Table 11: Factors for participating in exercise.

Factors for participating in exercise	**T1D**	**T2I**	**T2T**
To keep well with diabetes	78%	100%	83.3%
Better control of BG	79.8%	100%	80.4%
Better HbA1c value	69.8%	88.9%	79.5%
Improvements health and fitness	93.2%	100%	83.3%
Loss of weight	63%	94.7%	87.5%
Family participates in sport	18.9%	28.9%	12.8%
Because friends do it	40.6%	7.1%	13.2%
Because I enjoy it	80.6%	84.2%	45.2%
To relieve stress	69.6%	37.5%	58.1%

When respondents were asked about the frustrating aspects about exercise, table 12 shows that finding time for exercise and motivation were the most cited reasons for T2T (57.4% and 55.7%),T1D (47.0% and 34.2%) and T2I (40.0% and 36.7%), respectively.

Table 12: Aspects of frustration about exercise.

frustrating issues about exercise	T1D	T2I	T2T
Finding time to exercise every day	47.0%	40.0%	57.4%
Motivating myself	34.2%	36.7%	55.7%
Having to change my diet	10.1%	3.3%	6.6%
Pain after exercise	10.7%	23.3%	18.0%

4.4.5.3 Type and intensity of exercise performed by T1D and T2D

About half 49% of T1D had membership with a Sports Centre or group, compared with 37.2% of T2T and 44.4% of T2I. Figure 17 shows that walking was the most preferred form of exercise by 93.5% of T1D, 92.1% of T2T and 93.8% of T2I. The vast majority of the respondents performed exercise at moderate to high intensity exercise (86% of T1D, 70% of T2T and T2I). Only 14% of T1D undertook exercise every day in comparison with 29% of T2T and 35% of T2I. About half of T1D and T2T, 47% and 48% respectively, performed exercise 3 – 5 days per week compared with 29.4% of T2I. In a typical exercise day the majority (72.2%) of respondents performed exercise one time per day and 81.4% of T1D, 94.2% of T2I normally spend from 30 mins to 2 hours in sport or exercise compared with 66.7% of T2T. Figure 18 shows where the respondents performed the exercise.

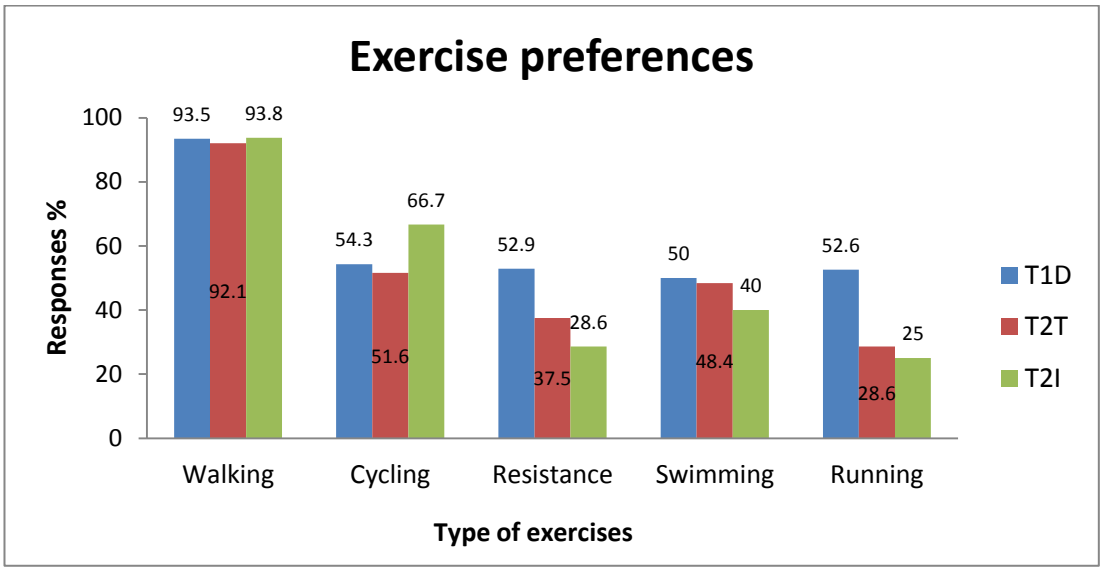

Figure 17: Type of exercises preferred by the participants.

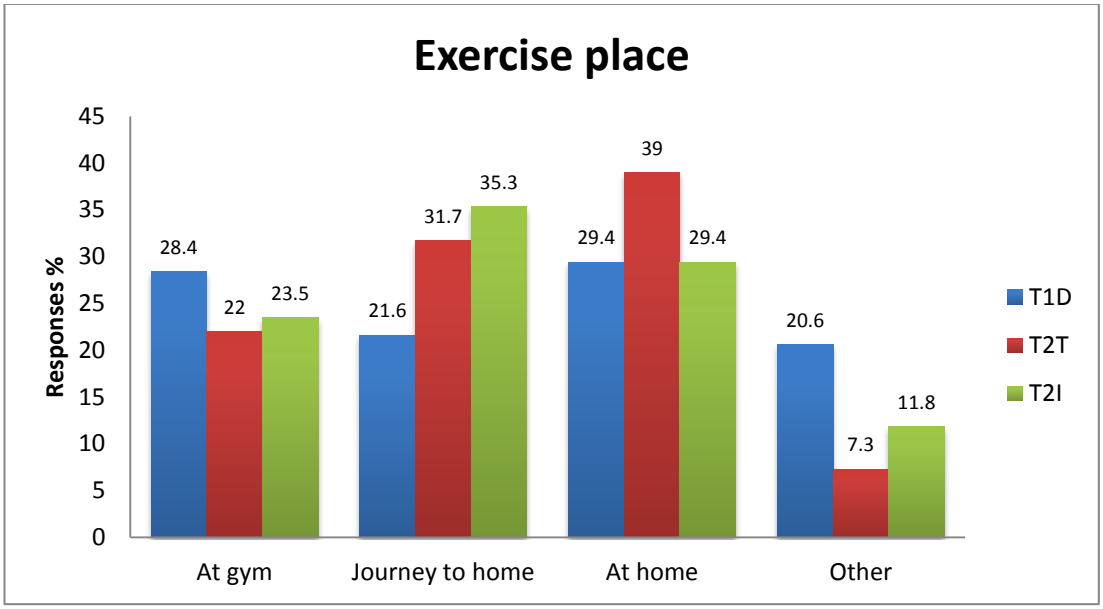

Figure 18: Exercise places.

4.4.5.4 BG management and Insulin dose on normal and exercise days

A greater proportion of T1D than T2T and T2I reported that they tested their BG more than four times on a non-exercise day (62%, 6% and 12.5% respectively).

When the respondents were asked whether they changed this on an exercise day, 57.4% of T1D said that they tested BG more often than usual on an exercise day compared with 13.9 of %T2T and no one of T2I. Furthermore, 77% of T2T and T2I did not change their testing BG habit on an exercise day in comparison with 42% of T1D. On an exercise day, respondents who inject insulin (T1D and T2I) did not change the number of insulin injections. Table 13 shows that 19% of T1D and 23.1% of T2I have taken their insulin dose before exercise and 35.9% of T1D and 23.1% of T2I administered their dose following exercise.

About 49% of T1D, 12% of T2T and 35.3% of T2I had hypoglycaemia events up to three times in the past month with the major risk period up to 2 hours following the exertion of exercise. To mitigate this threat, carbohydrate boosts were used and were more common before exercise than after and few disturbed the session for this purpose. Respondents with T1D were more likely to test their BG more than those with T2I, before exercise (59.2% and 34.6% respectively), during exercise (23.3 % and 3.8% respectively) and after exercise as well (50% and 19.6% respectively).

Respondents were asked what they would do if their BG were less than 4 mmol/L (72mg/dl), and the majority of all respondents (80%), said they would take some carbohydrate then exercise. More than 94% of T2T and T2I reported that they rarely or never had hypo during exercise compared to 68.6% of T1D. 29.4% of T1D said that they had it frequently. Moreover, when they asked about the previous month, a higher proportion of those with T1D (49%) had experienced hypoglycaemia events after exercise up to three times more than those with T2T and T2I, (11.5% and 35.3% respectively). In the event of hypoglycaemia after exercise, more than 96% of T1D and T2I would eat or drink some carbohydrate compared to 50% of T2T. These results indicate that T1D have more hypoglycaemic episodes and suggest that their current treatment with insulin is not optimal during exercise. It is also possible T2D patients

did not stress their body as much as T1D or perhaps exercise differently for example, short duration and lower intensity. It is well known that after exercise BG levels can drop several hours after exercise, the reason for this exercise makes muscle cells sensitive to insulin so following physical activity every unit of insulin covers a greater amount of carbohydrate producing a greater BG lowering effect. Extensive exercise depletes glycogen stores in the muscle and liver and when these stores replenish BG levels often drop.

When the respondents were asked about how many times in the last month they suffered from hyperglycaemia and their BG had been above 10mmol/L (180mg/dl) after exercise, the majority of T2T (87%) and 65% of T2I said none. This compared with 36.4% of T1D. However, T1D were most likely in the last month to have had up to three episodes of hyperglycaemia after exercise, with 41.4% compared with just 5.9% of T2I and 0% of T2T.

Crosstab calculations with 2 layers were made to find the impact of regular exercise on HbA1c between the three groups. This study showed that those who did exercise regularly among all the groups had a better HbA1c than those who did not. HbA1c with desirable values between 5% - 7% (31 - 53 mmol/mol) were observed more among the patients who did exercise regularly (35.3% of T1D, 46.5% of T2T and 45.5% of T2I) compared with (27.6% of T1D, 31.3% of T2T and 37.5% of T2I) who did not. Moreover, patients from all the groups who did not exercise were most likely to have a high HbA1c over 8% (37.9% of T1D, 25.1% of T2T and 37.5% of T2I) in comparison with those who did it in a regular basis (23.4% of T1D, 18.6% of T2T and 26.9% of T2I).

When the respondents were asked about the symptoms during or after exercise, Table 14 shows a variety of answers from respondents for following symptoms: bleeding, chafing, flushing, hives, hyperthermia and colour or blood in the urine. Less than quarter of T2I had muscle cramps compared with 16.9% of T1D and 14.3% of T2T. About quarter of T1D and T2I had shortness of breath compared with 21.4% of T2T. Some of these can be real barriers and diabetes patient need better support and advice about some or all of these symptoms.

Table 13: BG, insulin and carbohydrate as related to exercise.

When do you test your blood glucose?			
	A. Before exercise	**B. During exercise**	**C. After exercise**
T1D	59.2%	23.3 %	50%
T2I	34.6%	3.8%	19.6%
T2T	21.4%	3.6%	19.2%
When do you take your insulin dose?			
T1D	19%	6.3%	35.9%
T2I	23.1%	0%	23.1 %
When do you take carbohydrate?			
T1D	47.9%	20.4%	40.1%
T2I	34.6%	19.2%	19.2%
T2T	12.5%	1.8%	14.3%

Table 14: Symptoms during and after exercise.

Symptoms during and after exercise	T1D	T2I	T2T
Bleeding	0%	0%	0%
Chafing	4%	0%	7.1%
Flushing	6.3%	3.8%	3.6%
Hives	0.7%	0%	1.8%
Hyperthermia	2.8%	0%	1.8%
Muscle cramps	16.9%	23.1%	14.3%
Red face	27.5%	7.7%	12.5%
Shortness of breath	23.2%	23.1%	21.4%
Urinary (colour, blood)	0%	0%	1.8%

4.5 Conclusion

This study showed that those who did exercise regularly among all the groups had a better HbA1c, than those who did not. HbA1c with desirable values between 5% – 7% (31 – 53 mmole/L) were observed more among the patients who did exercise regularly (35.3% of T1D, 46.5% of T2T and 45.5% of T2I) compared with (27.6% of T1D, 31.3% of T2T and 37.5% of T2I) who did not. Moreover, patients from all the groups who did not exercise were most likely to have a high HbA1c over 8% (37.9% of T1D, 25.1% of T2T and 37.5% of T2I) in comparison with those who did it in a regular basis (23.4% of T1D, 18.6% of T2T and 26.9% of T2I).

Patients with T2T and T2I were observed to exercise less (73%) compared with T1D group (80.5%).

When physical exercise is considered, its type, duration, intensity, and target must be evaluated to be able to obtain the best benefits with the lowest rates of hypoglycaemia. Nevertheless it must be kept in mind that subjects with T1D or T2I and T2T have different requirements, which should be evaluated when exercise is

suggested as a part of diabetes management. BG testing self-monitoring should always be recommended, especially in patients exercising and using insulin.

BG testing frequency has been investigated. A large minority (almost 20%) of T2I users tested only once a day. They would have to estimate their calorie intake on several occasions daily, but their BG management is not likely to be as good as it should be. This is reflected in their HbA1c values and suggests that even if they know their target HbA1c, they are either choosing to ignore or are not being supported adequate in order to achieve it.

Chapter 5: Effects of combined resistance and aerobic exercise on metabolic and glycaemic control in T1D and T2D

5.1 Introduction

Diabetes Mellitus is associated with a high risk of CVD, CHD and other heart disease mortality (Chen, Pei et al. 2015, Li, Xiao et al. 2014, Jaiswal, Schinske et al. 2014). It has been known for decades that exercise and physical activity are one of the main cornerstones along with medication and diet to treat and manage diabetes and high lipid profiles (Yavari, Najafipoor et al. 2012, Sigal, Kenny et al. 2006). Dietary intervention, and changes in sedentary lifestyle by increasing physical activity contribute to the prevention and management of T2D and lead to significant benefit in risk factors that are known to be associated with development of CVD in patients with T2D such as HbA1c, BMI, SBP, DBP and lipid profile (Chen, Pei et al. 2015, Li, Xiao et al. 2014).

In addition, in young people with T1D, CVD in later life is considered to be a major risk and is linked with mortality (McVeigh, Gibson et al. 2013). Presence of lipid disorders can be found in both T1D and T2D and it is associated with the development of T2D (Billimek, Malik et al. 2015, Jaiswal, Schinske et al. 2014, Verges 2009, Hjerrild, Gravholt 2006). Therefore, it is crucial to investigate lipid abnormalities and to control lipids profile in people with T1D and T2D to reduce the risk of CVD and other diabetes complications such as hyperglycaemia, micro- and macrovascular complications (Jaiswal, Schinske et al. 2014, Maahs, Ogden et al. 2010). An improvement in glycaemia is suggested as an initial treatment for dyslipidaemia when caring for patients with T1D and T2D. Nevertheless, lipid-lowering medicine can also be administered if lipid goals are not achieved (Jaiswal, Schinske et al. 2014, Brunzell, Davidson et al. 2008, Buse, Ginsberg et al. 2007).

T1D patients who have reduced or sub-optimal glycaemic control will eventually present with heightened LDL levels in comparison to ND people and T1D patients with optimum glycaemic control (Guy, Ogden et al. 2009). Elevated HbA1c level has been

considered as a risk factor for CHD and CVD in patients with diabetes (Haring, Baumeister et al. 2014, Selvin, Coresh et al. 2005, Selvin, Marinopoulos et al. 2004). Furthermore, it is also has been observed that there is a direct correlation between raised HbA1c concentration and the severity of CAD and CVD in people with diabetes (Hong, Li et al. 2014, Jaiswal, Schinske et al. 2014).

HBA1c is often linked with alterations in lipids in adults who have T1D but not taking dyslipidaemia medications (Maahs, Ogden et al. 2010). It is reported that most patients with T1D and T2D could have dyslipidaemia at varying degrees, characterised by increased levels of TG, LDL and decreased HDL. Significantly higher rates of hypercholesterolemia and hyperlipidaemia have been observed in T2D with CVD compared to their counterparts who do not have CVD (Giansanti, Rabini et al. 1999), which may elevate the mortality rate of these patients (Sultan, Thuan et al. 2006).

It is a well-established fact that the long-term benefits of frequent aerobic physical activity for the general population can be applied to T1D patients and T2D (De Feo, Di Loreto et al. 2006). Exercise is linked with a heightened risk of hypoglycaemia during or after exercise because the increase of glucose uptake into the skeletal muscle during moderate exercise. In addition, exercise might lead to hyperglycaemic events if it is has been performed at high intensity exercise (anaerobic exercise) and this is due the hepatic glucose production which may reach 15 mg/kg body mass/min, an amount that exceeds muscular glucose disposal (Kapitza, Hovelmann et al. 2010, Riddell, Perkins 2009).

It has been suggested that the roles of intensive insulin as a treatment of T1D is not only to improve HbA1c and the prevention of premature cardiovascular events (Nathan, Cleary et al. 2005) but are also linked with lipid profile (Feitosa, A.,Feitosa-Filho,G.S., Freitas et al. 2013). An absolute decrease of 1% in HbA1c levels has been associated with a 15% to 20% decrease in major CVD events and a 37% decrease in microvascular complications (Selvin, Marinopoulos et al. 2004, Stratton, Adler et al. 2000). Thus, a significant reduction of 0.3 to 0.5% HbA1c levels achieved by combination exercise programme (AE + RE) might be expected to produce a 5% to 7% reduction in CVD risk and a 12% reduction in risk of microvascular complications

(Church 2011). The improvements of glycaemic control without weight gain has been associated with lipids control and this include TG, TC and LDL (Purnell, Hokanson et al. 1998). AE, RE or combined exercise programme is recommended in the management of T1D and T2D, and has physiological benefits including improved physical work capacity, body composition, blood pressure, blood lipid profile (Chen, Pei et al. 2015) and HbA1c. It is associated with less risk of diabetes complications and mortality in individuals with diabetes (Hordern, Dunstan et al. 2012).

5.2 Study aims

The purpose of this study was to examine the effects of six weeks of combination exercise (RE and AE), twice a week, on lipid profile, metabolic and glycaemic control in T1D and T2D. The ethical approval for this study was obtained from De Montfort University (DMU) Ethics Committee, Faculty of Health and Life Science, Leicester, UK.

5.3 Volunteers

Four groups of volunteers (n = 25) were involved in this study: ND = 7, T1D = 7, T2T = 7 and T2I = 4. The volunteers were 18-55 years old and not physically active or engaged in any regular exercise or formal training programmes, more details can be found on section 2.4. Volunteers were recruited and screened as detailed in Section 2.4.2 and 2.5.1.

5.4 Inclusion and exclusion criteria

The volunteers who participated in the exercise programme had met specific inclusion criteria as they were defined in section 2.4.2. Further information detailing recruitment response and excluded volunteers can be found in Sections 2.4 and 2.4.2.

5.5 Materials and methods

A brief description of the methods is provided below. Please refer to the methods in Chapter 2 for more detailed description of procedures associated with this chapter.

5.5.1 Experimental design

After the preliminary tests and familiarisation sessions (Refer to Section 2.5), volunteers participated in the main exercise trial which was a combined exercise session involving stretches, warm up on the bike for 10 min followed by 35 min of RE at 50-60% of 1RM (determined in Section 2.5.1.2). After RE they had 5 min of rest followed by 20 min of AE (cycling) at 50-60% of HRR (Section 2.5.1.3) and finally 10 min cooling down involves stretches (Figure 19). The chronic exercise programme involved 2 sessions (48 hours apart) for a total of 150 min each week for a 6-week period. Detailed description for the main exercise trial can be found in (Section 2.5.2).

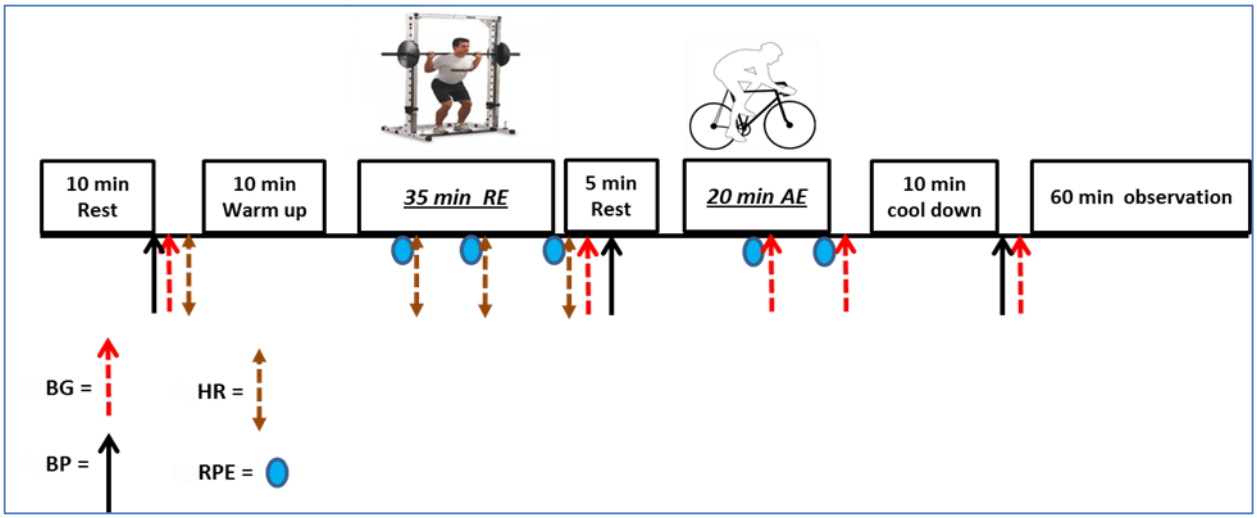

Figure 19: Schematic representation of the exercise session.

5.5.2 Anthropometric assessment

Measurements of body mass, height, BMI, %BF, % BW, waist and hip circumference were made as described in Section 2.3.19. Weight, %BF, %BW and BMI data were measured at three time points: before the exercise programme at the first session, after session 6 and at the end after session 12. Waist and hip measurements were

taken at two time points, before exercise at the first session and at the end after session 12.

5.5.3 Lipids, blood gases and electrolytes measurements

Lipids (HDL, LDL, TC, TG) were measured as previously described in Section 2.3.14 , blood gases (PCO_2, PO_2), electrolytes (Na^+, K^+, Ca^{2+}, C^{l-}) were analysed as outlined in Section 2.3.17. These variables were measured three time points: before the exercise programme at the first session, after session 6 and at the end after session 12.

5.5.4 HbA1c, BG, BP, HR and RPE

HbA1c and BG levels were measured as previously described in Sections 2.3.11 and 2.3.12, respectively. BG was measured 4 times in each exercise session: at rest before exercise, after RE exercise, after 10 min of AE and at the end of each session. HbA1c level was measured at session 1 and after session 12. BP (DBP and SBP) was measured (Section 2.3.13) and it was taken at different time points during exercise trials as outlined in Section 2.5.2. HR values were monitored (Section 2.3.8) at rest and continuously during the combined exercise trial as explained earlier in Section 2.5.2. RPE were obtained from the subjects using the Borg scale (Section 2.3.9) during RE and AE exercise as described in Section 2.5.2. RER values were calculated during the 20 min of AE using ADI system as described in Section 2.5.2.

5.5.5 Blood collection, C-peptide and insulin analysis

Venous blood samples were collected from the volunteers in EDTA tubes as described in (Section 2.3.15). It was of interest to investigate the effects of acute and chronic exercise on Insulin and C-peptide. Three blood samples were collected from the volunteer at the time points shown in (Figure 20). For the chronic effect, seven blood samples were collected as shown in (Figure 21). Insulin and C-peptide were determined using ELISA technique, full description of ELISA procedure and equipment can be found on Section 2.3.16.

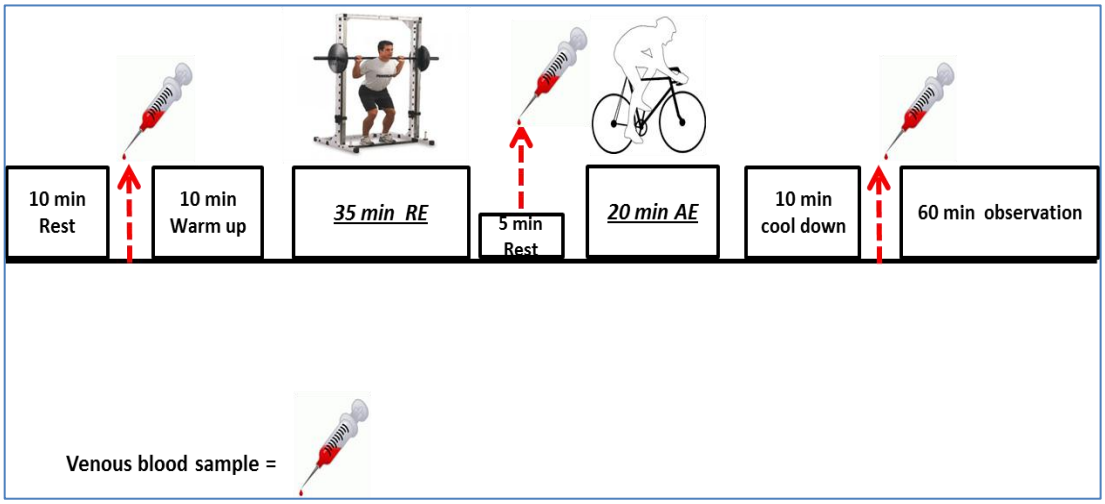

Figure 20: Venous blood samples from the first exercise session (acute effect).

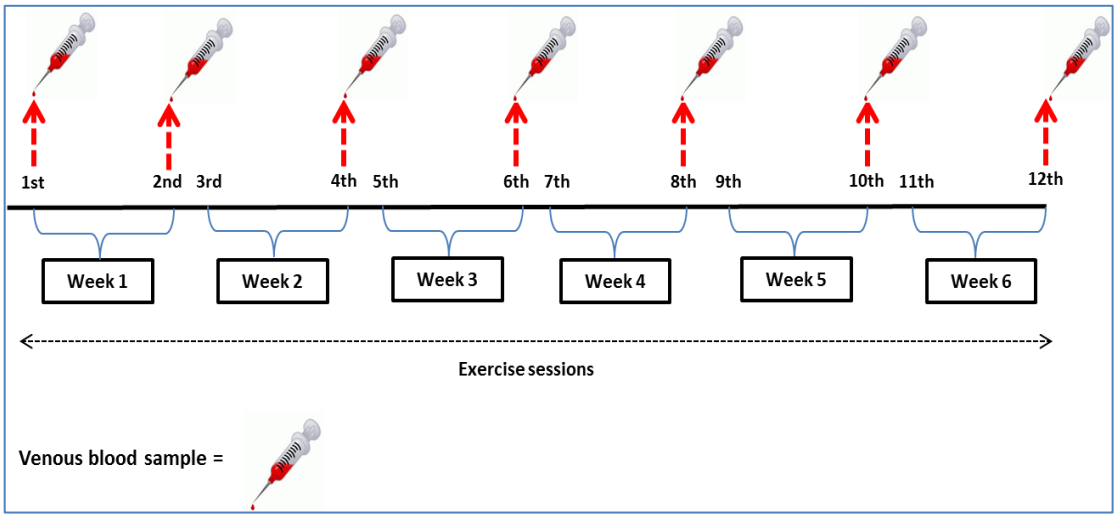

Figure 21: Venous blood samples throughout the exercise trial (chronic effect).

5.6 Results and discussion

5.6.1 Volunteers characteristics, anthropometrics and clinical variables:

Volunteers' characteristics and some clinical variables are presented in Table 15 for ND, Table 16 for T1D, Table 17 for T2T and Table 18 for T2I. It should be noted that the comparison in this section is (1st Pre-Ex vs 12th Post-Ex), ie: between the first session before exercise and at the end after the last session of the six weeks exercise trial because this demonstrate the change in these parameters as result of the exercise intervention.

Tables 15 - 18 demonstrate HR at rest values were significantly improved in all the study groups: ND from 72.3 ± 9.8 to 68.7 ± 9.0 ($p < 0.01$), T1D from 74.6 ± 7.4 to 70.7 ± 6.8 ($p < 0.01$), T2T from 77.4 ± 7.8 to 73.0 ± 6.8 ($p < 0.01$), T2I 69.7 ± 6.8 to 66.0 ± 6.1 ($p < 0.05$). SBP at rest readings were significantly decreased in ND from 130 ± 7.1 to 125 ± 5.8 ($p < 0.05$), T2T from 130 ± 11 to 121 ± 3.9 ($p < 0.05$) and in T2I from 126 ± 1.6 to 121 ± 2.1 ($p < 0.05$), and was improved in T1D ($p = 0.16$). DBP at rest readings were slightly decreased in all the study groups ND ($p = 94$), T1D ($p = 0.9$), T2T ($p = 0.12$) and T2I ($p = 0.16$).

Table 15 shows that ND volunteers at baseline were overweight with BMI = 26.2±3.3. Despite that ND weight and BMI did not change (1st Pre-Ex vs 12th Post-Ex), their BF% was reduced from 23.0 ± 7.3 to 21.5 ± 7.3, ($p = 0.07$) and their hip and waist were reduced, ($p = 0.06$, $p = 0.17$, respectively). As can be seen from tables 16, 17 and 18, T1D, T2T and T2I had smaller reductions in their weight and BMI. However, BF% in T2T was reduced significantly from 37.1 ± 8.6 to 34.8 ± 8.2 ($p < 0.01$), compared with a slight decrease in T1D ($p = 0.1$) and close to the level of significance in T2I from 28.1 ± 4.6 to 25.3 ± 3.2 ($p = 0.07$). As can be seen from tables 16 -18, T1D, T2T and T2I tested their BG levels significantly more times after the whole exercise trial compared to before. This is beneficial and important for diabetes patients. It indicates that their knowledge and understanding gained from the exercise trial provoked them to increase

the frequency of BG testing, which shows that they manage their diabetes more intensively than previously.

BW% was increased, but not at a significant level in ND ($p = 0.39$), T1D ($p = 0.72$), T2I (p 0.53) and was significantly increased in T2T from 42.7 ± 5.4 to 45.5 ± 4.9 ($p < 0.01$). Hip and waist measurements were slightly decreased in T1D, T2I and were significantly decreased in T2T, hip at ($p < 0.05$) and waist at ($p < 0.01$). All the study groups were overweight with BMI values: T1D = 29.3±6.9, T2T = 29.2±3.5 and T2I = 29.2±1.5 and BMI was not significantly improved in all study groups.

The above results from the present study can be supported by many previous studies such as a randomised trial by Sigal et al. 2007, which compared the effects of RE, AE or both in combination for 22 weeks on the glycaemic control in patients with T2T. They found that, none of the three different exercise regimens produced a significant change in BMI and body weight. BF% was improved from 36 ± 9.6 to 35 ± 9.6, and waist circumference was reduced from 112 ± 24 cm to 108 ± 24 (44 to 42 inch) as well as an improvement in SBP and no change in DBP with combined exercise group (Sigal, Kenny et al. 2007). There are some agreement between the results from the current study and those described by Sigal (2007).

In addition, exercise interventions investigated by Yavari et al 2012 and his colleagues who had compared between AE and RE alone or the combination of AE and RE three times per week for 52 weeks in patients with T2D (Yavari, Najafipoor et al. 2012). They found that combined exercise programme had positive impact after the exercise intervention on the HR and reduce significantly BMI, BF%, visceral fat%, muscular percentage%, SBP and DBP (Yavari, Najafipoor et al. 2012). The effect of combined training programme AE and RE has been investigated for 8 weeks in T2T, showed that BF%, Hip:Waist ratio at rest was reduced significantly ($p < 0.05$) after the training programme (Maiorana, O'Driscoll et al. 2002). Moreover, a research conducted the effect of combined RE and AE intervention for 16 weeks on glycaemic control in T2D, demonstrated that body weight and BMI did not change after 4 weeks and 16 weeks of the combined programme (Tokmakidis, Zois et al. 2004).

Fenicchia et al (2004) reported that participating in 3 days per week for six weeks of RE did improve BMI, weight and fat mass in patients with T2D. A meta-analysis study by Harris et al (2009) concluded that BMI was not improved after 6 months of physical activity in ND primarily elementary school children; although they had other beneficial health effects (Harris, Kuramoto et al. 2009) and this shows that if there is no change in BMI does not mean that overall health has not improved. Other research on T1D supported the current study results and showed that BMI did not change after 3 times per week for 12 weeks of RE (8 – 12 repetition of 9 RE) or AE (40 min walk or run). However, there was a reduction in waist circumference (Ramalho, de Lourdes Lima et al. 2006).

In contrast, ND overweight or obese volunteers who have done combined AE and RE at moderate intensity for 30 min, 5days/week for 12 weeks was reported to produce a significant improvement of BMI and body weight, compared to AE or RE alone which had no significant effects on BMI, weight, BF% and fat mass (Ho, Dhaliwal et al. 2012). Moreover, in this study BF%, waist, fat mass were significantly reduced with the combined model and some of these findings seem to be in agreement with the current study findings in ND group (Table 15). It was concluded that the combination of the RE and AE exercise was one of the optimal exercise strategy to reduce body weight, BMI, BF% and waist circumstances (Davidson, Hudson et al. 2009).

Other researchers have investigated the effects of 8 weeks of a combined RE and AE programme in T2T supported the findings from this research study and they reported that, BMI and body weight did not change. However, BF%, resting HR and waist/hip %, had reduced significantly ($p < 0.05$) after the combined training programme (Maiorana, O'Driscoll et al. 2002).

Furthermore, a moderate to high intensity AE (60 min/day, 2 to 3 times/week) for 16 weeks was observed to reduce BMI significantly in a ND moderate dyslipidemic volunteers (Yoshida, Ishikawa et al. 2010). A randomised controlled trial by Church et al. (2010) for 9 months of combination exercise showed a significant decrease in BMI compared to RE or AE alone in patients with T2D (Church, Blair et al. 2010). These

studies highlight that different exercise trials may produce conflicting result for the present study, however the general trend appear to be similar.

5.6.2 Blood gases and electrolytes

As can be seen from Tables 15 - 18, PCO_2 and PO_2 levels were in the normal ranges in ND and T2I and were slightly changed, but about normal in T1D and T2T and there was no severe reduction in PO_2. Electrolytes (Na^+, K^+, Ca^{2+}, Cl^-), pH and lactate were always in or just about the normal ranges with no drastic changes. This indicates that all the volunteers who participated in the exercise trial showed basic signs of good health during the 12 sessions. So for example, there were no sodium, potassium, calcium or pH profiles that suggested cardiac, respiratory or renal problems. In addition to this, no-one suffered angina or any distress and although one or two experienced some hypoglycaemia, this was mild, quickly detected and corrected. The blood pressure readings and heart rates that were recorded within the exercise periods showed no sharp changes. This set of observations suggested that exercise trials exclusion criteria were observed and adhered to.

Table 15: Characteristics, changes in anthropometric, clinical and physiological variables for ND volunteers at the first session (1st Pre-Ex), after the sixth session (6th Post-Ex) and the end (12th Post-Ex). Data are presented as Mean ± SD. (*) P < 0.05, (**) P < 0.01 for (1st Pre-Ex vs 12th Post-Ex)

	1st Pre-Ex	**6th Post-Ex**	**12th Post-Ex**	***P value***
Anthropometric and clinical variables				
Age (year)	31 ± 5.3	-	-	-
Height (cm)	175 ± 4.6	-	-	-
Weight (kg)	80.16 ± 9.9	80.46 ± 10	80.27 ± 10	0.86
BMI (Kg/m^2)	26.2 ± 3.3	26.2 ± 3.4	26.2 ± 3.3	1.0
SBP (mmHg)	130 ± 7.1	125 ± 6.9	125 ± 5.8*	**< 0.05**
DBP (mmHg)	79 ± 7.5	75 ± 8.2	78 ± 8.2	0.64
Body Fat (%)	23.0 ± 7.3	22.3 ± 7.4	21.5 ± 7.3	**0.07**
Body Water (%)	55.0 ± 9.4	54.6 ± 8.2	56.4 ± 8.2	0.39
Resting HR (bpm)	72.3 ± 9.8	-	68.7 ± 9.0**	**<0.01**
Hip (inch)	38.4 ± 5.0	-	37.8 ± 4.7	0.06
Waist (inch)	36.0 ± 3.9	-	34.7 ± 3.1	0.17
Hip/Waist Ratio	0.95 ± 0.1	-	0.92 ± 0.1	0.44
Blood gases and Electrolytes				
PCO_2 (mmHg)	33.7 ± 5.4	34.9 ± 4.7	34.3 ± 5.6	0.75
PO_2 (mmHg)	103.3 ± 8.9	105.1 ± 11.5	100.9 ± 13.4	0.67
K^+ (mmol/L)	4.5 ± 0.5	4.5 ± 0.3	4.2 ± 0.4	0.36
Na^+ (mmol/L)	128.0 ± 6.3	125.1 ± 10.4	126.6 ± 10.2	0.75
Ca^{2+} (mmol/L)	1.1 ± 0.1	1.1 ± 0.1	1.0 ± 0.2	0.18
Cl^- (mmol/L)	101.7 ± 3.8	100.4 ± 6.1	100.4± 4.4	0.39
Lactate (mmol/L)	1.6 ± 0.6	1.6 ± 0.6	1.5 ± 0.6	0.28
pH value	7.44 ± 0.04	7.43 ± 0.03	7.43 ± 0.03	0.86

Table 16: Characteristics, changes in anthropometric, clinical and physiological variables for T1D volunteers at the first session (1st Pre-Ex), after the sixth session (6th Post-Ex) and the end (12th Post-Ex). Data are presented as Mean ± SD. (*) P < 0.05, (**) P < 0.01 for (1st Pre-Ex vs 12th Post-Ex).

	1st Pre-Ex	**6th Post-Ex**	**12th Post-Ex**	***P value***
Anthropometric and clinical variables				
Age (year)	31 ± 12	-	-	-
Height (cm)	178.8 ± 6	-	-	-
Weight (kg)	91.3 ± 18.9	91.1 ± 19	90.6 ± 18.8	0.15
BMI (Kg/m^2)	29.3 ± 6.9	29.3 ± 6.9	29.1 ± 6.9	0.2
BG tests (per day)	4.6 ± 0.3	-	5.4 ± 0.3**	**<0.01**
SBP (mmHg)	129 ± 11	127 ± 11	124 ± 9.4	0.16
DBP (mmHg)	82 ± 8.3	78 ± 6.5	81 ± 4.1	0.81
Body Fat (%)	31.3 ± 10.9	30.8 ± 11.2	29.5 ± 11.0	0.1
Body Water (%)	49.5 ± 11.3	48.4 ± 9.9	50.2 ± 9.8	0.72
Resting HR (bpm)	74.6 ± 7.4	-	70.7 ± 6.8**	**<0.01**
Hip (inch)	40.2 ± 2.7	-	39.0 ± 3.8	0.24
Waist (inch)	38.1 ± 7.7	-	37.8 ± 7.7	0.11
Hip/Waist Ratio	0.94 ± 0.1	-	0.96 ± 0.1	0.34
Blood gases and Electrolytes				
PCO_2 (mmHg)	32.3 ± 8.7	31.1 ± 6.7	31.8 ± 4.6	0.87
PO_2 (mmHg)	116.1 ± 24.1	110.2 ± 25.6	111.1 ± 23.7	0.07
K^+ (mmol/L)	4.8 ± 0.4	4.6 ± 0.4	4.6 ± 0.2	0.29
Na^+ (mmol/L)	131.1 ± 12.6	121.7 ± 10.0	124.4 ± 10.2*	**<0.05**
Ca^{2+} (mmol/L)	0.8 ± 0.3	0.8 ± 0.3	0.8 ± 0.3	0.31
Cl^- (mmol/L)	106.9 ± 9.6	104.9 ± 7.6	104.9 ± 7.8	0.19
Lactate (mmol/L)	1.1 ± 0.6	0.9 ± 0.6	1.0 ± 0.5	0.49
pH value	7.42 ± 0.05	7.49± 0.12	7.47 ± 0.11	0.19

Table 17: Characteristics, changes in anthropometric, clinical and physiological variables for T2T volunteers at the first session (1st Pre-Ex), after the sixth session (6th Post-Ex) and at the end (12th Post-Ex). Data are presented as Mean ± SD. (*) P < 0.05, (**) P < 0.01 for (1st Pre-Ex vs 12th Post-Ex).

	1st Pre-Ex	6th Post-Ex	12th Post-Ex	*P value*
Anthropometric and clinical variables				
Age (year)	44 ± 8.3	-	-	-
Height (cm)	174.4 ± 11.7	-	-	-
Weight (kg)	89.9 ± 21.3	89.4 ± 20.7	89.4 ± 21.1	0.39
BMI (Kg/m^2)	29.2 ± 3.5	29.1 ± 3.4	29.1 ± 3.5	0.60
BG tests (per day)	2.6 ± 1.0	-	3.4 ± 1.0**	**<0.01**
SBP (mmHg)	130 ± 11	125 ± 10	121 ± 3.9	**<0.05**
DBP (mmHg)	80 ± 5	72 ± 7.2	76 ± 6.7	0.11
Body Fat (%)	37.1 ± 8.6	35.5 ± 8.7	34.8 ± 8.2**	**<0.01**
Body Water (%)	42.7 ± 5.4	45.1 ± 3.7	45.5 ± 4.9**	**<0.01**
Resting HR (bpm)	77.4 ± 7.8	-	73.0 ± 6.8**	**<0.01**
Hip (inch)	41.4 ± 3.3	-	40.9 ± 3.1*	**<0.05**
Waist (inch)	41.5 ± 3.3	-	40.4 ± 3.1**	**<0.01**
Hip/Waist Ratio	1.0 ± 0.1	-	0.99 ± 0.1	0.06
Blood gases and Electrolytes				
PCO_2 (mmHg)	33.8 ± 6.3	32.4 ± 7.1	29.5 ± 8.5	0.9
PO_2 (mmHg)	111.7 ± 20.9	113.5 ± 22.3	123.8 ± 20.0	0.07
K^+ (mmol/L)	4.2 ± 0.6	4.7 ± 0.5	4.6 ± 0.5	0.07
Na^+ (mmol/L)	125.7 ± 1.3	123.0 ± 2.4	128.7 ± 2.6	0.05
Ca^{2+} (mmol/L)	0.9 ± 0.2	1.0 ± 0.2	1.0 ± 0.1	0.26
Cl^- (mmol/L)	99.6 ± 5.2	105.6 ± 7.2	103.0 ± 4.0	0.14
Lactate (mmol/L)	1.6 ± 0.8	1.5 ± 0.8	1.5 ± 0.7	0.5
pH Value	7.42 ± 0.02	7.46 ± 0.07	7.47 ± 0.04	0.07

Table 18: Characteristics, changes in anthropometric, clinical and physiological variables for T2I volunteers at the first session (1st Pre-Ex), after the sixth session (6th Post-Ex) and at the end (12th Post-Ex). Data are presented as Mean ± SD. (*) P < 0.05, (**) P < 0.01 for (1st Pre-Ex vs 12th Post-Ex).

	1st Pre-Ex	**6th Post-Ex**	**12th Post-Ex**	***P value***
Anthropometric and clinical variables				
Age (year)	45 ± 4.5	-	-	-
Height (cm)	175 ± 7.6	-	-	-
Weight (kg)	88.8 ± 4.8	88.4 ± 5.1	88.7 ± 5.0	0.8
BMI (Kg/m^2)	29.2 ± 1.5	29.0 ± 1.3	29.1 ± 1.7	0.4
BG tests (per day)	3.8 ± 0.5	-	4.5 ± 1.0*	**<0.05**
SBP (mmHg)	126 ± 1.6	119 ± 6.1	121 ± 2.1*	**<0.05**
DBP (mmHg)	80 ± 5	72 ± 7.2	76 ± 6.7	0.16
Body Fat (%)	28.1 ± 4.6	26.3 ± 4.2	25.3 ± 3.2	0.07
Body Water (%)	48.9 ± 3.1	48.8 ± 3.0	49.7 ± 3.1	0.53
Resting HR (bpm)	69.7 ± 6.8	-	66.0 ± 6.1*	**<0.05**
Hip (inch)	40.0 ± 3.0	-	39.8 ± 3.3	0.42
Waist (inch)	37.8 ± 2.1	-	37.3 ± 2.1	0.25
Hip/Waist Ratio	0.95 ± 0.04	-	0.94 ± 0.03	0.06
Blood gases and Electrolytes				
PCO_2 (mmHg)	39.1 ± 3.8	39.9 ± 2.7	33.5 ± 3.4	0.28
PO_2 (mmHg)	103.3 ± 4.8	94.8 ± 7.0	109.3 ± 22.3	0.74
K^+ (mmol/L)	4.4 ± 0.7	4.3 ± 0.6	4.3 ± 0.3	0.76
Na^+ (mmol/L)	134.7 ± 2.1	131.3 ± 1.2	132.0 ± 2.6	0.09
Ca^{2+} (mmol/L)	0.8 ± 0.3	0.8 ± 0.2	0.7 ± 0.2	0.79
Cl^- (mmol/L)	109.0 ± 5.3	105.0 ± 4.4	102.0 ± 8.2	0.39
Lactate (mmol/L)	1.7 ± 0.4	1.4 ±0.6	1.6 ± 0.5	0.13
pH value	7.39 ± 0.01	7.41 ± 0.02	7.42 ± 0.11	0.75

5.6.3 Changes in RER, 1RM and RPE across whole trial

Figure 22 shows Mean RER values during the 20 min of AE across the whole exercise trial (12 sessions) for all the 4 study groups. RER is the ratio of the volume of carbon dioxide released to the volume of oxygen taken up into the lungs at the same time. RER normal ranges are between 0.7 and 1.2 and this factor is used as an indicator of substrate oxidation, where 1.0 indicates total carbohydrate oxidation, while 0.7 refers to total fat oxidation and 0.85 suggests a mix of fat and carbohydrates (Simonson DC 1990, Ferrannini 1988). Data from Figure 22 shows that RER readings for all the groups were steady and most of the values were between 0.85 and 1.2 indicating that carbohydrates are being predominantly oxidised during the 20 min of AE in all the groups. These results correlate with and support the findings from the BG responses to AE exercise across the whole trial (12 sessions). BG levels fell during the AE which was evident by RER which shows CHO been oxidised as the predominate substrate.

Figure 23 illustrates percentages (after the six weeks exercise trial vs before) of the 1RM strength improvement for the five different RE exercises working upper and lower muscle group (Chest, Squat, Back, Biceps and Triceps) in all the study groups (ND, T1D, T2T and T2I). As can be seen from Table 19 and Figure 23, all the volunteers showed significant strength increases ranging from 16% to 75% in all exercises with p values of (<0.01) or (<0.05). T2T and T2I had a higher percentage of improvement than T1D and ND. As shown in Table 19, strength capability of all the volunteers has significantly improved and there was a strength gain in both upper and lower body muscle groups. This might be due increase in their lean body mass which lead to an improvement in the insulin sensitivity and fat oxidation (Lee, Boyko et al. 2011, Van Der Heijden, Wang et al. 2010). Some of these findings in line with results of past study examined the effects of RE on glucose control in patients with T2T by Fenicchia et al (2004) who reported that both T2T and ND volunteers had a significant percentage of improvement in their 1RM after six weeks of RE ranging from 19% to 57% in all RE exercises ($p < 0.01$) and improvement in integrated glucose concentration after single bout of RE (Fenicchia, Kanaley et al. 2004).

Furthermore, another study investigated a combined training programme for 8 weeks in T2T which supported the current study about the improvement in the muscle strength. It has shown that muscle strength in upper and lower muscle groups has improved significantly ($p < 0.001$) after the training programme (Maiorana, O'Driscoll et al. 2002). Moreover, other researchers have conducted a combined AE and RE for 16 weeks in T2T, and they reported results are consistent with this study. They found that muscular strength bench press, seated row, leg extension, pull-down, and leg curl was significantly improved after 4 weeks (<0.01) as well as after 16 weeks (<0.001) of exercise (Tokmakidis, Zois et al. 2004).

In addition, a study has investigated the effects of RE or AE + RE on the muscular strength in T2D and they found that both groups had significant improvements in the lower and upper muscles at 3 and 6 months (Larose, Sigal et al. 2012). Furthermore, results from other study have been conducted on overweight/ obese ND volunteers who participated in 16 weeks of RE are in line with findings from the present study. This study showed that there were statistically significant improvement ($p < 0.05$) in muscular strength of chest press and front lat pull-down (Tibana, Navalta et al. 2013). In addition, It was reported that the combination of the RE and AE exercise was one of the optimal exercise strategy to improve muscular strength for the lower and upper body muscles (Davidson, Hudson et al. 2009).

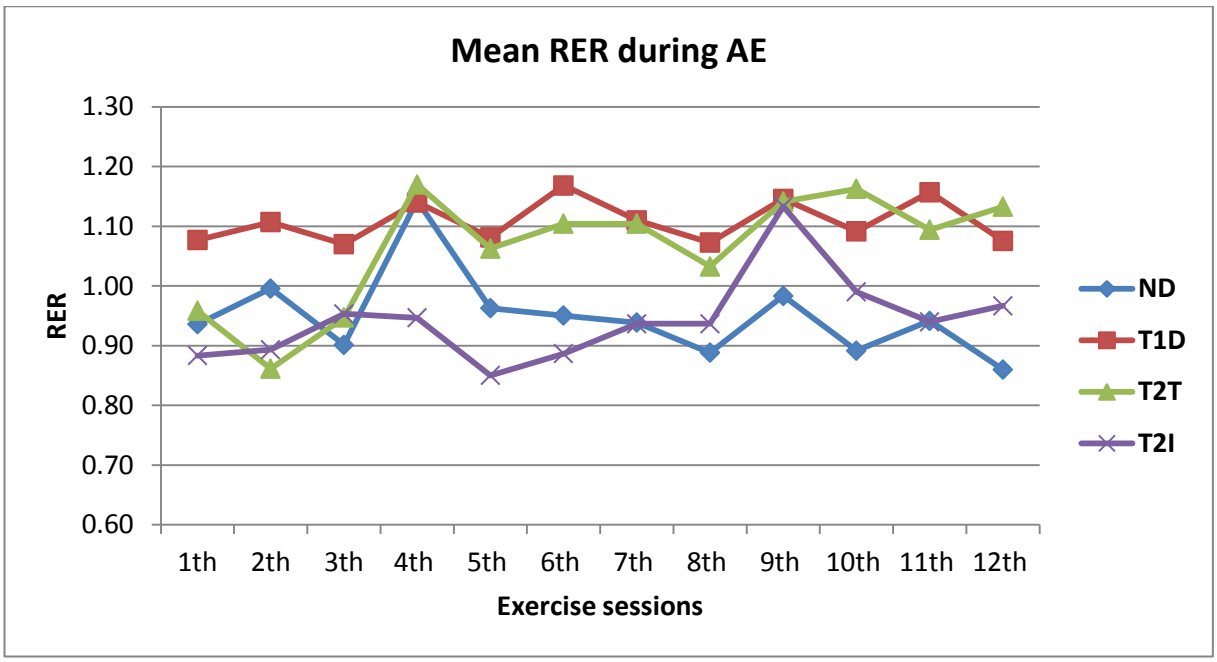

Figure 22: Mean RER values during the 20 of AE across the whole exercise trial (12 sessions) for all the study groups.

Table 19: Percentages of 1RM improvement Post-Ex trial vs Pre-Ex trial for all the study groups (ND, T1D, T2T and T2I).

% Change	ND	P. value	T1D	P. value	T2T	P. value	T2I	P. value
SQUAT	36%	<0.01	41%	<0.01	75%	<0.01	47%	<0.05
CHEST	19%	<0.01	27%	<0.01	27%	<0.01	26%	<0.05
BACK	21%	<0.01	17%	<0.01	33%	<0.05	21%	<0.05
TRICEP	17%	<0.01	20%	<0.01	48%	<0.05	37%	<0.05
BICEP	16%	<0.01	21%	<0.01	25%	<0.01	26%	<0.01

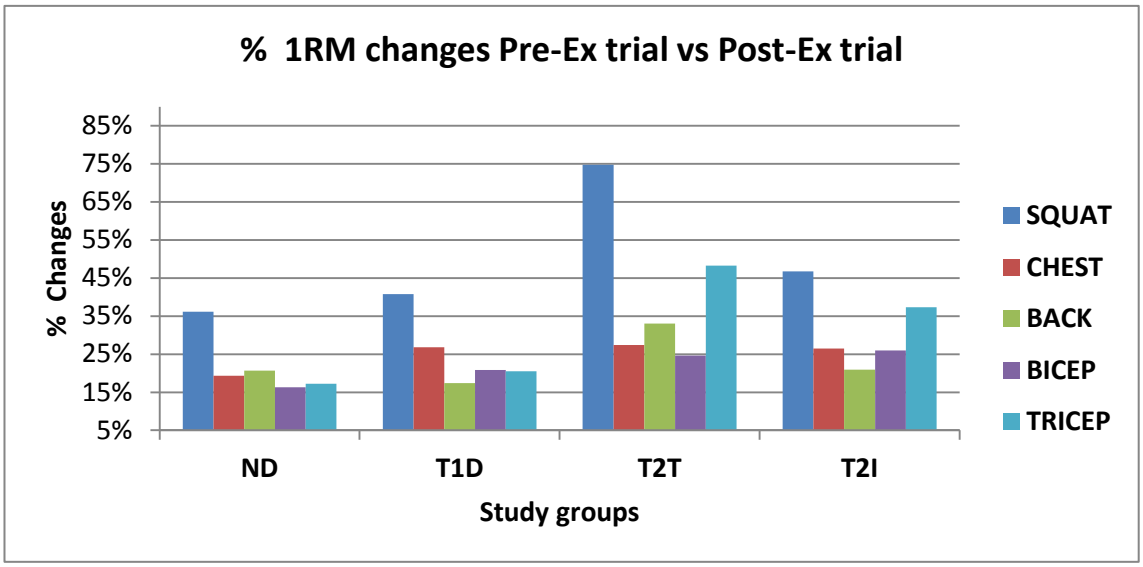

Figure 23: percentage % of improvements in 1RM Post-Ex trial vs Pre-Ex trial.

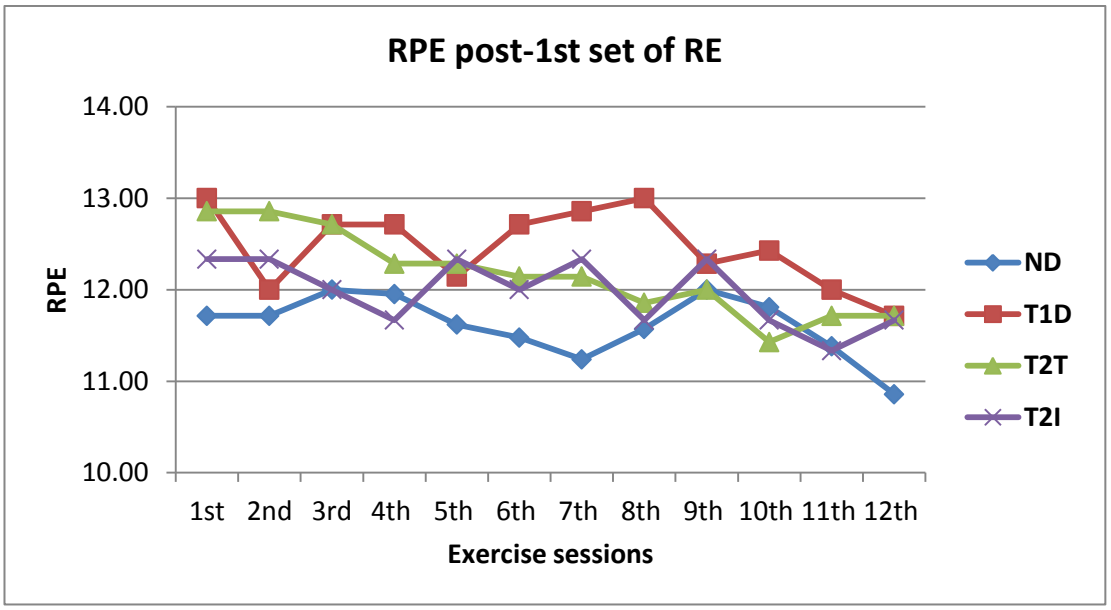

Figure 24: RPE Post-1st set of RE across whole trial (12 sessions) for all the study groups (ND, T1D, T2T and T2I).

RPE is valid method for exercise prescription and determination intensity of exercise (Iellamo, Manzi et al. 2014, Scherr, Wolfarth et al. 2013). RPE was recorded 5 times in each exercise session; after 1st, 2nd and 3rd sets of RE and recorded twice after 10 and 20 minutes of AE. RPE value over the 12 week exercise trial period in all the study groups reveals that there has been downward slope in RPE value which would indicate that over time across the whole exercise trial (12 sessions) the volunteers perceived exertion to RE became lower and showed an improvement in the final session when compared to the first session in the four study groups (ND, T1D, T2T and T2I). This suggests that they found RE become easier and their performance and strength had improved which is in agreement with significant improvement in all the volunteers strength as can be seen from 1RM results Post-Ex trial vs Pre-Ex trial in Table 19 and Figure 24 – 26. This is consistent with previous study reported that participating in 3 days per week for six weeks of RE in T2T improved strength of upper and lower muscle groups (Fenicchia, Kanaley et al. 2004).

Figures 24 - 28 indicate that all the volunteers performed the exercise (RE and AE) at the target intensity (moderate intensity) and these figures show that mean RPE values across the 12 sessions of the exercise trial were between (10.9 and 14.5). In addition, mean RPE values between the 1st and the 3rd set of RE became progressively higher and there has been gradual increase in 2nd and 3rd set for all the study groups. As would be expected this increase occurs because the volunteer would have exerted energy in the first two sets making the third more difficult. RPE plotted in Figure 27 and 28 clearly show that there has been a steady decline in mean RPE values at 10 and 20 min of AE throughout the whole exercise trial (12 sessions) and they found it become more easier indicating an improvement of their cardiovascular fitness level.

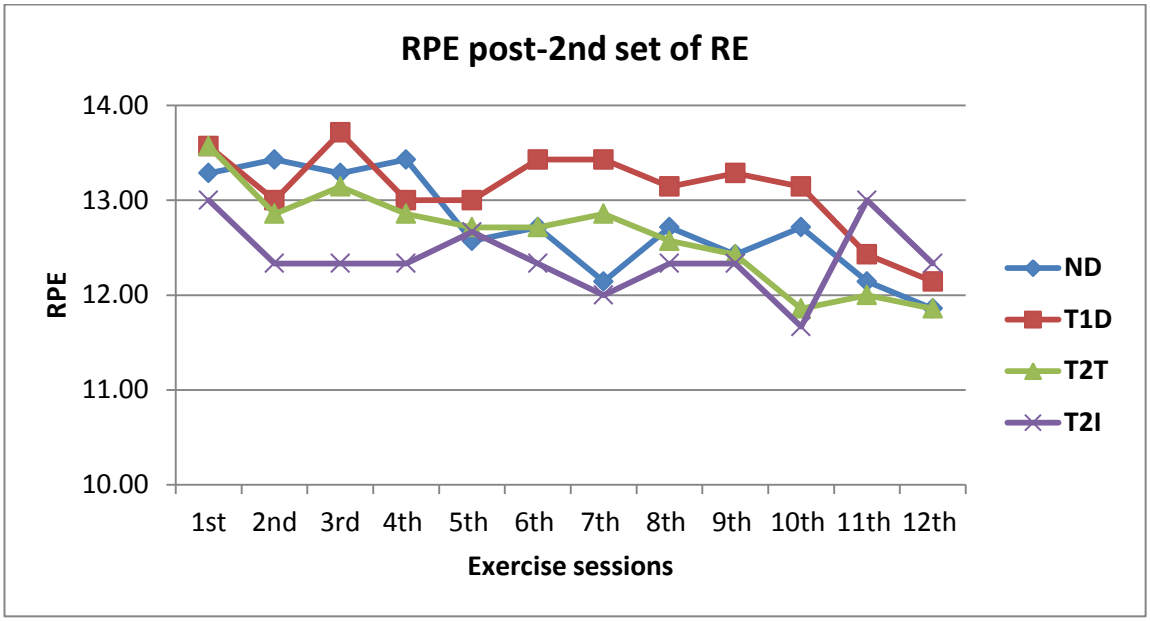

Figure 25: RPE Post-2nd set of RE across whole trial (12 sessions) for all the study groups (ND, T1D, T2T and T2I).

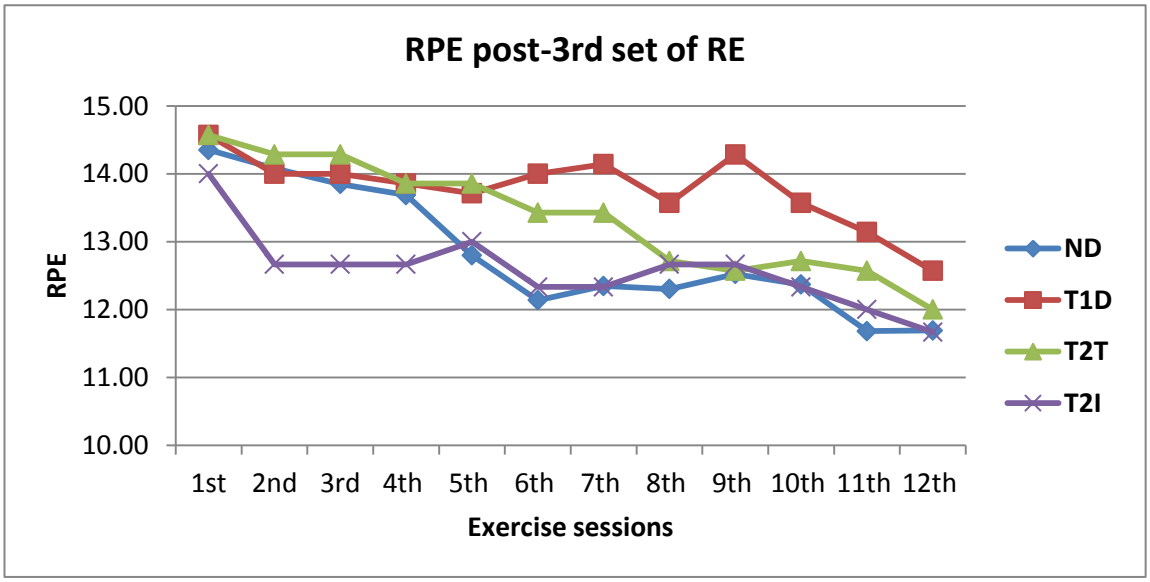

Figure 26: RPE Post-3rd set of RE across whole trial (12 sessions) for all the study groups (ND, T1D, T2T and T2I).

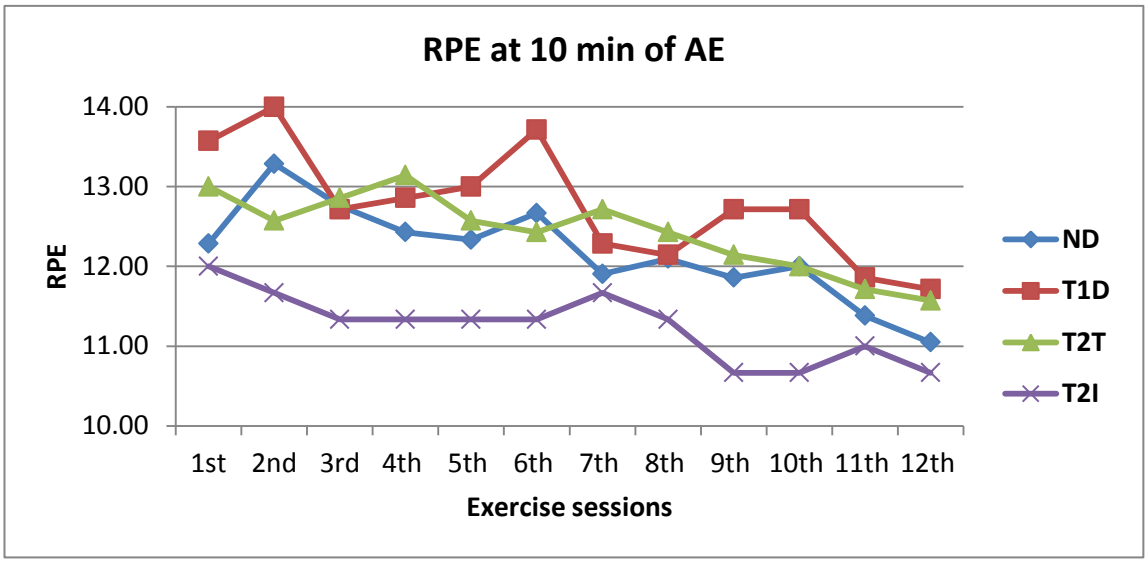

Figure 27: RPE at 10 min of AE across whole trial (12 sessions) for all the study groups (ND, T1D, T2T and T2I)

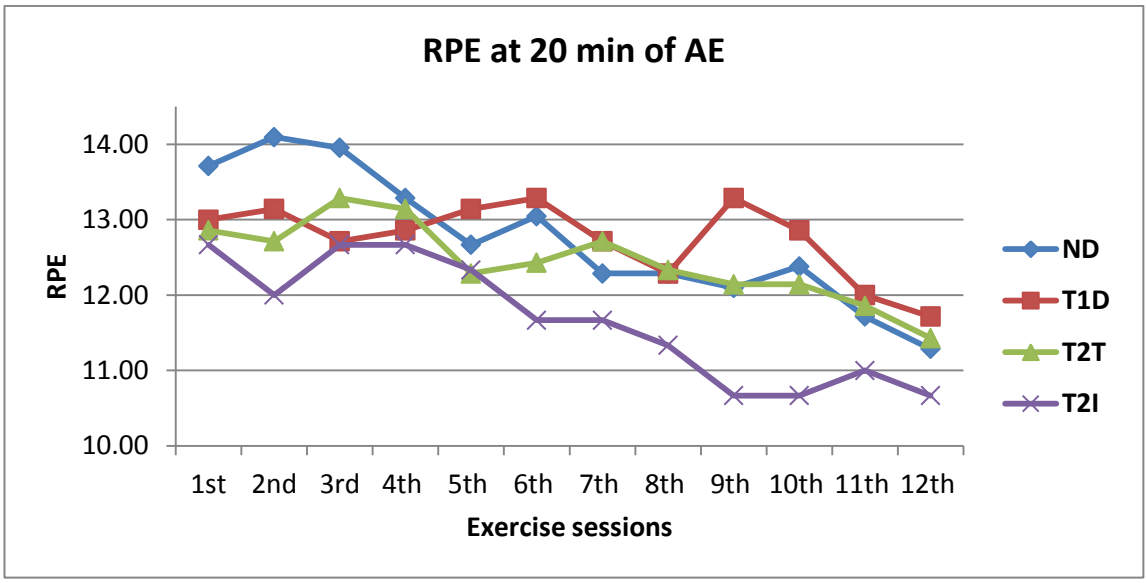

Figure 28: RPE at 20 min of AE across whole trial (12 sessions) for all the study groups (ND, T1D, T2T and T2I).

5.6.4 Changes in cardiovascular fitness parameters across whole exercise trial

Table 20 and 21 compares SBP and DBP, respectively across whole exercise trial (12 sessions) between all the study groups (ND, T1D, T2T and T2I). Table 20, 21 and (Figures 29 – 34) show that there has been a general gradual decrease for SBP and DBP across the exercise trial in all the study groups. All the study groups had same BP reaction to the 1^{st} , 2^{nd} and 3^{rd} set of RE across whole 12 sessions. Figure 30 shows that SBP readings Post RE were declined significantly ($p < 0.05$) in ND, but were more resistant in diabetic volunteers especially T2I where it was not responsive. Figure 31 demonstrate that SBP Post AE decreased moderately in all the groups, except T2I where it was not responsive. As can be seen from Table 20 , SBP at rest readings were significantly decreased in 12^{th} session compared to 1^{st} session for ND from 130 ± 7.1 to 125 ± 5.8 ($p < 0.05$). Similarly, for T2T from 130 ± 11 to 121 ± 3.9 ($p < 0.05$), T2I from 126 ± 1.6 to 121 ± 2.1 ($p < 0.05$), however showed an improvement for T1D ($p = 0.16$). In addition, Table 21 shows that DBP at rest readings had a steady decrease in all the study groups ND ($p = 64$), T1D ($p = 0.81$), T2T ($p = 0.11$) and T2I ($p = 0.16$).

HR at rest was measured before commencing and after finishing the 6 week exercise trial and a significant decrease in all the study groups was observed: ND from 72.3 ± 9.8 to 68.7 ± 9.0 ($p < 0.01$), T1D from 74.6 ± 7.4 to 70.7 ± 6.8 ($p < 0.01$), T2T from 77.4 ± 7.8 to 73.0 ± 6.8 ($p < 0.01$), T2I 69.7 ± 6.8 to 66.0 ± 6.1 ($p < 0.05$). Table 22 shows HR readings Pre-EX, Post 1^{st} , 2^{nd} and 3^{rd} set of RE across whole 12 sessions for all the study groups (ND, T1D, T2T and T2I). It can be seen from Table 22 that HR Pre-Ex was always within the normal range of 68 and 83 for all groups.

As would be expected, Figure 36 and 37 illustrates that during RE, HR became progressively higher and there was a gradual increase in the 2^{nd} and 3^{rd} set during each exercise session for all the study groups. This correlate with earlier data from RPE (Figures 24 – 26) where values of RPE multiply by ten give HR values similar those in (Figures 35 – 37) these findings are similar to those of Borge et al 1983. However, across the whole 12 sessions there has been a slight decrease in HR readings between

Pre-EX and the 3rd set of RE, suggesting that volunteers from all the study groups showed an improvement in their cardiovascular fitness level. HR results from the present study are in a partial agreement with (Goto, Ishii et al. 2007), who found that the mean value of HR during AE endurance exercise was significantly higher when it was preceded by RE with 20 min of rest compared to trial with only AE exercise. A study by Burleson et al. 1998 reported that mean values of HR and RER were significantly greater during RE than during treadmill AE (Burleson, O'Bryant et al. 1998).

High BP (hypertension) is common comorbidity of diabetes, and it has been estimated to affect 20–60% of T1D and T2D (Arauz-Pacheco, Parrott et al. 2002). Hypertension is a major risk for the development of the macrovascular and microvascular complications in ND, T1D and T2D (North, Palmer 2015, Takao, Matsuyama et al. 2014, Frontoni, Solini et al. 2014, Pal, Radavelli-Bagatini et al. 2013, Arauz-Pacheco, Parrott et al. 2002).

Additional blood pressure lowering was independently associated with reduced cardiovascular mortality and improved renal outcome (Lovshin, Zinman 2014, Poulter 2009). The current study showed a significant reduction in HR and BP at rest which indicate an improvement of the cardiovascular fitness level and could lead to a decrease in risk factors of CVD and heart diseases mortality (Lovshin, Zinman 2014, Poulter 2009). Improvements in BP like what the present study showed, have been reported in previous studies after different modes of exercise such as AE (Montero, Roche et al. 2014, Collier, Kanaley et al. 2008), RE (Drenowatz, Sui et al. 2014, Collier, Kanaley et al. 2008) and a combination of AE and RE (Laoutaris, Adamopoulos et al. 2013, Sigal, Kenny et al. 2007).

As mentioned above, the present study showed that HR at rest was reduced significantly in all the study groups. SBP values were also reduced significantly in ND, T2T and T2I as well as showed an improvement for T1D. DBP at rest readings showed a steady decrease in all the study groups, however not at a significant level. Some of the above findings in the current study in agreement with a previous research showed that a combination of AE and RE exercise programme three times per week for 52 weeks in patients with T2D had a positive impact after the exercise programme on the HR and reduced significantly SBP and DBP (Yavari, Najafipoor et al. 2012).

Improvement was reported in SBP and no change in DBP with combined exercise group 3 times weekly for 22 weeks in T2D (Sigal, Kenny et al. 2007). In addition, the effect of combined training programme AE and RE has been investigated for 8 weeks in T2T, showed that HR at rest was reduced significantly ($p < 0.05$) after the training programme (Maiorana, O'Driscoll et al. 2002). Moreover, another study on T2T investigated the effect of different modalities of exercise (AE, RE or combined both AE + RE) showed that combined exercise had reduced significantly SBP and DBP, these results in partially agreement with the findings from the current work with regard T2T (Jorge, de Oliveira et al. 2011).

A study on sedentary ND volunteers with normal BP (<140/90 mm Hg), showed that 12 weeks of moderate AE (30 minutes, 5 days per week) had significantly decreased resting BP (Maeda, Tanabe et al. 2004). Moderate AE compared with baseline significantly reduced SBP (124±13 vs. 112±9 mm Hg; $P < 0.05$) and DBP (73±11 vs. 66±6 mm Hg; $P < 0.05$) (Maeda, Tanabe et al. 2004). In contrast, a study with ND, sedentary subjects without high BP, found that 60 minutes of walking (either single bouts of 20 minutes on 3 days per week, or accumulated bouts of two 10 minutes walks on 3 days per week) for 12 weeks was not sufficient to cause changes in BP post-intervention or compared with control (Murtagh, Boreham et al. 2005). It was concluded that the combination of the RE and AE exercise was the optimal exercise strategy for improvements in insulin resistance and functional limitation (Davidson, Hudson et al. 2009).

Table 20: SBP Pre-EX , Post-RE and Post-AE across whole trial (12 sessions) for all the study groups (ND, T1D, T2T and T2I). Data expressed as Mean±SEM.

SBP SYSTOLIC		1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th
ND	**Pre-EX**	130±3	128±2	127±2	126±3	125±2	125±3	126±3	126±3	125±3	124±3	125±3	125±2
	Post-RE	140±4	138±5	131±3	145±4	131±4	141±7	125±7	134±5	128±9	133±3	135±4	131±5
	Post-AE	129±6	129±4	131±3	131±5	127±7	126±5	128±6	128±5	127±5	128±5	123±5	128±5
T1D	**Pre-EX**	129±4	126±5	126±4	127±5	132±5	127±4	126±5	124±5	124±4	126±4	125±3	124±4
	Post-RE	134±7	136±4	129±2	137±7	132±3	135±6	128±6	134±6	132±8	131±4	134±4	132±4
	Post-AE	126±5	128±4	128±5	124±4	125±3	127±4	124±3	126±3	121±3	123±5	125±2	123±3
T2T	**Pre-EX**	130±4	126±3	131±4	126±3	129±4	125±4	128±5	125±5	123±4	123±3	123±4	121±4
	Post-RE	134±11	131±7	138±7	133±3	130±3	136±8	131±6	127±5	130±5	134±5	134±6	129±5
	Post-AE	134±5	129±3	126±5	125±6	126±4	126±6	127±4	129±5	127±6	126±5	122±5	129±5
T2I	**Pre-EX**	126±1	127±6	118±3	117±5	120±3	119±2	119±2	118±4	118±7	121±2	122±4	121±1
	Post-RE	128±1	126±3	129±5	130±4	128±6	130±3	126±9	133±3	128±2	126±2	130±1	126±1
	Post-AE	118±4	121±3	119±1	127±3	120±1	119±4	119±4	122±4	121±3	122±3	118±2	121±1

Table 21: DBP Pre-EX , Post-RE and Post-AE across whole trial (12 sessions) for all the study groups (ND, T1D, T2T and T2I). Data are expressed as Mean±SEM.

DBP		1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th
ND	**Pre-EX**	79±3	79±2	78±3	77±3	72±4	75±3	80±5	80±4	78±4	74±2	73±3	78±3
	Post-RE	77±2	84±3	74±1	74±2	76±2	75±1	72±3	75±1	72±2	76±2	75±2	77±3
	Post-AE	74±5	73±5	74±4	69±4	72±5	76±4	77±5	75±3	72±4	76±3	73±3	75±4
T1D	**Pre-EX**	82±4	80±3	78±4	80±3	79±4	78±2	79±4	80±2	77±4	81±3	85±2	81±2
	Post-RE	80±7	82±4	69±2	73±2	76±2	75±2	72±3	75±3	71±2	73±2	74±2	74±2
	Post-AE	79±2	83±3	81±4	76±3	79±3	83±3	82±5	81±2	77±4	81±3	82±2	77±4
T2T	**Pre-EX**	80±2	79±3	76±3	77±3	77±3	72±3	77±3	73±5	80±2	74±2	80±2	76±3
	Post-RE	72±3	67±3	77±2	69±2	71±2	71±2	72±3	70±3	72±2	74±3	76±3	73±3
	Post-AE	78±3	74±3	76±4	75±2	73±2	72±2	75±3	74±3	76±3	73±2	75±2	77±3
T2I	**Pre-EX**	76±1	73±3	78±5	73±2	78±4	78±2	75±2	74±5	79±4	76±4	73±0	72±1
	Post-RE	79±2	73±2	76±2	72±2	77±2	72±1	72±1	74±1	71±3	72±2	72±6	69±5
	Post-AE	71±3	76±5	78±2	81±4	79±5	84±4	79±4	79±2	79±4	78±5	77±4	75±2

Table 22: HR Pre-EX , Post 1st , 2nd and 3rd set of RE across whole trial (12 sessions) for all the study groups (ND, T1D, T2T and T2I). Data are expressed as Mean±SEM.

HR (BPM)		1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th
ND	**Pre EX**	76±2	76±4	76±3	75±2	74±4	75±3	73±3	72±5	72±2	72±3	71±2	68±3
	Post 1st set	120±5	122±4	115±3	121±6	119±2	124±5	122±5	128±4	126±3	119±3	120±4	123±3
	Post 2nd set	130±8	127±9	121±8	127±9	126±8	128±8	128±9	131±9	128±8	126±7	123±8	123±7
	Post 3rd set	144±6	140±2	141±7	144±7	134±3	141±7	142±7	140±4	143±4	137±5	135±5	142±6
T1D	**Pre EX**	81±6	80±3	73±5	77±5	71±5	77±3	79±5	77±4	82±4	82±5	80±5	81±4
	Post 1st set	126±4	123±4	124±6	126±6	121±4	129±4	127±5	121±3	121±5	123±5	122±3	119±5
	Post 2nd set	133±6	132±4	132±6	133±6	128±6	135±4	133±5	130±5	132±6	131±6	131±6	128±6
	Post 3rd set	139±6	138±6	136±6	138±7	133±6	141±5	139±7	134±5	136±7	134±6	134±5	132±6
T2T	**Pre EX**	77±3	78±2	75±2	75±2	76±1	73±2	78±2	78±3	74±3	73±3	76±2	73±4
	Post 1st set	126±4	127±3	132±3	128±2	124±2	127±3	128±2	125±3	122±4	123±5	122±4	119±3
	Post 2nd set	144±8	135±3	135±4	131±3	133±3	133±3	133±3	126±3	125±4	126±6	127±5	125±5

	Post 3rd set	142±5	144±4	143±5	140±3	140±4	137±4	136±4	132±4	131±4	132±6	134±5	130±5
T2I	**Pre EX**	77±1	81±4	82±5	77±4	80±7	74±3	74±4	76±10	83±4	76±6	76±6	75±5
	Post 1st set	120±8	119±5	125±0	114±4	118±5	112±2	118±4	112±2	118±2	122±2	113±4	109±1
	Post 2nd set	132±5	131±4	128±3	125±3	124±5	123±5	130±3	117±4	124±3	123±5	120±3	118±4
	Post 3rd set	138±3	136±3	134±5	129±4	126±6	128±6	129±3	120±5	123±8	129±6	123±7	120±4

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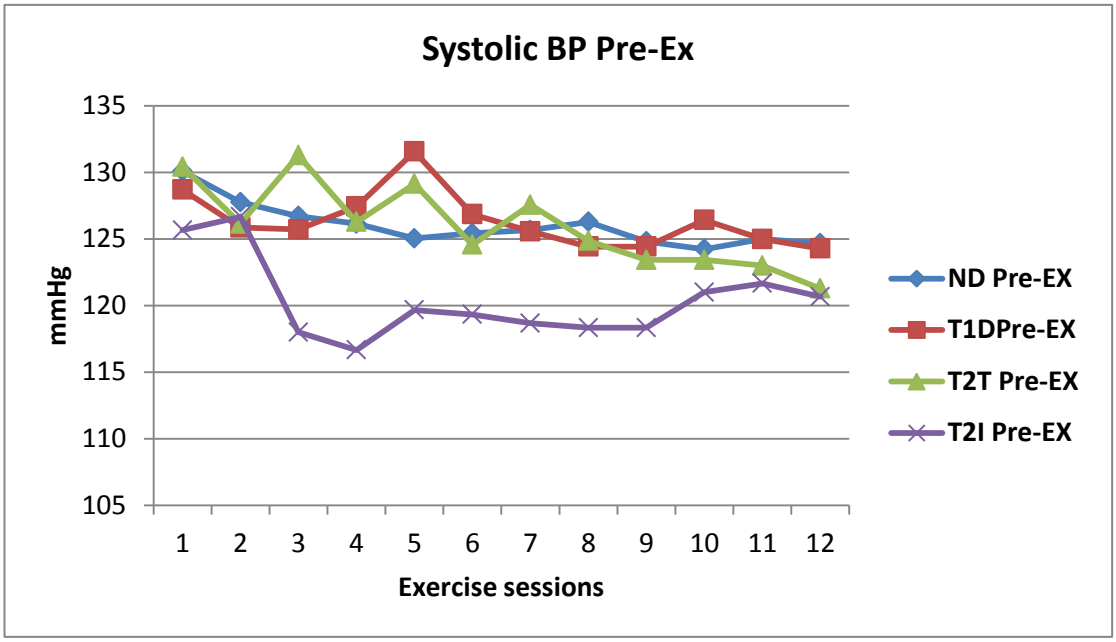

Figure 29: SBP Pre-Ex across whole trial (12 sessions) for all the study groups (ND, T1D, T2T and T2I).

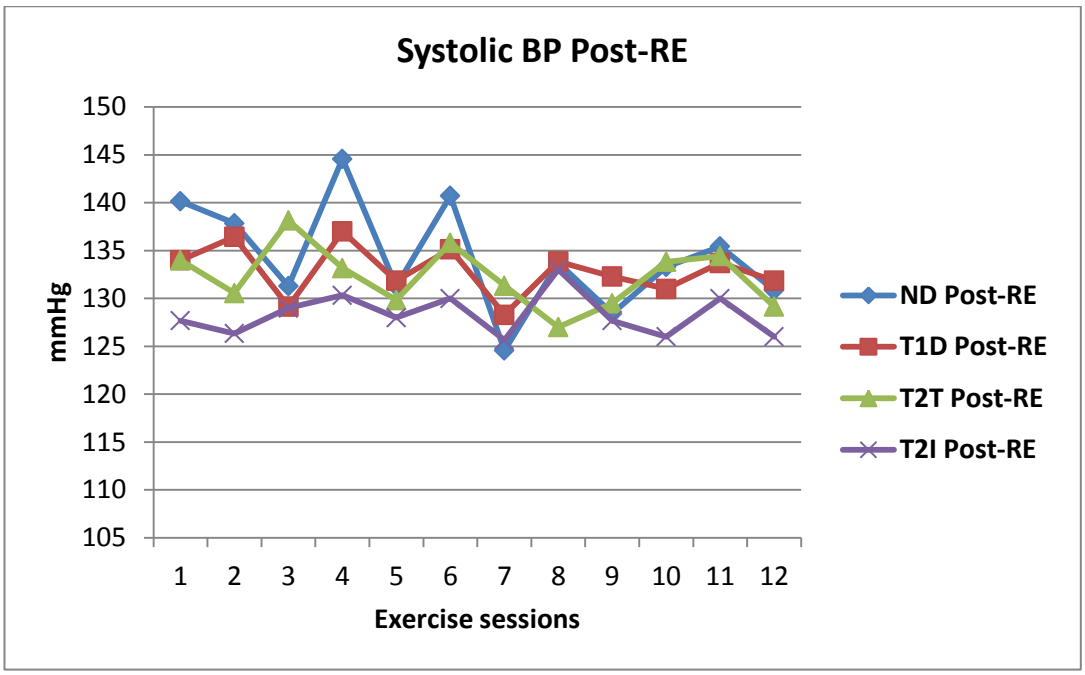

Figure 30: SBP Post-RE across whole trial (12 sessions) for all the study groups (ND, T1D, T2T and T2I).

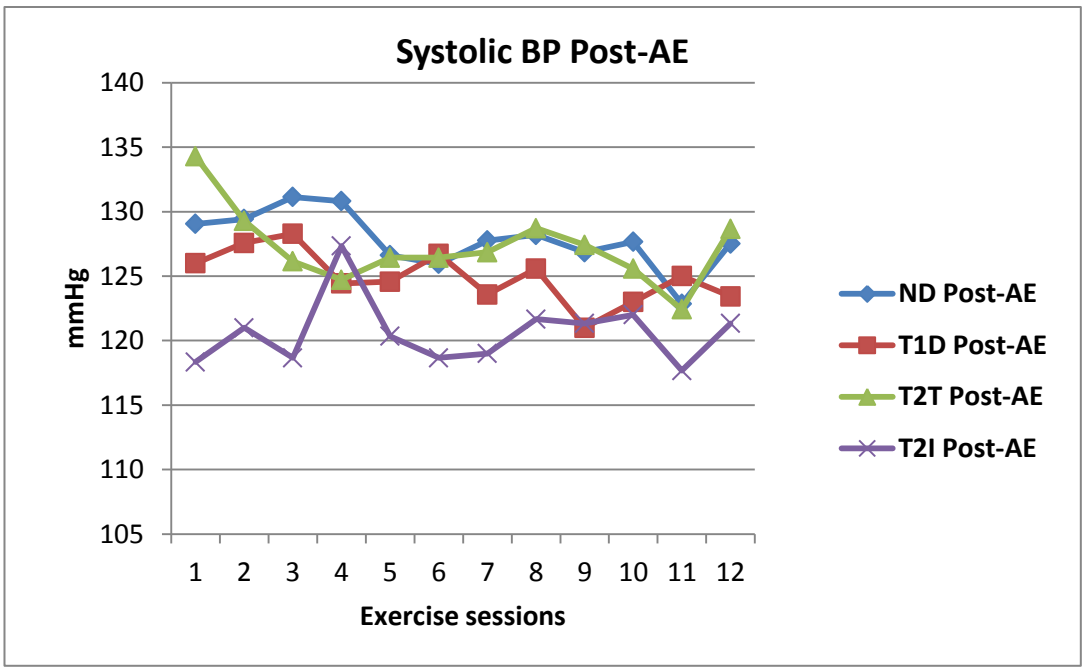

Figure 31: SBP Post-AE across whole trial (12 sessions) for all the study groups (ND, T1D, T2T and T2I).

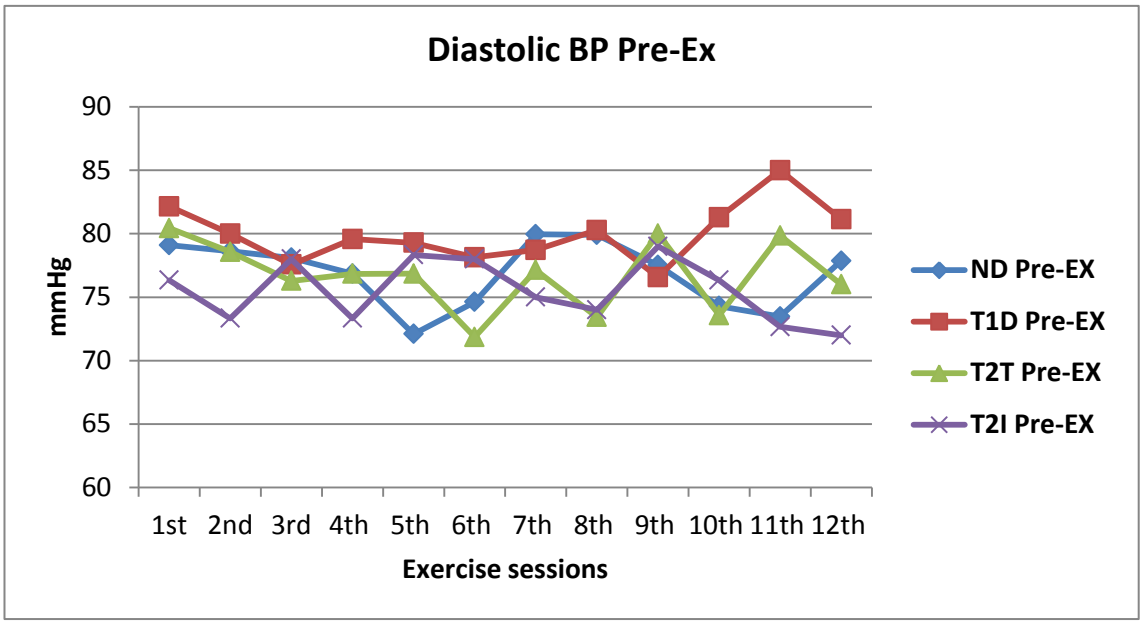

Figure 32: DBP Pre-Ex across whole trial (12 sessions) for all the study groups (ND, T1D, T2T and T2I).

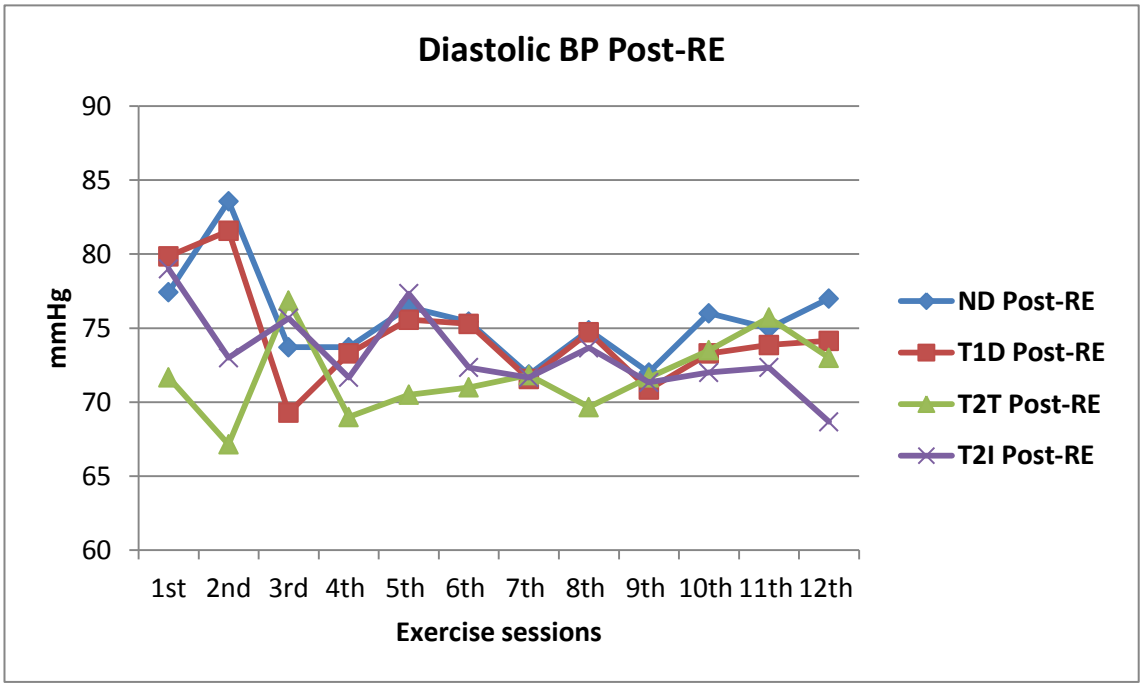

Figure 33: DBP Post-RE across whole trial (12 sessions) for all the study groups (ND, T1D, T2T and T2I).

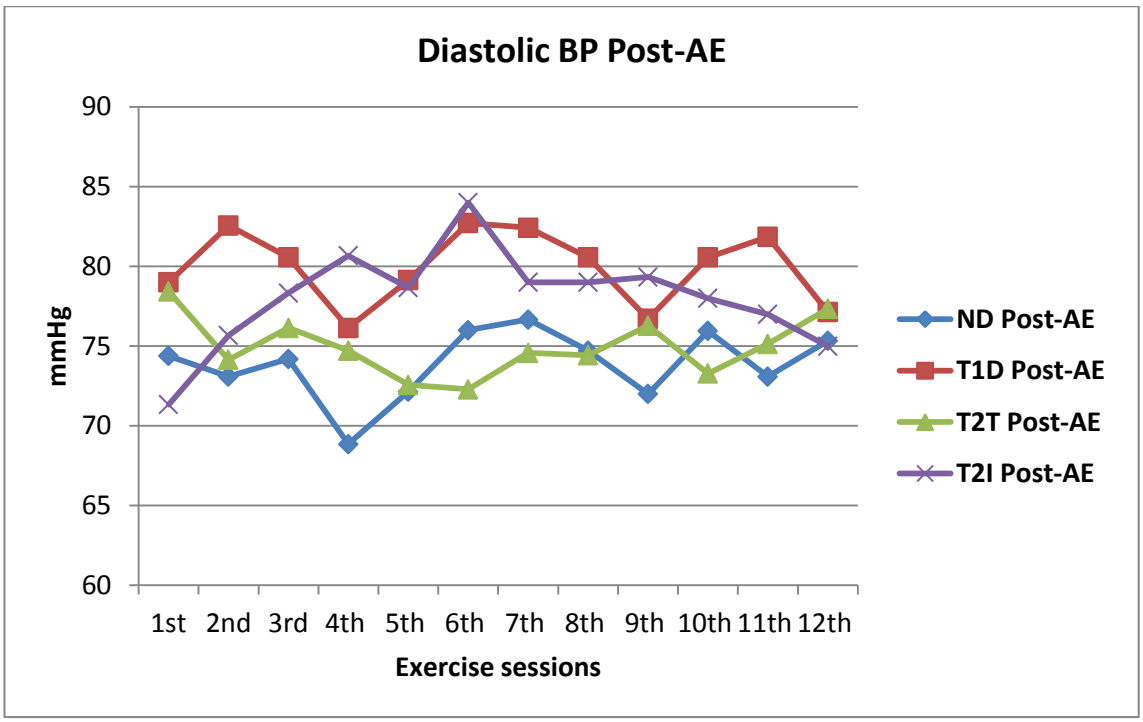

Figure 34: DBP Post-AE across whole trial (12 sessions) for all the study groups (ND, T1D, T2T and T2I).

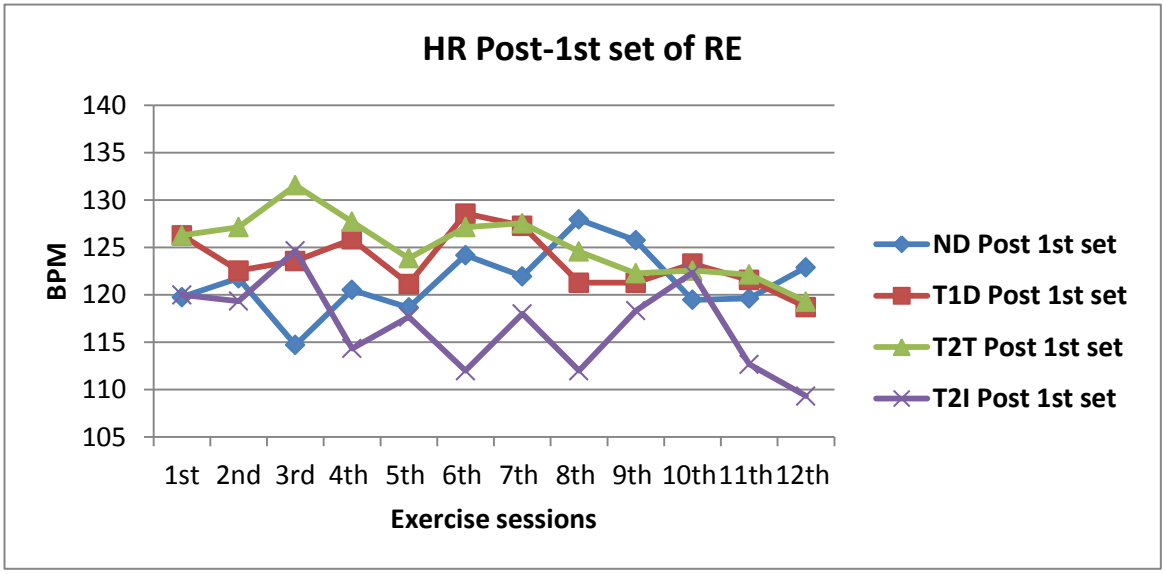

Figure 35: HR Post-1st set of RE across whole trial (12 sessions) for all the study groups (ND, T1D, T2T and T2I).

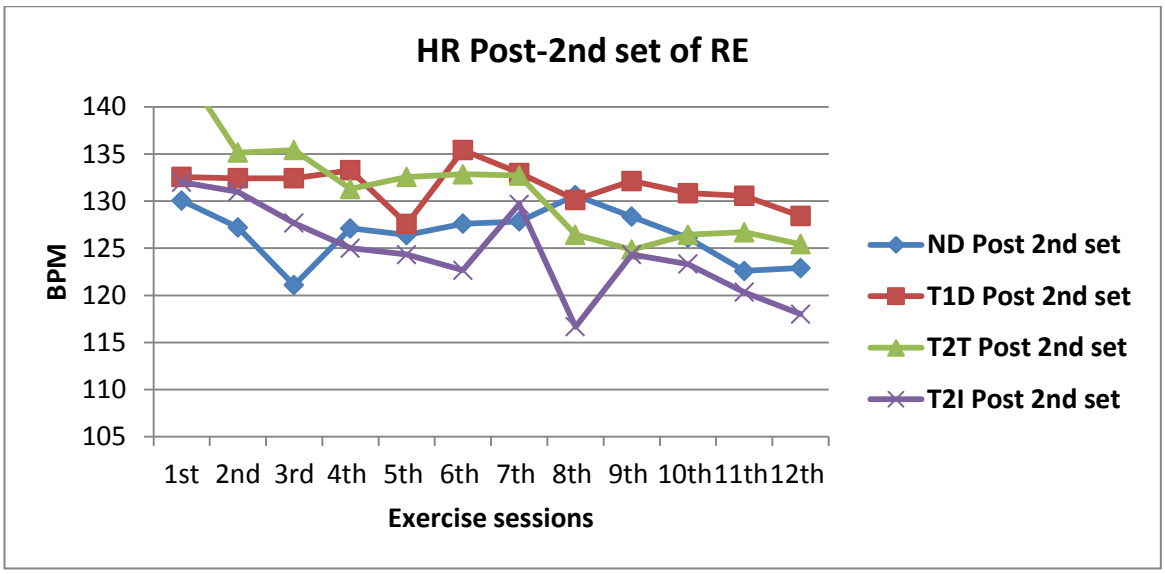

Figure 36: HR Post-2nd set of RE across whole trial (12 sessions) for all the study groups (ND, T1D, T2T and T2I).

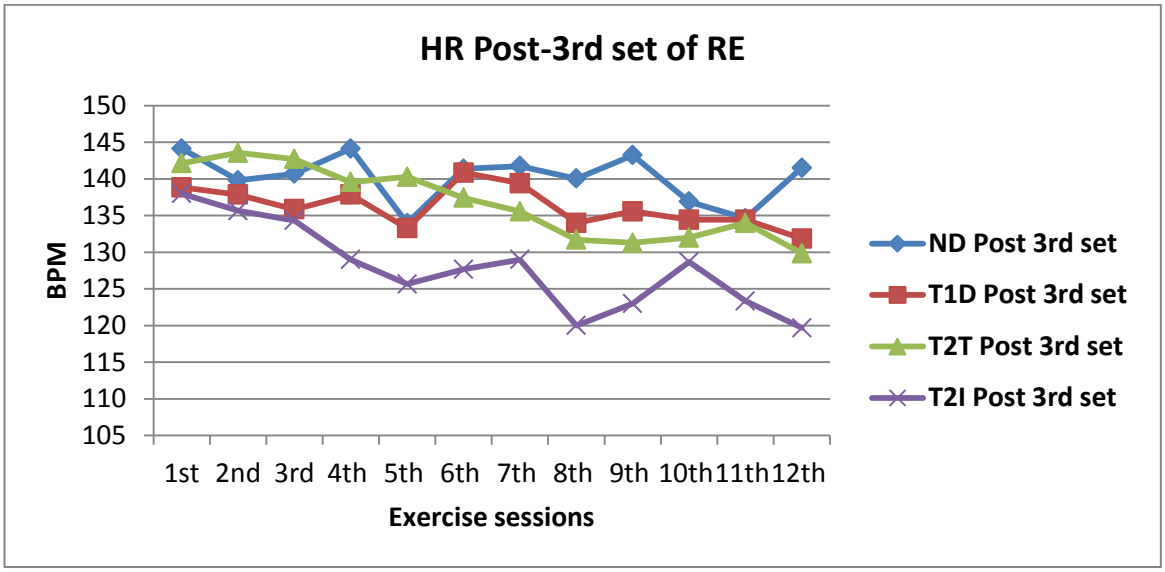

Figure 37: HR Post-3rd set of RE across whole trial (12 sessions) for all the study groups (ND, T1D, T2T and T2I).

5.6.5 Metabolic responses to exercise

5.6.5.1 Glucose control and HbA1c

BG levels during every single exercise session (Pre-Ex, Post-RE and Post-AE) and over the whole exercise trial (12 sessions) have been demonstrated in Figure 39 for ND, Figure 40 for T1D, Figure 41 for T2T and Figure 42 for T2I. Figure 39 shows that all ND volunteers were on the normoglycaemic range (4 – 8 mmol/L), for every session throughout the exercise trial (12 sessions).

There was a slight increase in BG level after RE and this may be due to hepatic production of BG during RE exercise which is fuelled mainly by creatine phosphate (CP), adenosine triphosphate ATP and glycogen, due to a reliance on anaerobic glycolysis. However, it can be seen that after AE at the end of each exercise session BG levels tended to decrease because during moderate to high intensity exercise the source of energy is a mixture of both carbohydrate and fat.

Figure 40 demonstrated that T1D volunteers in every session started in the hyperglycaemic range (8.5 – 10.5 mmol/L) which would indicate poor BG control. Therefore, after the (RE + AE) exercise session most of their BG values had returned to within the normoglycaemic range. These volunteers had deviated from the normal range prior the exercise session using their current insulin regimen. The benefits of exercise showed better glucose management, however T1D have to deal with diabetes on a daily basis, therefore, it is not surprising they would intensively managed their BG, but their insulin regimen was not ideal.

Figure 42 shows that T2I exhibited hyperglycaemic BG (10.5 – 13.5 mmol/L) Pre Ex in almost every session which was higher than T1D. Some of these volunteers must have been exhibiting DKA symptoms on arrival prior to exercise sessions. This group of volunteers have more difficulties with BG management and with their current insulin regimen than T1D. This is not surprising as T2D who inject insulin are usually the most insulin resistant (Lovre, Fonseca 2015). After each exercise session BG value fell in a similar way to the other groups. In most session BG value returned to the normoglycaemic range, highlighting the benefits of the current combined exercise trial.

Figure 41 shows that T2T were above or near the upper high for normoglycaemic range Pre EX, these BG values suggest that they are not as insulin resistant as T2I who displayed much higher BG values at the beginning of each exercise session. This indicate that their insulin resistance is not as prevalence as T2I, and their residual pancreatic activity is still be able to maintain their BG value close to normoglycaemic range. This group T2T would benefit most from the exercise trial as a decrease in insulin resistant could prevent excursion into hyperglycaemia. Therefore, preventing diabetes complications and introducing insulin injections later in their lives.

The present study show that BG level was generally reduced after AE more than RE but not at hypoglycaemia level and this result in consistent with other study by Yardley, Iscoe et al. (2013) who studied the effect of performing RE pre- vs post AE on glucose control in T1D. They had similar reductions in glucose levels during moderate AE when performed after RE, they concluded that performing RE before AE improves glycaemic control (Yardley, Kenny et al. 2013).

Moreover, Guelfi et al 2009, compared the effect of 30 min of moderate AE to 30 min of intermittent high-intensity exercise concluded that the decrease in BG levels was higher with moderate AE compared with intermittent high-intensity exercise in T1D (Guelfi, Jones et al. 2005). As shown in this study the AE is more likely to result in a reduction of BG level than RE. Yardley, Kenny et al. (2012) in agreement with this and they recommend performing AE after RE as in the present study protocol. BG levels are expected to drop steadily by this exercise protocol more than when exercise is performed in the opposite order (Yardley, Kenny et al. 2012).

Figure 38 compares HbA1c values Pre-Ex in the first session with Post-Ex in the last session of the exercise trial (session 12) and this is one of the main findings in the present work. As shown in figure 38, HbA1c values decreased significantly in Post-Ex of 12^{th} session compared to the base line reading before exercise trial (Pre-Ex 1^{st} session) in all the study groups: ND from 5.4-5.2% *or 36-33mmol/mol* ($p < 0.01$), T1D 7.0 to 6.7% *or 53-50mmol/mol* ($p < 0.01$), T2T 7.6 to 7.2% *or 60-55mmol/mol* ($p < 0.05$), T2I 7.3 to 6.8 *or 56-51mmol/mol* ($p < 0.05$).

A decrease in HbA1c level was associated with a 15% - 20% reduction in major CVD episodes and a 37% fall in microvascular complications (Selvin, Marinopoulos et al. 2004, Stratton, Adler et al. 2000). Hence, in this work HbA1c levels showed a significant reduction of 0.3 to 0.5% which could produce a 5% to 7% reduction in CVD risk as well as a 18% reduction in microvascular risks. In contrast, other research has shown that 12 weeks of either RE (8 – 12 repetition of 9 RE) or AE (40 min walk or run) performed 3 times a week by T1D showed no improvement in HbA1c (Ramalho, de Lourdes Lima et al. 2006). In addition, healthy overweight or obese volunteers who have done combined AE and RE at moderate intensity for 30 min, 5 days/week for 12 weeks was reported to produce a no significant changes in BG and insulin after week 8 as well as at week 12 of the combined exercise intervention (Ho, Dhaliwal et al. 2012).

Other study has been conducted on overweight/ obese ND volunteers who participated in 16 weeks of resistance training, showed that there were no statistically significant alterations on BG, HbA1c and insulin (Tibana, Navalta et al. 2013). However, other researchers have investigated the effects of 8 weeks of a combined RE and AE programme in T2T supported the findings from this research study and they reported that, fasting BG and HbA1c reduced significantly ($p < 0.05$) after the combined training programme (Maiorana, O'Driscoll et al. 2002). Moreover, research conducted on the effect of combined RE and AE intervention for 16 weeks on glycaemic control in T2D, demonstrated that HbA1c, BG and insulin were improved significantly after 4 weeks and these variables were further significantly improved after 16 weeks (Tokmakidis, Zois et al. 2004).

Salem, Aboelasrar et al. (2010) reported that 6 months of structured AE and RE exercise improved glycaemic control among children with T1D (Salem, Aboelasrar et al. 2010). Regular physical activity has been recommended to control glycaemia without increasing the risk for severe hypoglycaemia (Herbst, Bachran et al. 2006). Physical activity has provided clear evidence of improved glycaemic control in T1D and T2D patients (Chimen, Kennedy 2012). In 2007 the Diabetes AE and RE (DARE) study, which

compared AE, RE, or both with changes in HbA1c in individuals with T2D. They found a reduction in HbA1c for all exercise groups compared with the control group, with the combination group producing a larger reduction (−1.0%) compared with the RE (−0.4%) and aerobic (−0.5%) groups, so they concluded that AE and RE alone each could result in reduction of glycaemic control. However a combined of AE and RE would be more effective than those of either programme alone (Sigal, Kenny et al. 2007). However, in this study the combination exercise (AE and RE) was performed for a total of 270 minutes (135 minutes for each of AE and RE) per week of exercise, so it is unclear whether the additional benefit observed was due to the combination of AE and RE or to the duration of exercise time. In the present work it could be attributed that the reduction in HbA1c was from the effects of the six week exercise trial, because all the different study groups (ND, T1D, T2T and T2I) had the same intensity and duration of the combined RE and AE exercise regimen.

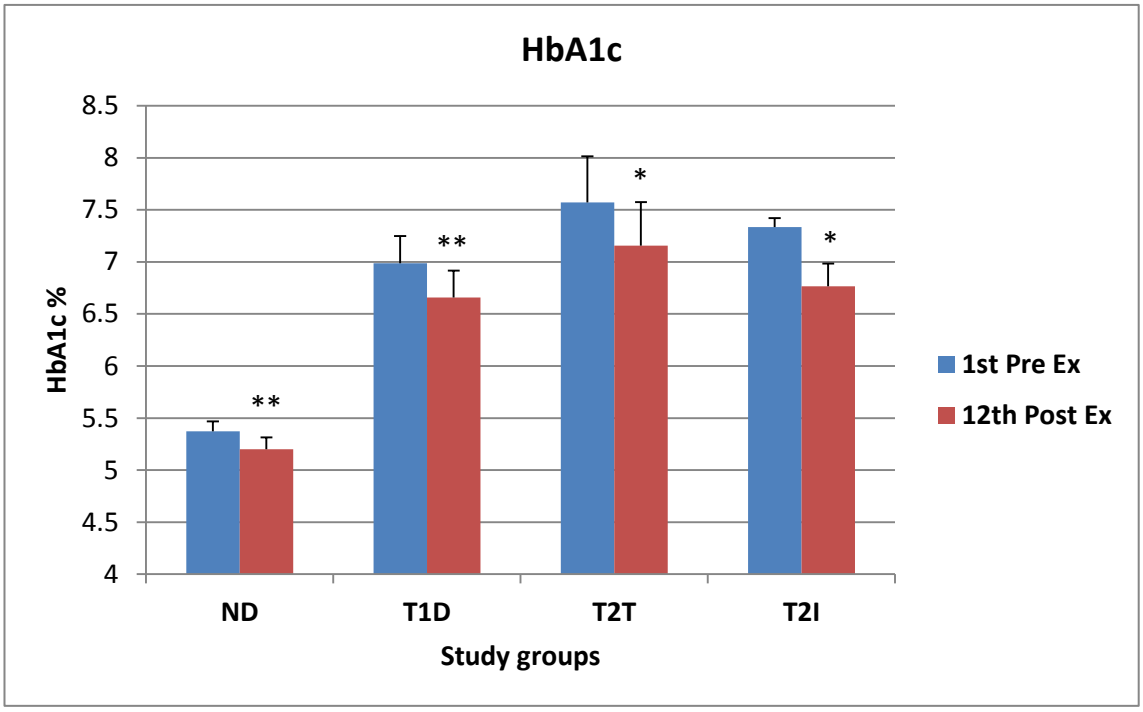

Figure 38: HbA1c levels Pre-Ex (1st session) and Post-Ex (12th session) for all the study groups (ND, T1D, T2T and T2I). Data are presented as Mean ± SEM. (*) P < 0.05, (**) P < 0.01 for (1st Pre-Ex vs 12th Post-Ex).

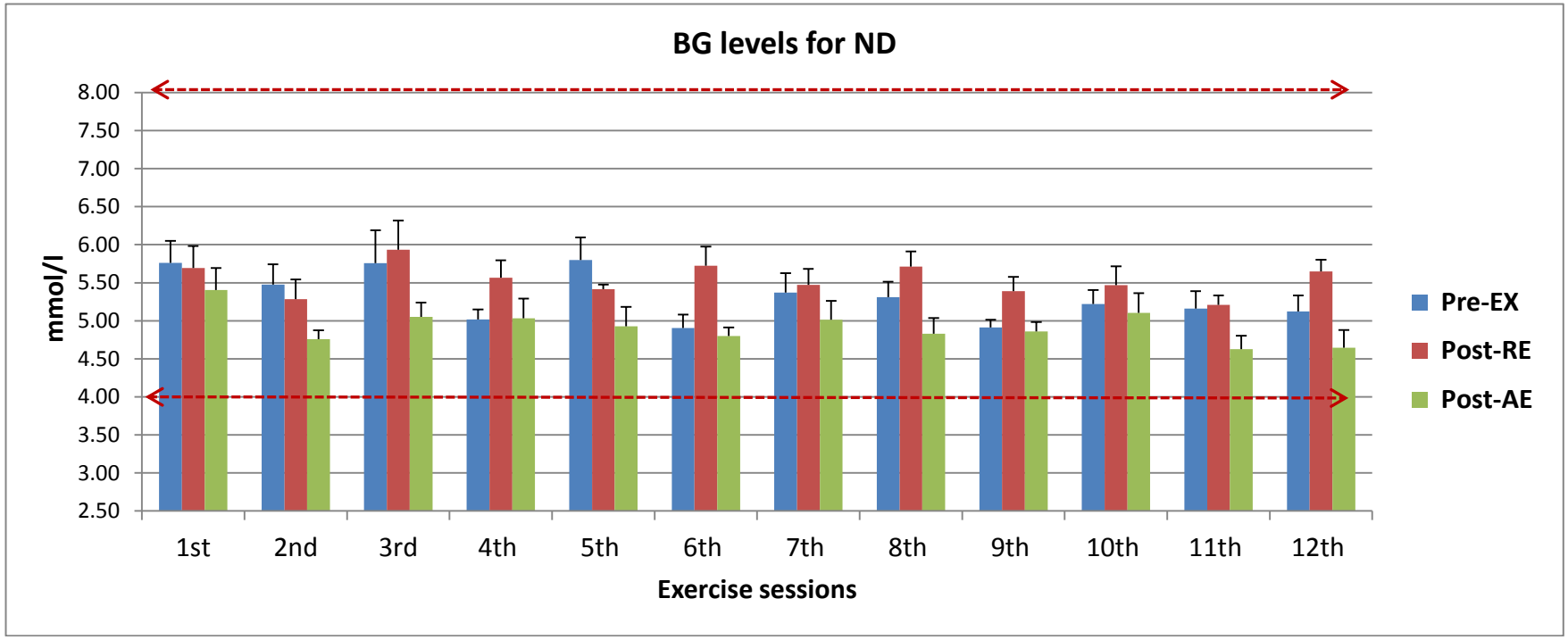

Figure 39: BG levels across the whole exercise trial (12 sessions) for ND volunteers. Data are presented as Mean ± SEM. Red lines indicate acceptable range.

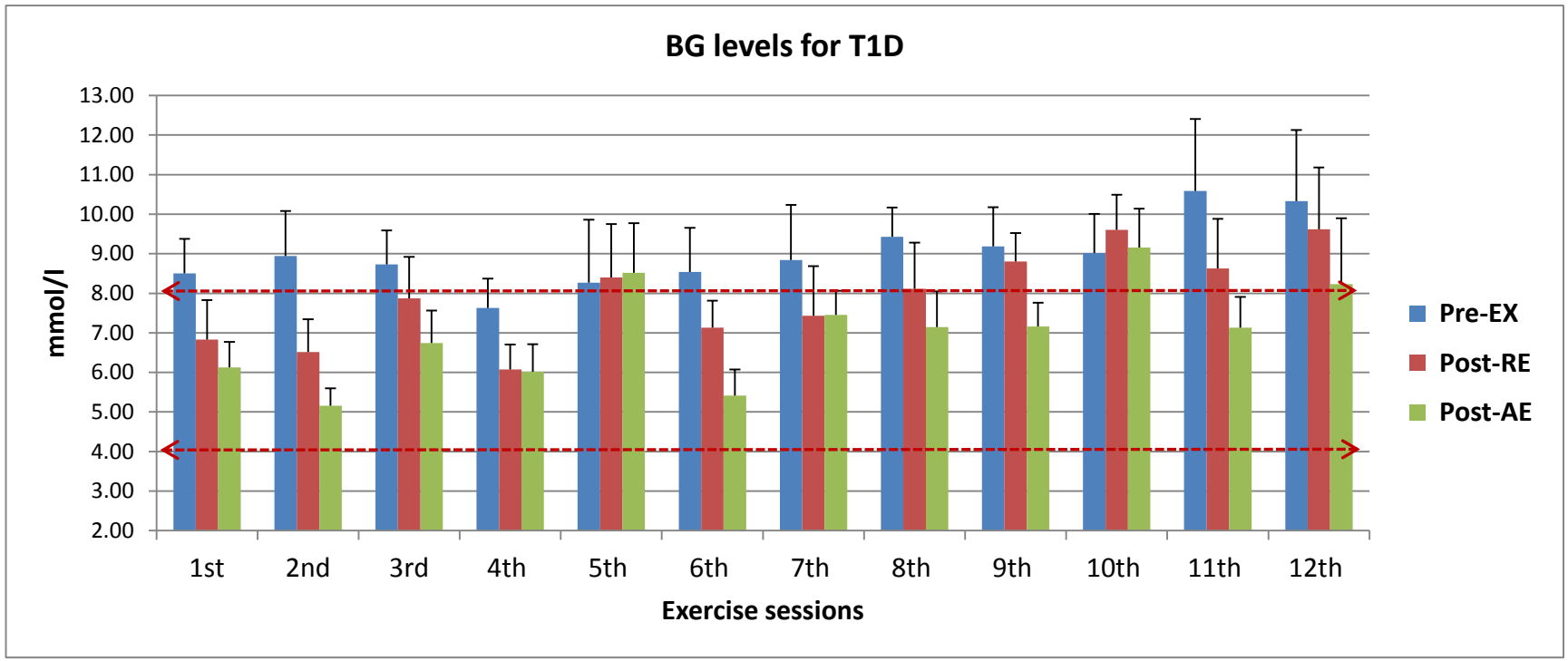

Figure 40: BG levels across the whole exercise trial (12 sessions) for T1D volunteers. Data are presented as Mean ± SEM. Red lines indicate acceptable range.

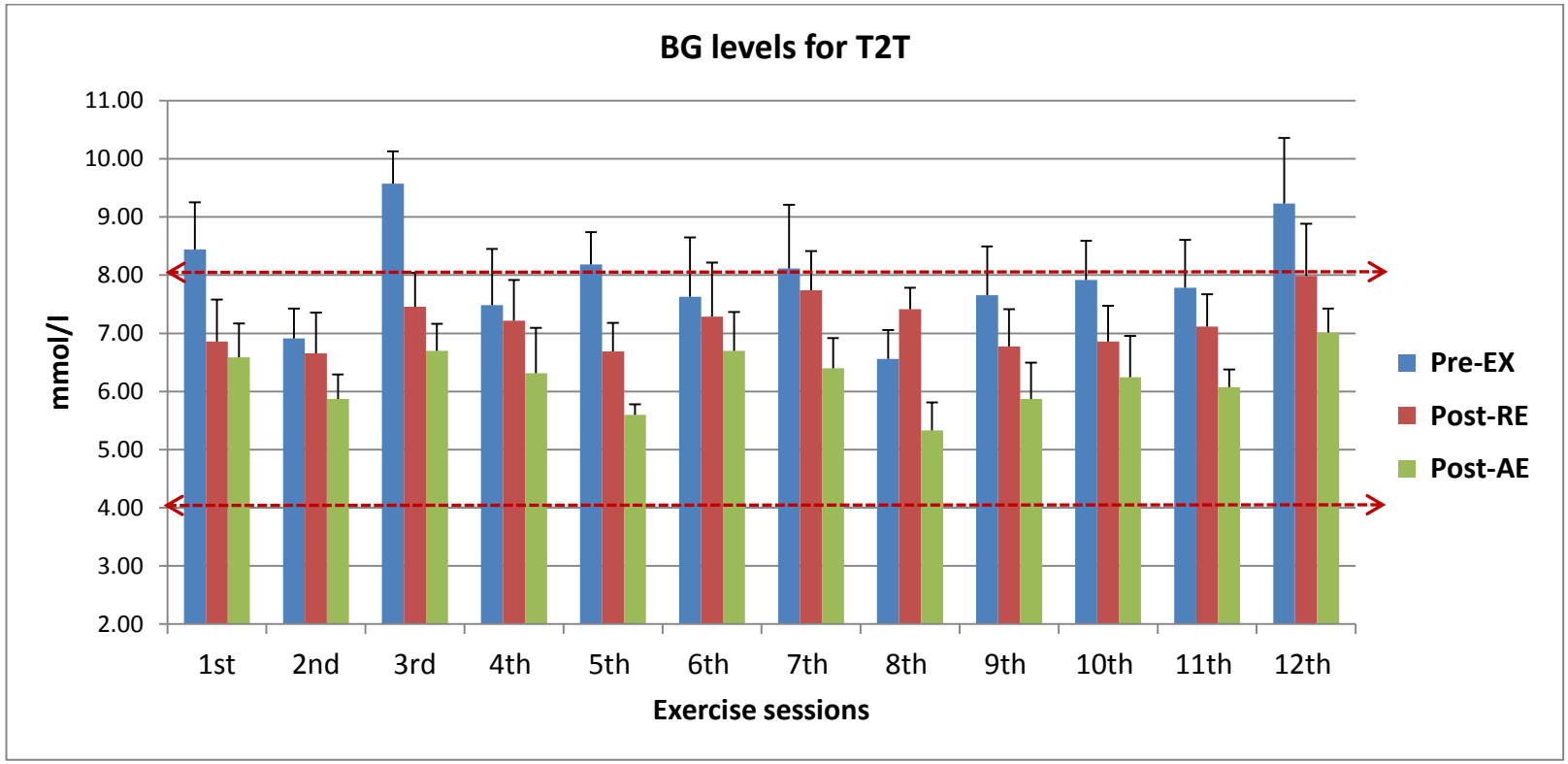

Figure 41: BG levels across the whole exercise trial (12 sessions) for T2T volunteers. Data are presented as Mean ± SEM. Red lines indicate acceptable range.

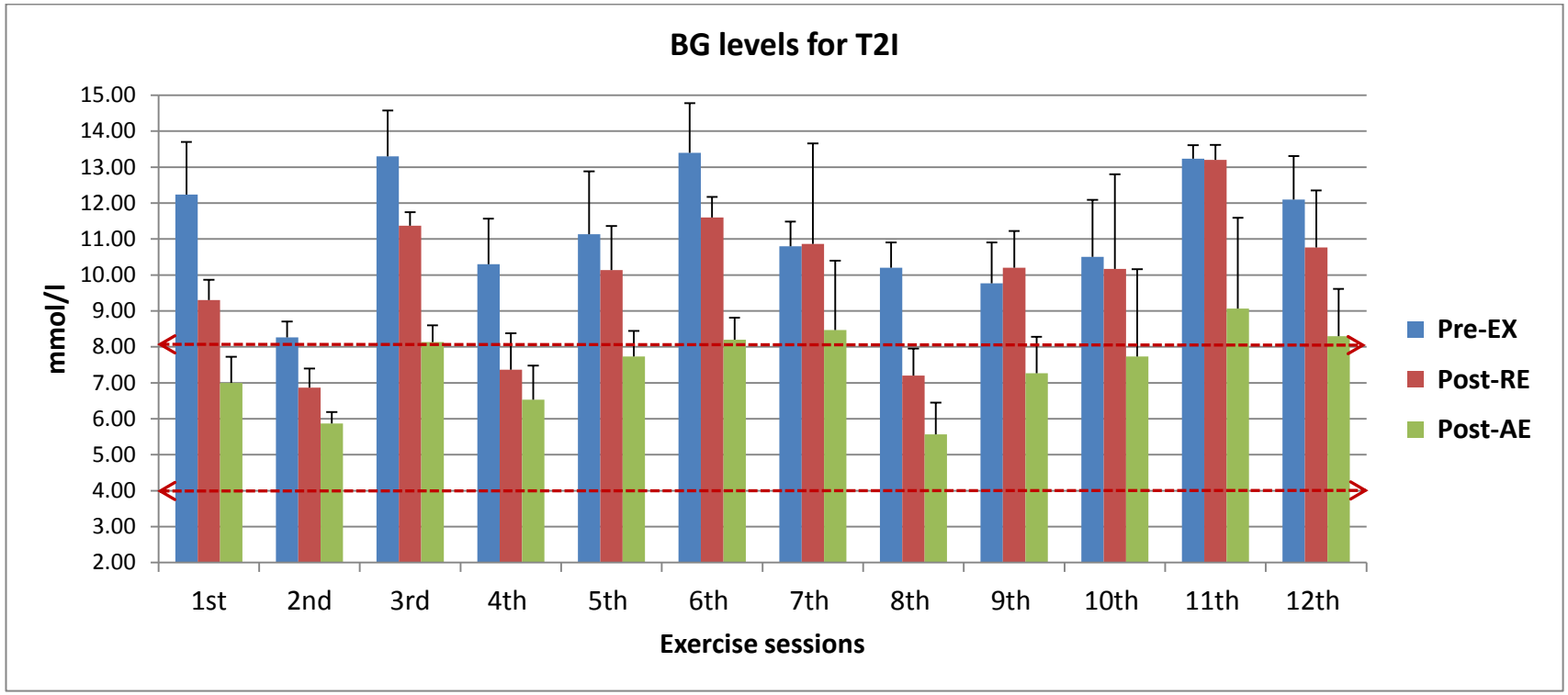

Figure 42: BG levels across the whole exercise trial (12 sessions) for T2I volunteers. Data are presented as Mean ± SEM. Red lines indicate acceptable range.

5.6.5.2 Mean plasma TC responses

Figure 43 shows that mean TC concentrations in all the study groups (ND, T1D, T2T and T2I) were gradually decreased after the 6th session as well as at the end after the 12th session. However, the reduction was not at significant level in ND, T1D and T2I. On the other hand, mean TC levels in T2T were significantly decreased as follows: 1st Pre-Ex = 4.04±0.44 mmol/L, 6th Post-Ex = 3.9±0.36 mmol/L and 12th Post-Ex = 3.7±0.49 mmol/L. Significant levels were 12th Post-Ex vs. 1st Pre-Ex ($p < 0.05$) and 12th Post-Ex vs. 6th Post-Ex ($p < 0.05$).

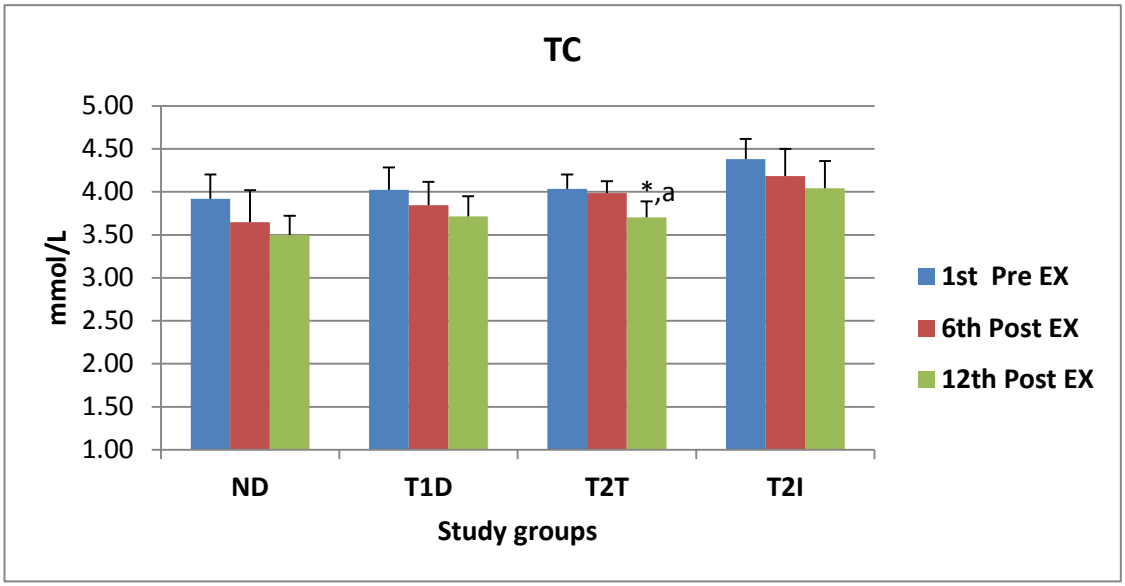

Figure 43: Mean TC levels at three time points (1st Pre-Ex, 6th Post-Ex and 12th Post-Ex) for all the study groups (ND, T1D, T2T and T2I). Data are presented as Mean ± SEM. (*) P < 0.05 for (1st Pre-Ex vs 12th Post-Ex). (a) P < 0.05 for (1st Pre-Ex vs 6th Post-Ex).

5.6.5.3 Mean plasma LDL responses

Figure 44 presents the mean LDL concentrations at 3 different time points throughout the exercise trial (1st Pre-Ex, 6th Post-Ex and 12th Post-Ex) for all the study groups (ND, T1D, T2T and T2I). Mean LDL concentrations were slightly increased after 6th Post-Ex in T1D, T2T and T2I and no change was observed in ND compared to 1st Pre-Ex. However, mean LDL concentrations were decreased at 12th Post-Ex compared to 1st Pre-Ex and 6th Post-Ex but did not reach significant level in ND, T2T and T2I. A significant reduction was observed in T1D from 6th Post-Ex = 1.76±0.77 mmol/L to 12th Post-Ex = 1.59±0.74 mmol/L, with ($p < 0.01$).

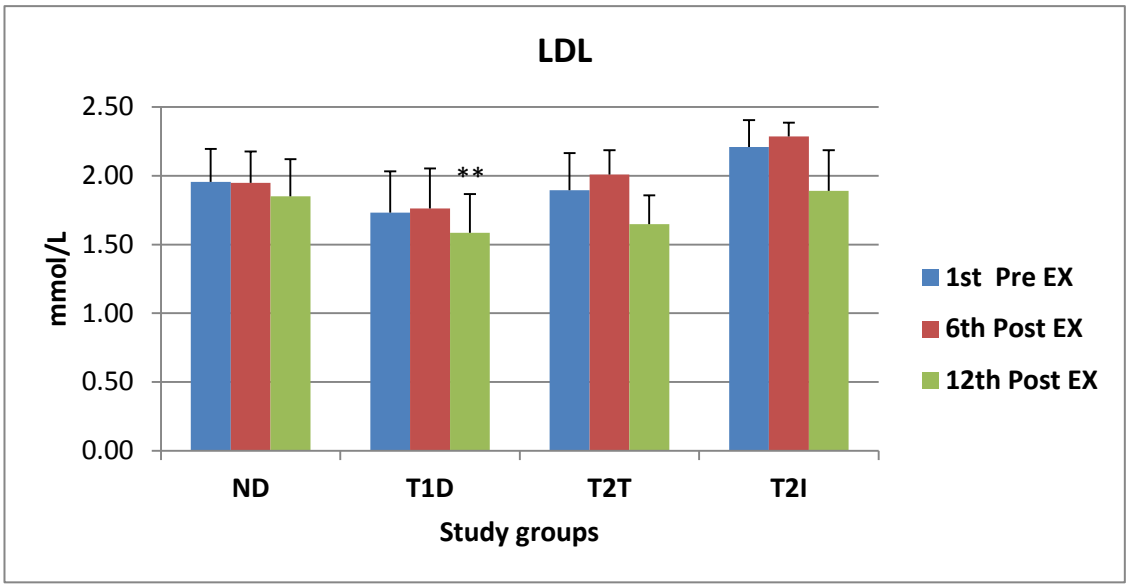

Figure 44: LDL levels at three time points (1st Pre-Ex, 6th Post-Ex and 12th Post-Ex) for all the study groups (ND, T1D, T2T and T2I). Data are presented as Mean ± SEM. (**) P < 0.01 for (6th Post-Ex vs. 12th Post-Ex).

5.6.5.4 Mean plasma HDL responses

Figure 45 compares the mean HDL concentrations at 3 different time points throughout the exercise trial (1st Pre-Ex, 6th Post-Ex and 12th Post-Ex) for all the study groups (ND, T1D, T2T and T2I). Mean HDL concentrations were gradually improved in all the study groups at 6th Post-Ex and 12th Post-Ex compared to 1st Pre-Ex, but not at a significant level in T2T and T2I. However, mean HDL concentrations were increased significantly in ND from 1st Pre-Ex =1.30±0.56 mmol/ to 12th Post-Ex = 1.62±0.51 mmol/L, with ($p < 0.05$), and in T1D from 1st Pre-Ex =1.27±0.50 mmol/ to 12th Post-Ex = 1.52±0.55 mmol/L, ($p < 0.05$).

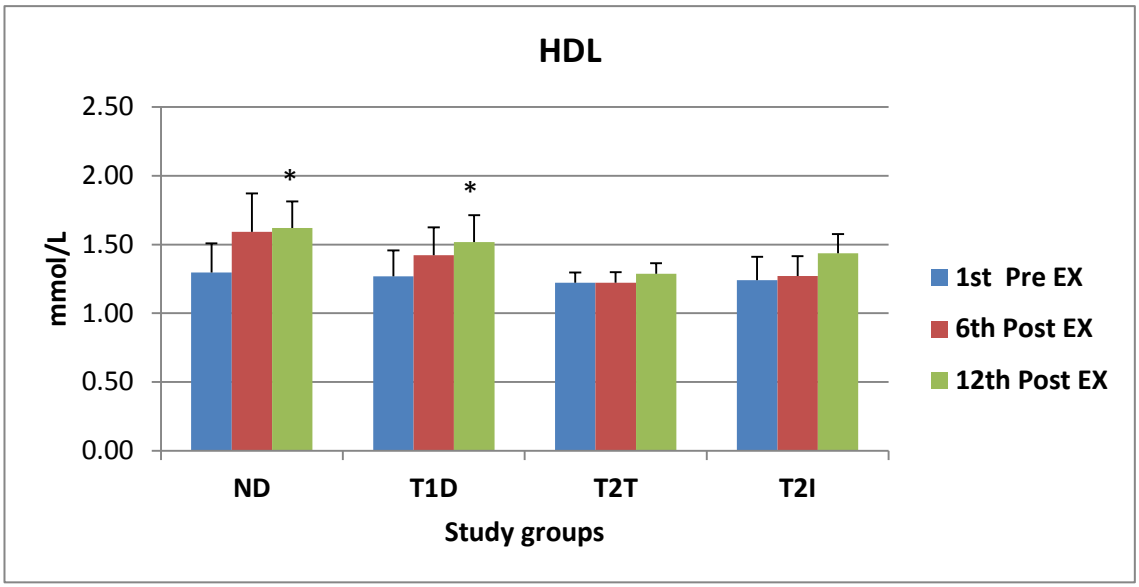

Figure 45: HDL levels at three time points (1st Pre-Ex, 6th Post-Ex and 12th Post-Ex) for all the study groups (ND, T1D, T2T and T2I). Data are presented as Mean ± SEM. (*) P < 0.05 for (1st Pre-Ex vs. 12th Post-Ex).

5.6.5.5 Mean plasma TG responses

Figure 46 shows the mean of TG concentrations at 3 different time points throughout the exercise trial (1st Pre-Ex, 6th Post-Ex and 12th Post-Ex) for all the study groups (ND, T1D, T2T and T2I). Mean TG concentrations were reduced in 12th Post-Ex compared to 1st Pre-Ex, but did not reach the significant level in all the study groups: ND (p = 0.30), T1D (p = 0.34), T2T (p = 0. 26) and T2I (p = 0.96).

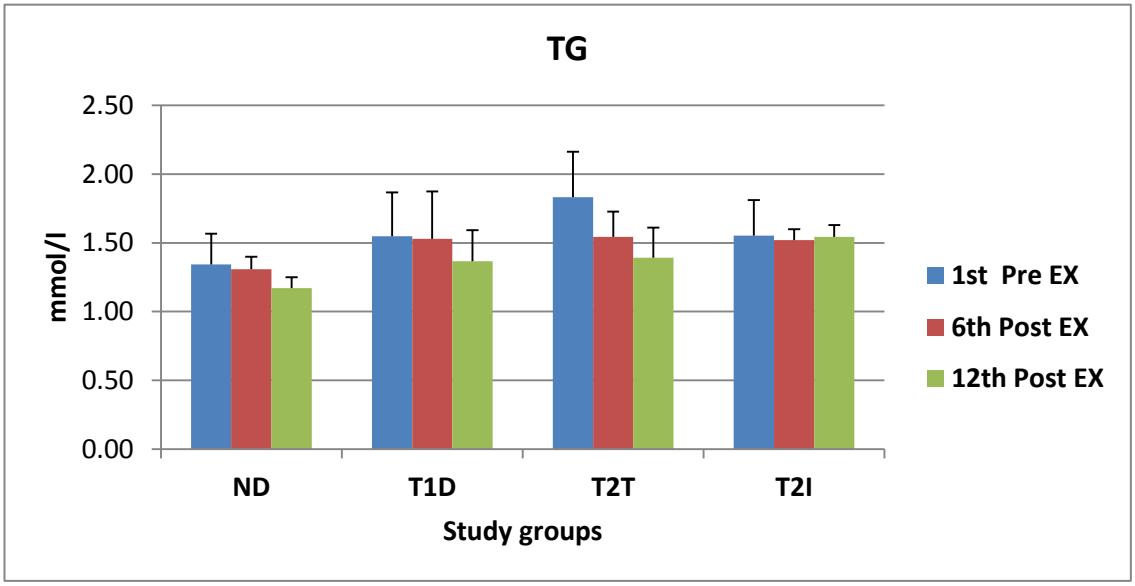

Figure 46: TG levels at three time points (1st Pre-Ex, 6th Post-Ex and 12th Post-Ex) for all the study groups (ND, T1D, T2T and T2I). Data are presented as Mean ± SEM.

All the volunteers from the different study groups (ND, T1D, T2T and T2I) started the exercise trial with well controlled lipid profile, most likely because of the restricted exclusion criteria and high percentage of T2T and T2I volunteers taking medication.

It should be note that during the last few years efforts have been made to simplify blood sampling by replacing fasting lipid profile with non-fasting lipid profile as it has been found that lipids and lipoproteins were not much different in fasting and non-fasting state with the exception of TG which were higher in non-fasting state and all these were associated with cardiovascular risk prediction (Nordestgaard, Langsted et al. 2009). Interestingly, is that non-fasting TG levels may be even better predictor of

cardiovascular risk as compared to fasting TG (Bansal, Buring et al. 2007, Nordestgaard, Benn et al. 2007).

Mean TC, LDL, HDL and TG concentrations were gradually improved at 6th Post-Ex and 12th Post-Ex and were within the normal range for most of the volunteers. As would be expected ND volunteers had normal lipids profile because they were healthy, T1D were younger, and most T2T and T2I were on lipid lowering medication such as statin. Most common lipid abnormalities in T2D are increased plasma TG and low levels of HDL. Controlling lipid profile is very important In ND and even more crucial in T1D and T2D because high lipid profile would lead CVD and diabetes complications. It has been known for decades that exercise and physical activity one of the main cornerstone with medication and diet to treat and manage diabetes and high lipid profiles (Yavari, Najafipoor et al. 2012, Sigal, Kenny et al. 2006).

The findings from the present study in relation to lipid profile (TC, HDL, LDL and TG) are consistent with previous studies such as an exercise study investigated by Yavari et al 2012 and his colleagues who had compared between AE and RE alone or the combination of AE and RE three times per week for 52 weeks in patients with T2D. This study showed that a combination of RE and AE led to reduction in TC, TG, no change in HDL and decreased LDL level close to significant level ($P = 0.07$), (Yavari, Najafipoor et al. 2012).

Other researchers have investigated the effects of 8 weeks of a combined RE and AE programme in T2T supported parts of the findings from this research study and they reported that there was a significant reduction in HbA1c, HR at rest, no significant changes in TC, LDL, and a slight decrease in HDL and TG after the combined training programme (Maiorana, O'Driscoll et al. 2002). It is not surprising that there was a slight change detected in this study as the lipid profile for the volunteers was within the normal range in the untrained state. Similarly, the results in the present work also showed lipid profile prior to exercise well within the normal range, however showed significant improvement in some of the lipids over a shorter time period of six weeks.

In addition, a research study consisted of AE or a combined of AE and RE in obese T2D on diet treatment for 3 weeks, was partially consistent with the present study. Lucotti et al 2011 showed that TC and TG had a significant reduction and slight improvement in HDL after the combined Ex programme compared with no significant changes for the lipid profile with AE only (Lucotti, Monti et al. 2011). In addition, healthy overweight or obese volunteers who have participated in a combined AE and RE at moderate intensity for 30 min, 5 days/week for 12 weeks was reported to produce a no significant improvement of TG, TC, HDL and LDL after week 8 as well as week 12 (Ho, Dhaliwal et al. 2012). Another study has been conducted on overweight/ obese ND volunteers who participated in 16 weeks of resistance training, showed that there were no statistically significant alterations on BG, HbA1c, insulin, TG, and HDL (Tibana, Navalta et al. 2013). In contrast, the present study findings show significant increase in HDL level and decrease in HbA1c for ND; however it is in agreement with no significant change in TG, TC and LDL for ND volunteers.

Sigal et al 2007 investigated the effects of AE, RT and combined (AE + RT) training on cardiovascular risk factors in T2T individuals. Similar to the results of the present study, there was a significant fall in TC, LDL and TG after the combination exercise programme. Changes in body modification were only significantly produced with AE and combined training. After 22 weeks of RE associated with dietetic reduction, there was a decrease of HbA1c while combined training induced a superior decrease on HbA1c compared to only AE or RT (Sigal, Kenny et al. 2007).

Moreover, research on T2T investigated the effect of different modalities of exercise (AE, RE or combined both AE + RE) showed that combined exercise had reduced significantly TC and TG level and did change HDL level. These results in agreement with the findings from the current work with regard T2T (Jorge, de Oliveira et al. 2011). A randomised control trial also examined the effect of different exercise interventions (AE, RE or combined both AE + RE) for 6 months in ND older obese adults. In a study by Davidson et al. 2009, where nutritional intake was strictly controlled and the results obtained could be attributed to the exercise performed and the reduction in nutritional

intake. Improvements were obtained in total abdominal and visceral fat and cardiovascular fitness in both groups studied (Davidson, Hudson et al. 2009).

5.6.5.6 Mean plasma Insulin and C-peptide responses

Figure 47, 48 and 49 shows the acute response of the mean of insulin, BG and C-peptide concentrations, respectively at 3 different time points in the first exercise session (Pre-Ex, Post-RE and Post-AE) for all the study groups (ND, T1D, T2T and T2I). As can be seen from Figure 47 and 48, mean insulin and BG levels were decreased similarly, and no significant changes were observed in ND, T1D and T2I. However, in T2T mean BG level had significantly declined Post-AE compared to Pre-Ex (from 8.2±1.5 mmol/L to 5.6±0.5 mmol/L), ($P < 0.05$). Likewise, in T2T the mean insulin level was significantly decreased Post-AE compared to Pre-Ex (from 42.03±24.8 ulU/ml to 19.29±11.5 ulU/ml), ($P < 0.05$) and Post-RE compared to Pre-Ex (from 42.03±24.8 ulU/ml to 26.9±13.7 ulU/ml), ($P < 0.05$). Figure 49 shows that mean C-peptide levels were reduced Post-RE and Post-AE, which indicate that it had similar responses to exercise as Insulin in ND, T2T and T2I. C-peptide levels were reduced at a significant level Pre-Ex vs. Post-AE, in ND from 2.53±1.2 to 1.61±0.4 ng/ml, ($P < 0.05$) and in T2T from 7.01±3.3 to 4.33±1.9 ng/ml. As would be expected there were very low or almost no C-peptide in T1D. In T2I, mean C-peptide levels were reduced Post-RE and Post-AE, but no significant changes were observed.

Figure 50 and 51 show mean insulin and C-peptide levels, respectively across the whole exercise trial for all the study groups (ND, T1D, T2T and T2I). Insulin and C-peptide levels were decreased after the 2^{nd} session then had similar trend. In general, Insulin and C-peptide levels were decreased in 12^{th} Post-Ex compared to 1^{st} Pre-Ex. BG control depends on neuroendocrine system activities, at rest cellular BG uptake rely on insulin, where the glucose transporter 4 (GLUT-4) is translocated to the cell membrane, allowing glucose to ingress the cell cytoplasm. The presence of GLUT-4 in the cell membrane is magnified with exercise, leading to elevated glucose uptake, even in low insulin concentrations (Krook, Wallberg-Henriksson et al. 2004). Exercise stimulates a fall in BG, which is related to the duration and intensity of the exercise, BG control

before the exercise and state of physical training (Asano, Sales et al. 2014). Higher C-peptide levels are associated with elevated lipid profile and complications such as nephropathy vascular disease in T2D (Mavrakanas, Frachebois et al. 2009). During moderate intensity exercise in ND individual, the rise in peripheral glucose uptake is matched by an equal rise in hepatic glucose production, the result being that BG does not change except during prolonged, glycogen-depleting exercise (Borghouts, Wagenmakers et al. 2002, Burke, Hawley 1999) and this in agreement with the findings from the current study, (Refer to Figure 39).

In individuals with T2D performing moderate exercise, BG utilisation by muscles usually rises more than hepatic glucose production, and BG levels tend to decline (Minuk, Vranic et al. 1981), this support the results from the present study (Refer to Figure 41). The effects of one AE session on insulin sensitivity would be dependent on factors such as duration, intensity, and subsequent diet; a single session would promote insulin sensitivity and glucose tolerance for more than 24 h but usually less than 72 h (Boule, Weisnagel et al. 2005, Cartee, Young et al. 1989). A single bout of exercise increase skeletal muscle BG uptake by enhance insulin clearance in T2D, although the resultant, insulin action after exercise is generally short-lived and disappears after about 48 hours (Hawley, Lessard 2008, King, Baldus et al. 1995). Directly after exercise, glycogen depletion increase BG uptake, which might last for several hours after an acute exercise session with little insulin required (Halse, Bonavaud et al. 2001). Musi et al, 2001 has shown that decline of the insulin concentration was also observed in T2D during a moderate exercise (Musi, Fujii et al. 2001), but not during intense exercise (Kjaer, Hollenbeck et al. 1990).

After exercise a fall in BG when performing AE accompanied by a decrease of insulin and C-peptide level in T2D was reported and in line with the findings from the current study. A reduction in insulin concentration directly after exercise is a desirable phenomenon as it assures better glucose supply (Zajadacz, Skarpańska-Stejnborn et al. 2009).

Insulin and C-peptide are released by β cells in the pancreas in similar amounts; however, a significant proportion of insulin is removed by the liver. Healthy overweight

or obese volunteers who have done combined AE and RE at moderate intensity for 30 min, 5 days/week for 12 weeks were reported to produce a no significant changes in BG and insulin after week 8 as well as at week 12 of the combined exercise intervention (Ho, Dhaliwal et al. 2012). A study has been conducted on overweight/ obese ND volunteers who participated in 16 weeks of resistance training, showed that there were no statistically significant alterations on BG, HbA1c and insulin (Tibana, Navalta et al. 2013). It was concluded that the combination of the RE and AE exercise was the optimal exercise strategy for improvements to insulin resistance and functional limitations (Davidson, Hudson et al. 2009). Moreover, a research conducted the effect of combined RE and AE intervention for 16 weeks on glycaemic control in T2D, demonstrated that HbA1c, BG and insulin were improved significantly after 4 weeks and these variables were further significantly improved after 16 weeks (Tokmakidis, Zois et al. 2004). A combination of AE and RE may be more effective for BG management than either type of exercise alone (Jorge, de Oliveira et al. 2011, Sigal, Kenny et al. 2007).

An increase in muscle mass resulting from RE would promote BG uptake without altering the muscle's ability to respond to insulin. AE enhances this uptake by a greater insulin, despite any changes in muscle mass or aerobic capacity. AE and RE in combination can improve BG control than either form of exercise alone; however, more studies are needed to determine if total caloric expenditure, exercise, duration, or exercise mode are responsible.

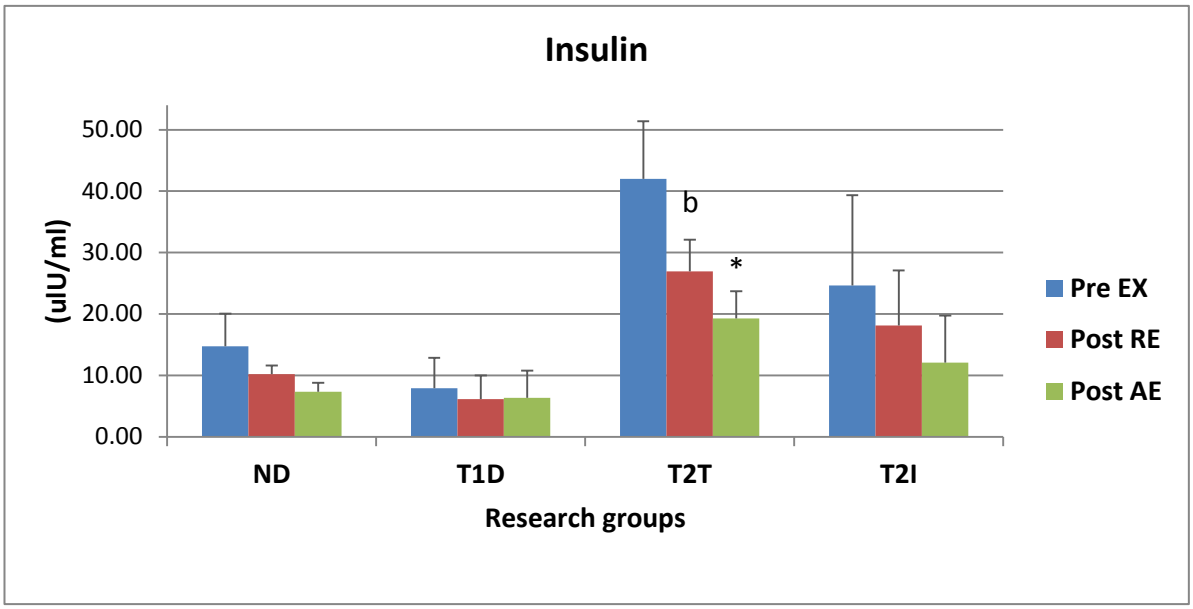

Figure 47: Acute response of Insulin levels to exercise on the first session (Pre-Ex, Post-RE and Post-AE) for all the study groups (ND, T1D, T2T and T2I). Data are presented as Mean ± SEM. (*) P < 0.05 for Pre-Ex vs. Post-AE). (b) P < 0.05 for Pre-Ex vs. Post-RE.

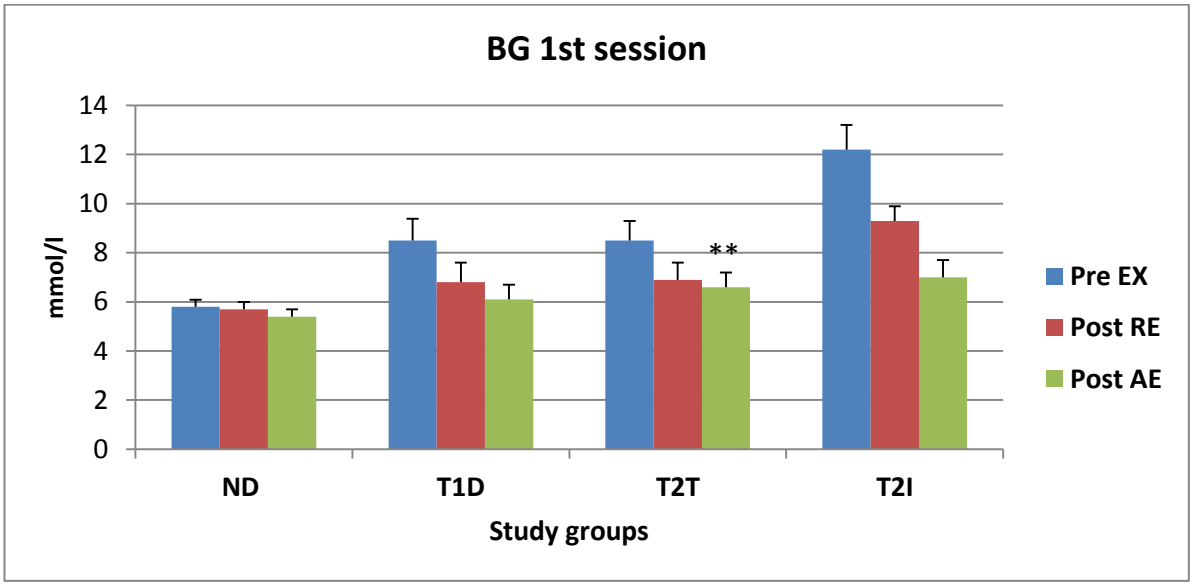

Figure 48: Acute response of BG levels to exercise on the first session (Pre-Ex, Post-RE and Post-AE) for all the study groups (ND, T1D, T2T and T2I). Data are presented as Mean ± SEM. (**) P < 0.01 for Pre-Ex vs. Post-AE).

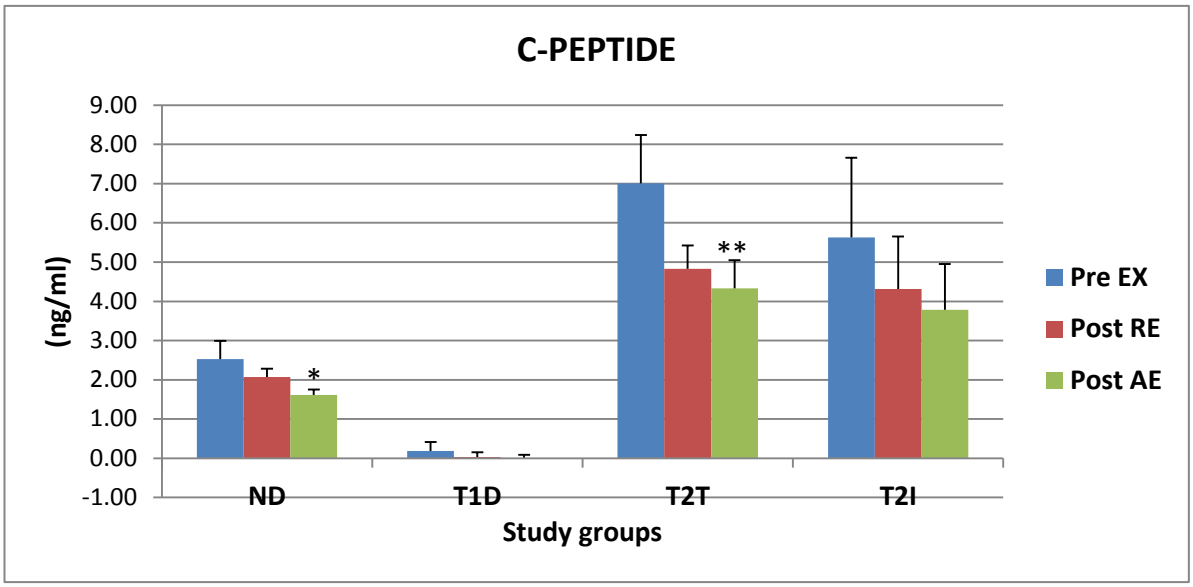

Figure 49: Acute response of C-peptide levels to exercise on the first session (Pre-Ex, Post-RE and Post-AE) for all the study groups (ND, T1D, T2T and T2I). Data are presented as Mean ± SEM. (*) P < 0.05 for (Pre-RE vs Post-AE) (**) P < 0.01 for (Pre-Ex vs Post-AE).

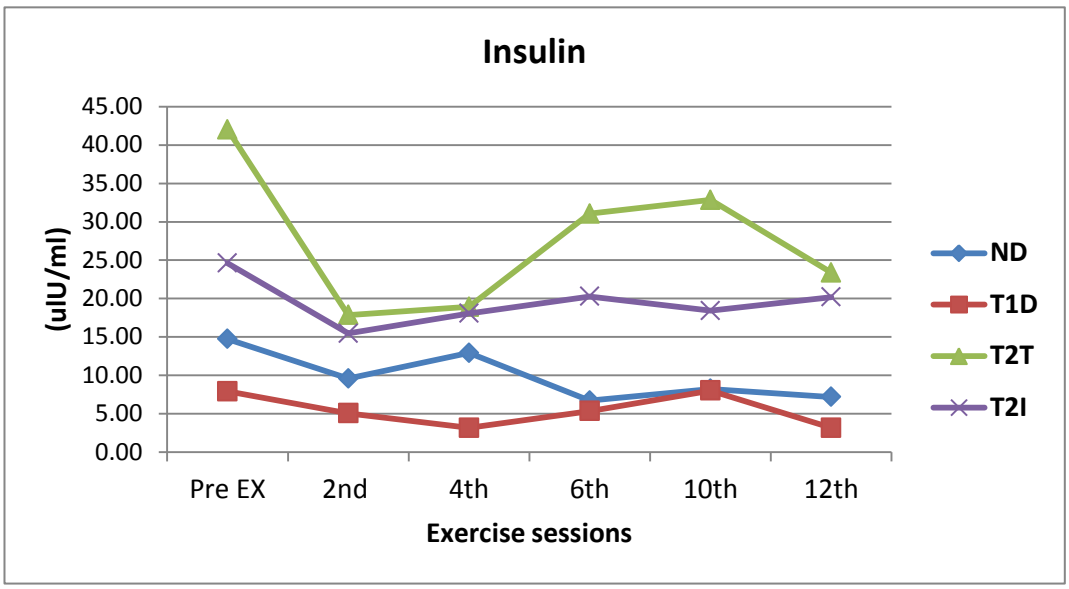

Figure 50: Mean insulin levels across the whole exercise trial for all the study groups (ND, T1D, T2T and T2I).

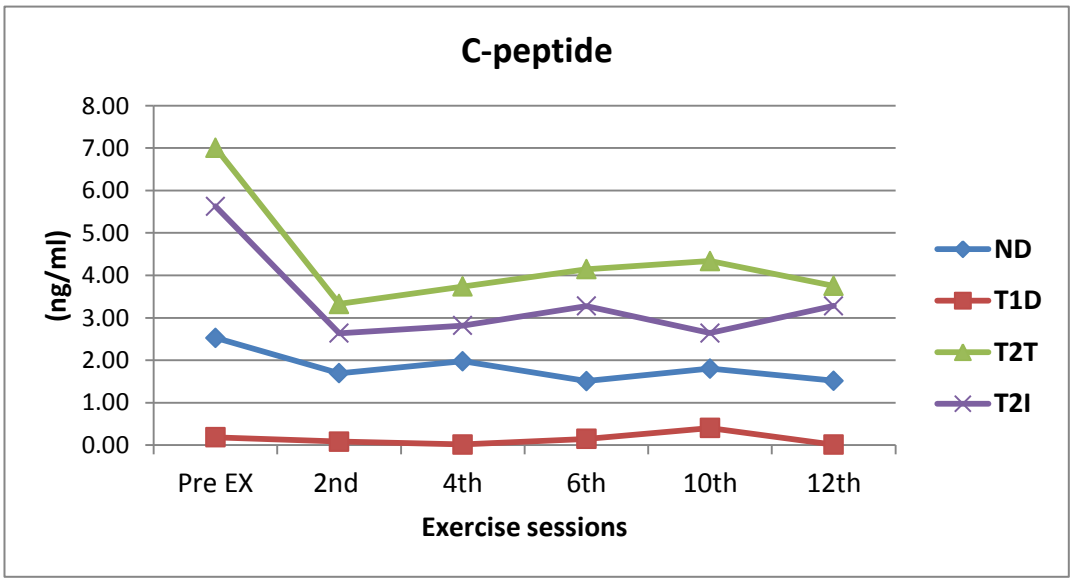

Figure 51: Mean C-peptide levels across the whole exercise trial for all the study groups (ND, T1D, T2T and T2I).

5.7 Conclusion

This work examined the effects of a combination exercise protocol of RE and AE modalities on cardiovascular parameters, objective and subjective assessment of strength, metabolic metrics, as well as glucose and lipid profile in T1D and T2D compared with ND. It is the first study to report significant improvements in aerobic capacity, as well as strength, in T1D and T2D subjects following same combined exercise programme of RE and AE for six weeks.

Resting HR was significantly improved in all the study groups: eg ND from 72.3 to 68.7, T1D from 74.6 to 70.7, T2T from 77.4 to 73.0, T2I 69.7 to 66.0. Similarly both resting blood pressures (SBP and DBP) were reduced.

The protocol minimised local muscle fatigue but the 1RM strength improvement was clear for the five different RE exercises working upper and lower muscle group (Chest, Squat, Back, Biceps and Triceps) in all the study groups (ND, T1D, T2T and T2I). All the volunteers showed significant strength increases ranging from 16% to 75% in all exercises. T2T and T2I had the highest percentage of improvement than T1D and ND.

The RPE data over the 12 week exercise trial period in all the study groups reveals that there has been downward slope in the volunteer's perceived exertion to RE, agreeing with others (Fenicchia, Kanaley et al. 2004).

In addition, HbA1c decreased and can be linked to Increases in muscle mass as skeletal muscle represents the largest mass of insulin sensitive tissue. Glucose was measured by HbA1c while BG was also linked to insulin levels. As shown in Figure 38, HbA1c values were decreased significantly in Post-Ex of 12^{th} session compared to the base line reading before exercise trial (Pre-Ex 1^{st} session) in all the study groups.

Mean Insulin and BG levels were decreased similarly in all groups for the acute phase of both exercise types, significantly in the case of T2T. This was also true for mean C-peptide levels which were reduced Post-RE and Post-AE, indicating similar responses to exercise as Insulin in all groups. Not surprisingly, there were very low C-peptide in T1D while in T2I, mean C-peptide levels were reduced Post-RE and Post-AE as receptors were made more effective when exercised.

The RER readings for all the groups were steady and most of the values were between 0.85 and 1 which indicates that carbohydrates are being predominantly used during the 20 min of AE in all the groups. These results correlate and support the findings from the BG responses to exercise across the whole trial (12 sessions).

The mean TC concentrations in all the study groups were gradually decreased after the 6^{th} session as well as at the end after the 12^{th} session. However, the reduction was not at significant level in ND, T1D and T2I. Mean LDL concentrations were decreased at 12^{th} Post-Ex compared to 1^{st} Pre-Ex and 6^{th} Post-Ex but did not reach significant level in ND, T2T and T2I. A significant reduction was observed in T1D. Mean HDL concentrations were gradually improved in all the study groups at 6^{th} Post-Ex and 12^{th} Post-Ex compared to 1^{st} Pre-Ex, but not at a significant level in T2T and T2I. However, mean HDL concentrations were increased significantly in ND and T1D. Mean TG concentrations were reduced in 12^{th} Post-Ex compared to 1^{st} Pre-Ex. Blood lipids probably relate to body size. In the present study, %BF and waist:hip ratio decreased, body weight did not change and upper and lower muscle strength improved significantly, suggesting that lean body mass increased.

Although the exercise programme here was tightly regimented and supervised for the purpose of documenting its effects, the principles of such a programme should be generally applicable to diabetic subjects able to undertake exercise at a gym or sport centre.

Chapter 6: Effects of acute and chronic combined exercise programme on immune-inflammatory markers in T1D and T2D

6.1 Introduction

A complex interaction between innate and adaptive immune system cells and pancreatic β-cells is considered to be behind the development of T1D (Lehuen, Diana et al. 2010). Insulin resistance and β-cells destruction suggest have a primarily role in the development of T2D. Variation in blood circulation adipokines levels along with other elements produced by adipose cells, develop a significant link between extra adiposity in obesity and both of those factors earlier mentioned (Dunmore, Brown 2013). Obesity and abnormal (visceral) fat distribution increase the risk for metabolic (T2D and dyslipidaemia), cardiovascular (hypertension, CAD, stroke) diseases (Blüher, Mantzoros 2015, Van Gaal, Mertens et al. 2006).

Inflammatory markers released from adipose tissues and other tissues contribute to alteration in the body composition and endocrine gland dysfunction in obesity (Labouesse, Gertz et al. 2014, Prestes, Shiguemoto et al. 2009, Forsythe, Wallace et al. 2008). Some studies have mentioned that there is association between obesity and increases in the levels of TNF-α, IL-6 and CRP inflammatory markers and high risk of CHD (Akbarpour 2013, Bouassida, Chamari et al. 2010, Beavers, Hsu et al. 2010). Cytokines IL-6 and TNFα each play a significant role in the pathogenesis of T2D (Hossain, Faruque et al. 2010, Rodriguez-Caballero, Garcia-Montero et al. 2004). Pro-inflammatory cytokines TNFα and IL-6 might results in deteriorate of the pancreatic β-cells (Donath, Storling et al. 2003). However, chronic effect of exercise induced insulin sensitivity as a result of hypertrophy and replication of the pancreatic β-cells. In addition, GLUT-2 and protein kinase B were significantly increased after regular exercise (Giovanni Vinetti, Chiara Mozzini et al. 2015). Interestingly , IL6 released from skeletal muscle during exercise seems to promote Glucagon-like-peptide 1 (GLP-1) secretion which in turn elicit insulin release (more precisely glucose-induced insulin release) and regeneration of β cells, so In this particular circumstance interleukin acts

as an anti-inflammatory agent. Interestingly is GLP-1 released from α pancreatic cells and not from ileal cells (Ellingsgaard, Hauselmann et al. 2011).

Initially, the function of adipose tissue was thought to be as largest source of energy storage in the body; however, it has become clear that adipose tissue is in fact the largest endocrine organ in the body, secreting hormones and many bioactive substances (adipocytokines) such as IL-6, TNFα , resistin and leptin that are required for normal body function and are found at altered levels in metabolic disease (Poulos, Hausman et al. 2010, Galic, Oakhill et al. 2010). Adipocytokines appear to contribute to inflammation and atherosclerosis and may be involved in the development of T2D, possibly constituting the missing link between obesity and insulin resistance (Havel 2002). Obesity-related insulin resistance is strongly associated with a relative increase in inflammation in adipose tissue. It is suggested that adipocytokines secreted by adipose tissue play a role in the development of obesity-related complications and diabetes. TNFα is one of the major inflammatory mediators secreted by macrophages upon stimulation with pro-inflammatory molecules. Leptin is identified as an adipokine related to the body fat mass and the loss of weight and fat percentage is often accompanied by a decrease in the leptin levels (Koerner, Kratzsch et al. 2005, Sinha, Ohannesian et al. 1996). An increase in the level of leptin is observed in heart diseases and diabetes. Leptin could have impact on glucose metabolism via different actions, such as muscle glucose uptake, liver glucose production and glucagon release by pancreatic α-cells. Leptin suppresses insulin secretion, as well as induces fatty acid oxidation, while insulin promotes leptin release (Park, Ahima 2015).

Resistin is a hormone identified as one of the markers of atherosclerosis and is one of the important predicting factors of CVD (Kadoglou, Perrea et al. 2007). The increase in the level of resistin mostly happens in inflammatory conditions and it is shown that resistin stimulates the synthesis and the release of pre-inflammatory cytokines such as TNFα (Silswal, Singh et al. 2005). The inflammatory cytokines, TNFα and interleukin IL-6 have been associated with insulin resistance, obesity, T1D and T2D. Any improvement in these inflammatory cytokines would improve and decrease the risk factors for some chronic diseases and conditions such as diabetes, obesity and heart diseases (Blüher,

Mantzoros 2015). AE and RE (acute and chronic) have different impacts on inflammatory adipocytokines (Cullen, Thomas et al. 2015, Moran, Barwell et al. 2011, Goldhammer, Tanchilevitch et al. 2005).

It is well-known that a single bout of strenuous or moderate exercise acutely increases systemic IL-6 levels, as well as concentrations of other cytokines such as TNFα (Christiansen, Bruun J. et al. 2013, Pedersen, Steensberg et al. 2001). In acute exercise, IL-6 is released by muscles and the level of IL-6 may increase significantly (Christiansen, Bruun J. et al. 2013, Petersen, Pedersen 2005). Chronic exercise for different duration and intensities reduce the basal level of TNFα, IL-6 , resistin and leptin (Reihmane, Dela 2014, Rashidlamir, Saadatnia 2012, Moran, Barwell et al. 2011).

Exercise has been shown to lower levels of inflammatory markers. However, results are inconsistent, indicating different modes, durations and intensities of exercise may have different effects on inflammatory cytokines. Exercise may lower the risk for coronary heart disease (CHD) by mitigating inflammation.

6.2 Study aims

The purpose of the present study is to examine the effects of one exercise session (acute effect) and 12 sessions (chronic effect) of combination RE and AE exercise on selected immune-inflammatory parameters such as IL-6, TNFα, leptin and resistin in ND, T1D and T2D.

6.3 Volunteers

Four groups of volunteers (n = 25) were involved in this study: ND = 7, T1D = 7, T2T = 7 and T2I = 4. The volunteers were 18-55 years old and not physically active or engaged in any regular exercise or training programmes. Volunteers were recruited and screened as detailed in Section 2.4.2 and 2.5.1.

6.4 Inclusion and exclusion criteria

Subjects who volunteered in this study had to meet specific inclusion criteria as they were defined in section 2.4.1. Further information detailing recruitment response and excluded volunteers can be found in 2.4 and 2.4.2.

6.5 Materials and methods

A brief description of the methods is provided below. Please refer to the methods in Chapter 2 for more detailed description of procedures associated with this chapter.

6.5.1 Experimental design

After the preliminary tests and familiarisation sessions (Section 2.5.1), volunteers participated in the main exercise trial which was a combined exercise session involving stretches, warm up on the bike for 10 min followed by 35 min of RE at 50-60% of 1RM (determined in Section 2.5.1.2). After RE they had 5 min of rest followed by 20 min of AE (cycling) at 50-60% of HRR (Section 2.5.1.3) and finally 10 min cooling down involves stretches (Figure). The chronic exercise programme involved 2 sessions (48 hours apart) for a total of 150 min each week for a 6-week period. Detailed description for the main exercise trial can be found in (see Section 2.5.2).

6.5.2 Blood collection, IL-6, TNFα, leptin and resistin

Venous blood samples were collected from the volunteers in EDTA tubes as described in (Section 2.3.15). It was of interest to investigate the effects of acute and chronic exercise on immune-inflammatry markers IL-6, TNFα, leptin and resistin. Three blood samples were collected from the volunteer at the time points shown in (Figure 52). For the chronic effect, seven blood samples were collected as shown in (Figure 53). IL-6, TNFα, leptin and resistin were determined using ELISA technique by Randox machine (Section 2.3.18).

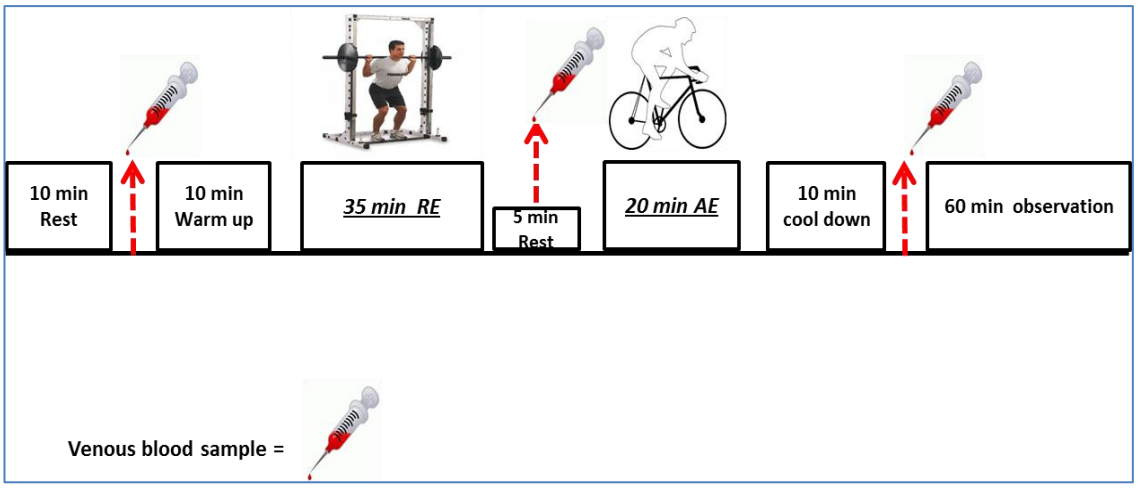

Figure 52: Venous blood samples from the first exercise session (acute effect).

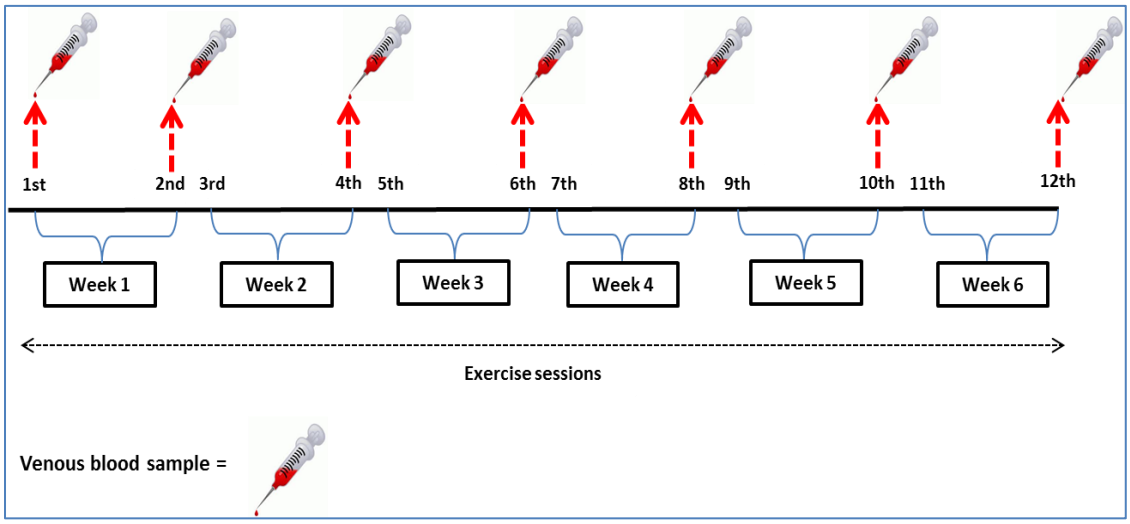

Figure 53: Venous blood samples throughout the exercise trial (chronic effect).

6.6 Results and discussion

6.6.1 Mean plasma IL-6 responses to exercise

Figure 54 shows the acute response of IL-6 concentrations to a single bout of RE and AE exercises, there was gradual elevation of IL-6 concentrations after RE then after AE as well in all the study groups (ND, T1D, T2T and T2I). There were no significant differences between the baseline concentrations Pre EX and Post RE or Post AE, as well as no significant changes detected Post-RE vs. Post-AE in ND, T1D and T2I. However, in T2T a significant increase in IL-6 concentration was detected Post-AE vs Pre-EX (3.67 vs. 1.66 pg/ml) with $p < 0.05$. Table 23 presents the chronic response of IL-6 concentrations across the exercise trial for six weeks (12 sessions) for all the study groups. There were reductions in IL-6 concentrations after the last session (12^{th} Post-Ex) compared to the concentrations at the first session (1^{st} Pre-AE) in all the study groups, but it did not reach the significant levels and can be summarised as follows: ND (from 3.97±4.3 to 2.7±3.0 pg/ml, $p = 0.25$), T1D (from 2.15±1.2 to 1.02±0.2 pg/ml, $p = 0.22$), T2T (from 3.67±0.3 to 2.72±1.4 pg/ml, $p = 0.30$) and T2I (from 3.66±2.7 to 1.17±0.4 pg/ml, $p = 0.22$).

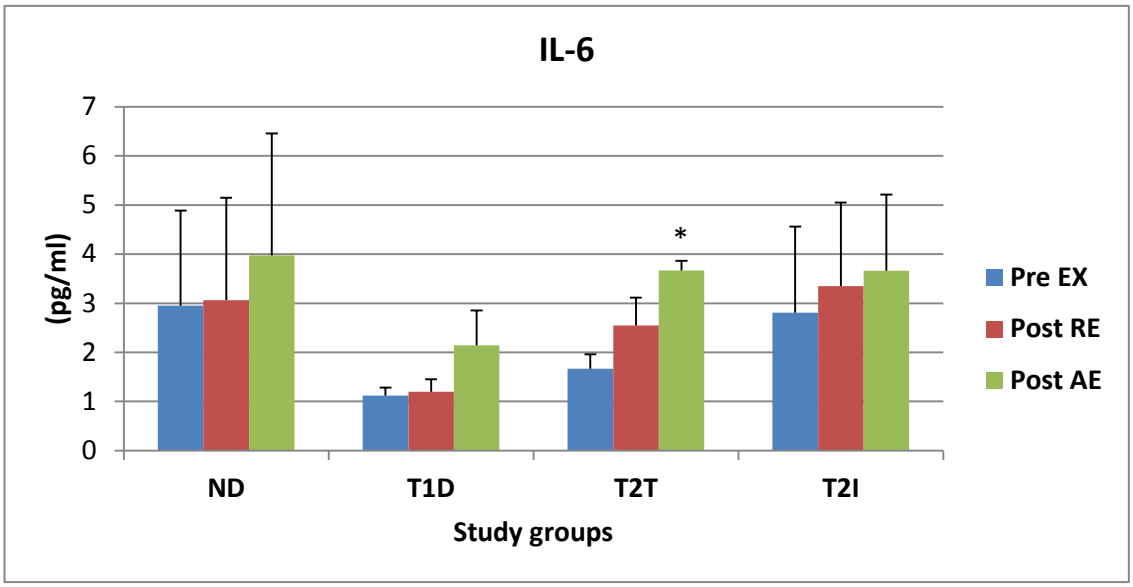

Figure 54: Acute response of IL-6 levels to exercise on the first session (Pre-Ex, Post-RE and Post-AE) for all the study groups (ND, T1D, T2T and T2I). Data are presented as Mean ± SEM. (*) P < 0.05 for (Pre-Ex vs. Post-RE).

Table 23: Mean IL-6 concentrations across the whole exercise trial for all the study groups (ND, T1D, T2T and T2I). Data are presented as Mean±SD. P value is for 1st Post-AE vs. 12th Post-EX.

IL-6	1st Post AE	2nd	4th	6th	10th	12th	P value
ND	3.97±4.3	3.65±3.7	3.59±4.2	4.06±4.8	3.74±3.3	2.7±3.0	0.25
T1D	2.15±1.2	1.50±1.0	1.97±1.0	1.64±0.9	1.56±1.3	1.02±0.2	0.22
T2T	3.67±0.3	4.44±4.3	4.81±4.6	2.19±0.8	2.43±0.7	2.72±1.4	0.30
T2I	3.66±2.7	3.53±3.3	2.17±1.7	1.44±0.5	1.11±0.3	1.17±0.4	0.22

6.6.2 Mean plasma TNFα responses to exercise

Figure 55 shows the acute response of TNFα concentrations to a single bout of RE and AE exercises. There was slight reduction of TNFα concentrations Post RE 3.79±1 pg/ml then Post AE 3.63±0.4 pg/ml as well, in ND compared to the baseline reading Pre Ex 4.15±1 pg/ml. There was a slight decrease in T1D and small increase in T2I after both types of exercise RE and AE. A minor increase Post RE 4.19±1.0 pg/ml has been detected in T2T, however, TNFα level was back close the baseline reading Pre EX 3.74±0.8 pg/ml at the end of the session Post AE 3.93±1.1 pg/ml. None of the above differences were statistically significant. Table 24 presents the chronic response of TNFα concentrations across the exercise trial for six weeks (12 sessions) for all the study groups. There were reductions in TNFα concentrations after the last session (12^{th} Post-Ex) compared to the concentrations at the first session (1^{st} Post-AE) in all the study groups (ND, T1D, T2T and T2I), but it did not reach the significant levels and can be summarised as follows: ND (from 3.63±0.4 to 3.42±0.3 pg/ml, p = 0.5), T1D (from 3.11±2.0 to 2.89±1.6 pg/ml, p = 0.4), T2T (from 3.93±1.1 to 3.56±0.6 pg/ml, p = 0.4) and T2I (from 5.1±1.6 to 4.20±0.5 pg/ml, p = 0.3).

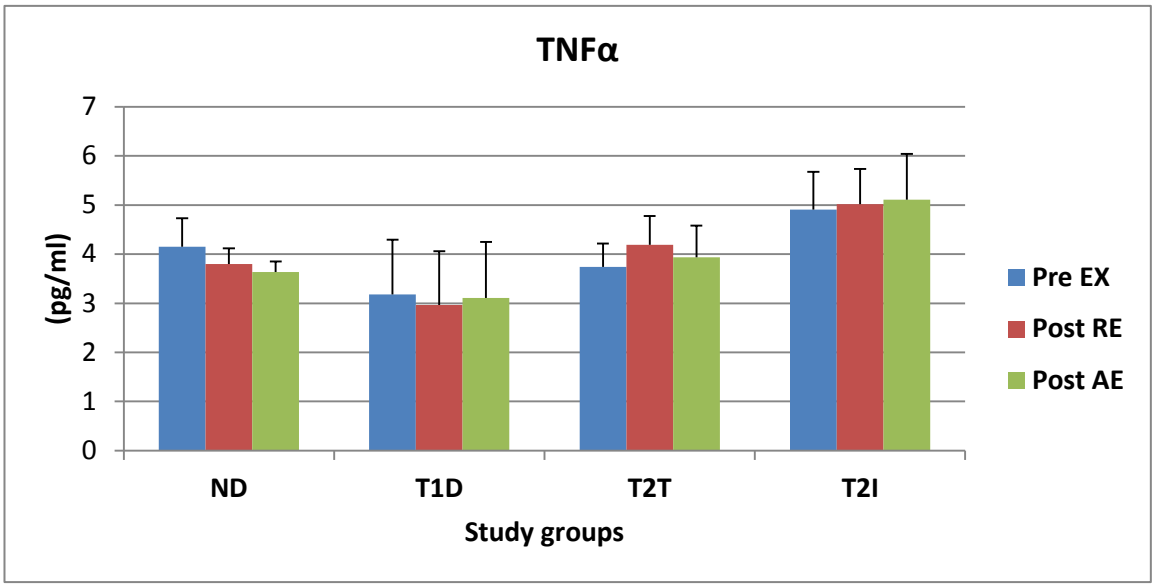

Figure 55: Acute response of TNFα levels to exercise on the first session (Pre-Ex, Post-RE and Post-AE) for all the study groups (ND, T1D, T2T and T2I). Data are presented as Mean ± SEM.

Table 24: Mean TNFα concentrations across the whole exercise trial (12 sessions) for all the study groups (ND, T1D, T2T and T2I). Data are presented as Mean±SD. P value is for 1st Post-AE vs. 12th Post-EX.

TNFα	1st Post AE	2nd	4th	6th	10th	12th	P value
ND	3.63 ±0.4	3.26±0.6	3.52±0.6	3.89±0.8	4.18±0.8	3.42±0.3	0.5
T1D	3.11±2.0	3.45±2.2	3.42±2.1	3.81±2.5	3.14±1.8	2.89±1.6	0.4
T2T	3.93±1.1	4.12±1.0	4.35±0.8	4.09±0.6	4.09±1.0	3.56±0.6	0.4
T2I	5.10±1.6	5.98±2.4	4.35±0.8	4.15±0.8	4.19±0.8	4.20±0.5	0.3

6.6.3 Mean plasma leptin responses to exercise

Figure 56 shows the acute response of leptin concentrations to a single bout of RE and AE exercises. There was slight reduction of leptin concentrations which were non-significant after exercise as follows: ND (Pre Ex = 1.19±0.6 pg/ml, Post RE = 0.92±0.2 pg/ml and Post AE = 0.93±0.3 pg/ml), T1D (Pre Ex = 1.45±0.5 pg/ml, Post RE = 1.19±0.6 pg/ml and Post AE = 1.01±0.6 pg/ml), and T2I (Pre Ex = 1.67±1.0 pg/ml, Post RE = 1.63±1.0 pg/ml and Post AE = 1.49±0.8 pg/ml). Figure 56 shows that In T2T, there was

no change between the two types of exercise Post RE and Post AE as well as the baseline Pre Ex concentrations. No significant differences were found in between the exercises (Post RE and Post AE) and versus the baseline Pre EX in all the study groups (ND, T1D, T2T and T2I). Table 25 demonstrates the chronic response of leptin concentrations across the exercise trial for six weeks (12 sessions) for all the study groups. There were reductions in leptin concentrations after the last session (12th Post-Ex) compared to the concentrations at the first session (1st Post-AE) in all the study groups except in T2T, where leptin level had slightly increased. None of these differences were statistically significant and can be summarised as follows: ND (from 0.93±0.3 to 0.89±0.1 pg/ml, p = 0.9), T1D (from 1.01±0.6 to 0.95±0.4 pg/ml, p = 0.6), T2T (from 1.24±0.5 to 1.33±0.6 pg/ml, p = 0.6) and T2I (from 1.50±0.8 to 1.43±1.0 pg/ml, p = 0.2).

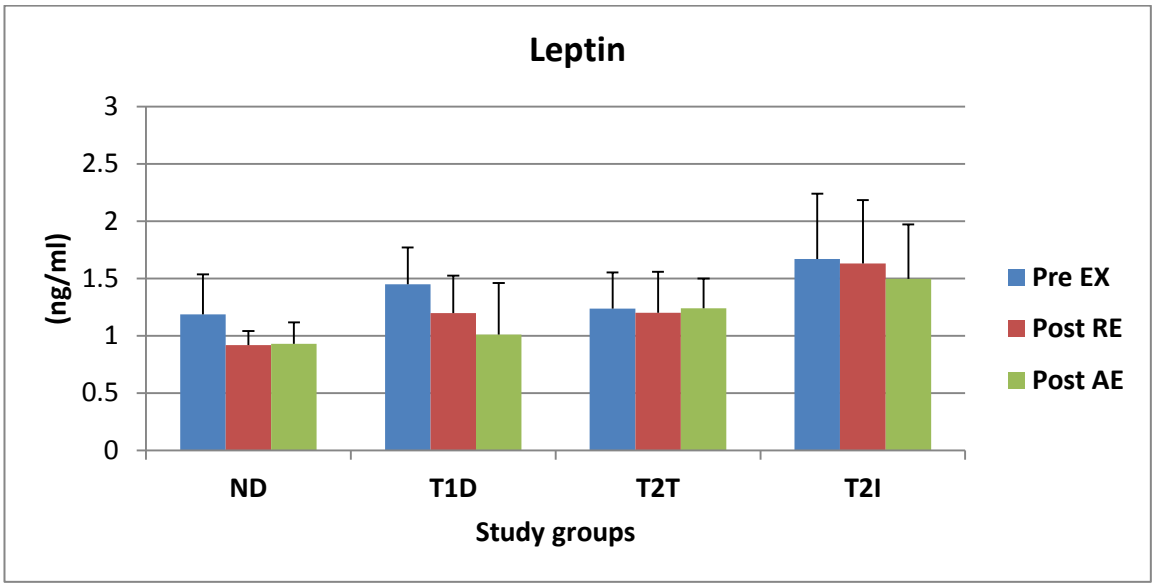

Figure 56: Acute response of Leptin levels to exercise on the first session (Pre-Ex, Post-RE and Post-AE) for all the study groups (ND, T1D, T2T and T2I). Data are presented as Mean ± SEM.

Table 25: Mean Leptin concentrations across the whole exercise trial (12 sessions) for all the study groups (ND, T1D, T2T and T2I). Data are presented as Mean±SD. P value is for 1st Post-AE vs. 12th Post-EX.

Leptin	1st Post AE	2nd	4th	6th	10th	12th	P value
ND	0.93±0.3	0.99±0.1	1.15±0.5	1.44±0.9	1.19±0.2	0.89±0.1	0.9
T1D	1.01±0.6	0.92±0.4	0.95±0.6	0.98±0.5	0.99±0.6	0.95±0.4	0.6
T2T	1.24±0.5	1.36±0.2	1.62±0.6	1.46±0.7	1.53±0.6	1.33±0.6	0.6
T2I	1.50±0.8	1.87±0.8	1.35±0.5	1.49±0.4	1.72±0.9	1.43±1.0	0.2

6.6.4 Mean plasma Resistin responses to exercise

Figure 57 shows the acute response of resistin concentrations to a single bout of RE and AE exercises. There was slight reduction of resistin concentrations have been observed after exercise in ND with no significant differences between the three time points (Pre Ex = 3.11±1.1 ng/ml, Post RE = 2.89±0.9 ng/ml and Post AE = 2.71±0.9 ng/ml). In contrast, as can be seen from Figure 57, with T2I there was a clear trend of increasing in resistin concentrations from Pre Ex = 1.92±0.2 ng/ml to Post RE = 2.06±0.4 ng/ml and Post AE = 2.21±0.4 ng/ml with $P < 0.05$ for Post-RE vs. Post-AE. In T1D, resistin concentrations have increased Post RE = 2.63±1.6 ng/ml compared to Pre Ex = 2.5±1.7 ng/ml and back to the Pre EX level in Post AE = 2.5±1.5 ng/ml. T2T had the same trend of resistin concentrations, it had increased Post RE and decreased Post AE although it was higher than the baseline reading: (Pre Ex = 2.79±0.4 ng/ml, Post RE = 3.42±0.8 ng/ml and Post AE = 3.01±0.8 ng/ml). There were no significant differences in these results for T1D and T2T.

Table 26 compares the chronic response of resistin concentrations across the exercise trial for six weeks (12 sessions) for all the study groups. There were reductions in resistin concentrations after the last session (12th Post-Ex) compared to the concentrations at the first session (1st Post-AE) in all the study groups (ND, T1D, T2T and T2I), but none of these differences were statistically significant and the results can

be summarised as follows: ND (from 2.71±0.9 to 2.56±0.9 ng/ml, p = 0.4), T1D (from 2.50±1.5 to 2.36±1.7 ng/ml, p = 0.5), T2T (from 3.02±0.8 to 2.73±0.6 ng/ml, p = 0.4) and T2I (from 2.21±0.4 to 1.84±0.5 ng/ml, p = 0.1).

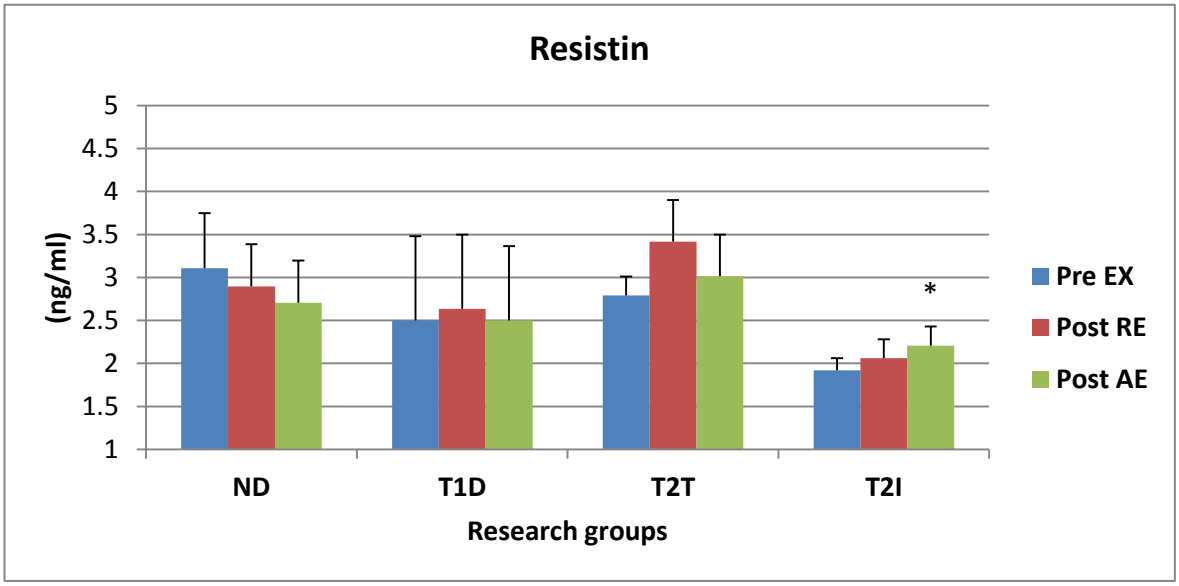

Figure 57: Acute response of resistin levels to exercise on the first session (Pre-Ex, Post-RE and Post-AE) for all the study groups (ND, T1D, T2T and T2I). Data are presented as Mean ± SEM. (*) P < 0.05 for Post-RE vs. Post-AE).

Table 26: Mean resistin concentrations across the whole exercise trial (12 sessions) for all the study groups (ND, T1D, T2T and T2I). Data are presented as Mean±SD. P value is for 1st Post-AE vs. 12th Post-EX.

Resistin	1st Post AE	2nd	4th	6th	10th	12th	P value
ND	2.71±0.9	2.85±0.9	2.50±0.7	2.72±0.8	3.42±2.2	2.56±0.9	0.4
T1D	2.50±1.5	2.90±1.8	2.97±2.0	3.34±2.4	2.53±1.6	2.36±1.7	0.5
T2T	3.02±0.8	2.98±1.0	2.59±1.0	2.88±1.0	3.21±1.2	2.73±0.6	0.4
T2I	2.21±0.4	2.10±0.8	2.18±1.1	1.93±0.8	1.74±0.9	1.84±0.5	0.1

The above results can be favourably compared with the work of others for the preventive and therapeutic effects of exercise in obesity and diabetes. Interestingly,

there have been relatively very few studies where a single exercise regime of AE and RE components has been applied to ND, T1D and T2D volunteers.

The current research has investigated the effects of acute and chronic combined exercise programme (AE and RE) on immune-inflammatory markers in ND, T1D and T2D. Specifically it has tested the hypothesis that exercise (AE and RE) would induce reduction and improvement in resistin, leptin, IL-6 and TNFα.

Exercise suppresses the production of proinflammatory cytokines and enhances anti-inflammatory cytokines. Because proinflammatory cytokines IL-6 and TNFα have cytotoxic actions, it can be proposed that regular exercise prevents further damage to insulin-producing β-cells by attenuating the production of these proinflammatory cytokines (Akbarpour 2013, Jorge, de Oliveira et al. 2011). However, the effects of IL-6 can be complex, as, despite its known proinflammatory effects, it can also promote insulin release and possibly pancreatic beta cell regeneration via activation GLP-1 peptide release from pancreatic α-cells (Ellingsgaard, Hauselmann et al. 2011).

It has been determined that regular physical activity and exercise decrease the levels of inflammatory markers and decrease the risk of CHD (Beavers, Hsu et al. 2010). The results of different researches investigated the effects of regular exercise in diabetes TD1, T2D as well as ND have reported significantly decreases in the levels of TNF-α, IL-6, IL-1β and CRP (Rosa, Heydari et al. 2011, Christiansen, Paulsen et al. 2010, Nicklas, Hsu et al. 2008, Kadoglou, Perrea et al. 2007, Kohut, McCann et al. 2006). There is a relationship between higher levels of physical activity/physical fitness and lower levels of these inflammatory markers (Akbarpour 2013). It has been established that IL-6 can be released locally from contracting skeletal muscle tissue and that the net release from the muscle can account for the exercise-induced rise in arterial concentration of IL-6 (Cullen, Thomas et al. 2015).

Typically, IL-6 is the first cytokine present in the circulation during exercise. The level of circulating IL-6 increases in an exponential fashion (up to 100-fold) in response to exercise and declines in the recovery stage after exercise (Petersen, Pedersen 2005, Suzuki, Nakaji et al. 2002, Pedersen, Hoffman-Goetz 2000, Pedersen, Steensberg et al.

2001). In addition, it has been demonstrated that the IL-6 protein is expressed in contracting muscle fibres (Hiscock, Chan et al. 2004, Penkowa, Keller et al. 2003) and that IL-6 is released (Steensberg, Keller et al. 2002) from skeletal muscle during exercise whereas TNF-α is not released by skeletal muscle during exercise (Febbraio, Steensberg et al. 2003, Steensberg, Keller et al. 2002, Steensberg, Van Hall et al. 2000). The current study found that in both ND and diabetics volunteers, levels of IL-6 consistently increased after moderate RE and AE compared to the baseline levels.

Moderate exercise has major effects on muscle-derived IL-6. In young healthy individuals, 3 hours of dynamic two-legged knee-extensor exercise at 50% of individual maximal power output only moderately increased HR (113 to 122 beats/min), but induced a 16-fold increase in IL-6 mRNA, a 20-fold increase in plasma-IL-6, likely due to marked IL-6 release from working muscle (Fischer, Hiscock et al. 2004).

When the same model was applied in elderly healthy untrained subjects, even higher amounts of IL-6 were released from working muscle during exercise at the same relative intensity (Pedersen, Steensberg et al. 2004). Higher levels of IL-6 are produced in response to acute exercise compared to any other cytokine, IL-6 is released locally in the skeletal muscle as a result of physical exercise, and IL-6 is known to stimulate hepatic glucose production and to provoke lipolysis (Gleeson 2007). Also paradoxically, as mentioned earlier, IL-6 can improve insulin release by stimulating GLP-1 secretion from α-cells (rather than solely from intestinal cells) which in turn have insulinotropic effect and which in diabetes improve β-cells function and regeneration (Ellingsgaard, Hauselmann et al. 2011). These facts suggest that IL-6 could possibly indicate an important link between contracting skeletal muscles and exercise-related metabolic alterations (Pedersen, Steensberg et al. 2001).

Moderate exercise can improve immune function; however, high or extreme exercise might disturb the immune system (Fitzgerald 1988, Liesen, Baum 1997). Evidence suggests that exercise intensity and duration as well as the form of contraction (e.g. eccentric or concentric) and muscle damage all influence IL-6 response to acute exercise (Reihmane, Dela 2014). The current study observation of a reduction in IL-6 with chronic exercise training is consistent with some previously published data from a

longer duration (12 weeks of AE) (Goldhammer, Tanchilevitch et al. 2005) and the current study results mostly not significant due, probably, to small sample size. Furthermore, in accordance with the present results, previous study has demonstrated that resistin and IL-6 concentrations have reduced significantly after 12 weeks of AE in T2T (Kadoglou, Perrea et al. 2007).

TNFα is one of the primary and most basic mediators of inflammatory processes that is highly produced by fat tissues (especially visceral fat) and its levels in the circulation indicates the production of this factor in fat tissues (Beavers, Hsu et al. 2010). There are different findings on the effect of exercise on the level of TNFα; some studies have reported a decrease (Bruun, Helge et al. 2006), and others have shown no change in response to exercise (Marques, Mota et al. 2013). Other research has determined that the serum level of TNFα did not change in response to 12 weeks of AE because the half-life of TNFα was low in the blood (Bruunsgaard 2005). The current study results in partially agreement with Bruunsgaard findings, however with shorter time for six weeks of combined RE and AE showing no significant changes in ND and diabetic volunteers after the exercise trial. Therefore, based on these findings, TNFα cannot be considered a stable marker for inflammation.

A recent study by Ho et al., 2013 investigated the effects of 12-week of RE, AE, or combination exercise programme at moderate intensity and showed a reduction in TNFα and IL-6 in healthy volunteers with obesity or overweight. They found that TNF-α levels were significantly decreased at week 12 compared to baseline by 20.8 % in AE group, 26.9 % in RE group, and 32.6 % in the combination group. Thus, combination exercise may help to reduce the risk of common chronic diseases such as diabetes, CHD and CVD (Ho, Dhaliwal et al. 2013). Furthermore, another study on patients with CAD, reported that a 12 weeks of AE at 70‑80% of individual maximal HR has reduced significantly baseline levels of inflammatory cytokines such as CRP, and IL-6 from 2.50 ±1.50 to 1.44±0.57 pg/ml (Goldhammer, Tanchilevitch et al. 2005).

Moreover, an investigation into the effect of 12 weeks of AE on inflammatory markers of CHD in obese men found decreases in the levels of CRP, IL-6, leptin and BF% and an

increase in the level of adiponectin in the experimental group relative to the control group. In addition, the level of TNFα in the experimental group decreased by 2.86% and 23.76% after 6 and 12-week AE, respectively, although this change was not statistically significant (Akbarpour 2013). These results were in line with the findings of the current study where a combined exercise trial (RE and AE) for six weeks led to a reduction by 19.3% in the level of TNFα in overweight ND, 10.2% in T1D, 4.9% in T2T and 15.4% in T2I and did not reach significant level. It might be that longer period more than (six weeks), for example (12 weeks) or larger sample size would detect significant results. For example, a research group has similarly investigated the effects of AE, RE or a combined of both exercise on inflammatory markers and metabolic control in T2T. They found that 12 weeks of the combined programme was more effective than AE or RE alone and had decreased HbA1c, TC, TG, resistin by 8.11%, TNFα by 11.3% and IL-6 by 3.4% (Jorge, de Oliveira et al. 2011). This result was In agreement with the current study findings with regards T2D which reported that resistin and TNFα had reduced by 2.2%, 4.9%, respectively.

A 12-week exercise intervention resulted in a significant decrease in circulating IL-6, alongside a decrease in visceral adipose tissue and waist circumference, in lean subjects, obese subjects and subjects with T2D who underwent an exercise programme without weight loss (Dekker, Lee et al. 2007). Furthermore, another study compared the effects of 12 weeks of AE to RE in T2T, reported that both AE and RE had decreased TNFα and IL-6. They mentioned that AE was preferable in T2D for controlling insulin resistance, adipocytokines and inflammatory cytokine levels than RE (Abd El-Kader 2011).

Many studies have investigated the relationship between body composition and plasma levels of leptin and adiponectin, and most of the findings have demonstrated a positive relationship between weight, body mass index, waist size, fat distribution (waist/hip ratio) and fat mass on one hand and leptin on the other hand, and a negative relationship between these factors and adiponectin (Bouassida, Chamari et al. 2010, Fu, Luo et al. 2005).

The results from studies investigating single exercise bouts including in T2D, suggest that serum leptin values tend to be unaltered short duration (41 minutes or less), low to moderate intensity exercise, but may be affected by short duration of high intensity exercise (Elias, Pandian et al. 2000, Kraemer, Chu et al. 2002). More convincingly, studies investigating long duration exercise bouts indicate that serum leptin concentrations are reduced with exercise durations ranging from one to multiple hours (Hulver, Houmard 2003). Exercise training protocols that result in reduced fat mass will lower leptin concentrations, thus, most investigators have reported lower leptin concentrations after accounting for fat loss.

Exercise training-induced reductions in leptin levels have been attributed to alterations in energy balance, improvements in insulin sensitivity, alterations in lipid metabolism, and unknown factors (Kraemer, Chu et al. 2002) and similar effects have been noted in diabetic subjects (Blüher, Mantzoros 2015, Hayashino, Jackson et al. 2014, Moran, Barwell et al. 2011, Sandoval, Galassetti et al. 2003). A common concept regarding the pathophysiological mechanisms of inflammation associated with atherosclerosis is the production of cytokines with inflammation in response to oxidised LDL stimulation and macrophages along with atherosclerotic plaques (Nicklas, Beavers 2010). It was determined in laboratory experiments that different combinations of cytokines stimulate the production of CRP and leukocytes (Akbarpour 2013). The anti-inflammatory effect of regular exercise may prolong the life of islet cells and empower them to produce insulin for a much longer period (Akbarpour 2013, Ellingsgaard, Hauselmann et al. 2011).

Research has shown that participation in regular sport activity decreases the level of oxidised LDL and the serum levels of IL-6 and CRP (Nicklas, Beavers 2010). Therefore, the effect of regular exercise on the levels of IL-6 may be responsible for the decrease in CRP in the experimental groups. In contrast, the relationship between physical activity and lower levels of inflammation can be created through the relationship between endurance training and lower degrees of general and abdominal obesity. It has been found that obese people produce higher levels of leptin and mediators of inflammation including , IL-8 and IL-6, compared with volunteers who have normal

weight in the control group, whereas obese volunteers have lower levels of adiponectin compared with ideal BMI volunteers (Jorge, de Oliveira et al. 2011, Fu, Luo et al. 2005, Jacobi, Ajuwon et al. 2004). In addition, TNFα is one of the primary and most basic mediators of inflammatory processes that is related to the high level in fat tissues (especially visceral fat) and its levels in the circulation indicates the production of this factor in fat tissues (Beavers, Hsu et al. 2010). There are different findings on the effect of exercise on the level of TNFα; some studies have reported a decrease (Bruun, Helge et al. 2006), and others have shown no change in response to physical training. Clearly this reflects the parabolic profiles as shown for several inflammatory markers after exercise (Petersen, Pedersen 2005).

Exercise decreases inflammatory cytokine (and IL-6) in patients with T1D and T2D. Exercise could be a therapeutic option for improving abnormalities in inflammation levels in patients with diabetes.

Combined RE and AE exercise training in patients with diabetes is an effective means of inducing reduction in IL-6, TNFα levels, thus, possibly improving coronary risk profile.

According to the results of this study, regular combined (RE and AE) exercise trial may be physiologically relevant in decreasing the potential risk of CVD, diabetes complications by improving the plasma levels of IL-6, TNFα, resistin and leptin. Additionally, combined RE and AE exercise trial can be used as effective non-pharmacological treatment to manage or prevent some chronic diseases such as diabetes.

Chapter 7: Conclusion

Aside from the serious personal consequences, the cost of diabetes and its complications equates to about £1m/h, but the effects of exercise are so beneficial that as a prescribed treatment, it could reduce both risk and cost.

The results from the first survey showed that current treatment and management of diabetes care poses difficulty for T1D and T2I diabetes patients and further improvement is required in their health provision. The second survey showed that patients from all the groups who did not exercise were most likely to have a HbA1c over 8% (64mmol/mol) in comparison with those who performed exercise on a regular basis. Type 2 respondents are more at risk because those with T2T and T2I exercised less compared with T1D group.

T2I users who test only once a day, as found in survey 2, form a large minority who are at risk because they are unlikely to be managing their daily calorie intake without more frequent information. This would have an impact on their HbA1c values and suggests poor attitude and/or support but hypoglycaemia and diabetic complications are dual hazards for these people. T2D people need the same intensive intervention and encouragement as T1D and also early diagnosis to counteract the insidious but dangerous course of their condition. In the exercise practical study, the HbA1c values decreased significantly in Post-Ex of 12th session compared to the base line reading before exercise trial (Pre-Ex 1st session) in all the study groups, indicating how diabetic people respond to exercise to reduce their overall risk. Mean BG, insulin and C peptide levels decreased similarly after RE and AE, for all the study groups indicating the increased efficiency of tissue responses.

Data from RER readings for all the groups were steady and most of the values indicated that carbohydrates was the predominant substrate during the 20 min of AE in all the groups. All the volunteers showed significant muscular strength improvement for the five different RE exercises working upper and lower muscle group (Chest, Squat, Back, Biceps and Triceps) as represented by 1RM. T2T and T2I had a higher percentage

improvement than T1D and ND. RPE data correlated well with the objective assessment. Increase in muscle mass correlates well with strength and also with glucose transfer into cells and thus with increasing sensitivity in both types of diabetes. Exercise that includes RE is therefore important and supports the idea of combined protocols.

Risk reduction is also clear from the mean TC, LDL and TG concentrations in all the study groups were gradually decreased after the 6th session as well as at the end after the 12th session. Mean HDL concentrations were gradually improved in all the study groups after the exercise programme. All study groups demonstrated that resting HR and blood pressure were significantly improved after six weeks of the exercise programme, so that lipids and cardiovascular efficiency are both positive outcomes delivered in exercise for diabetes.

Regular combined (RE and AE) exercise trial is physiologically relevant for improving the plasma levels of IL-6, TNFα, resistin and leptin and for improving abnormalities in inflammation levels in patients with diabetes.

Chapter 8: Limitations and Future work

Limitations

The main limitation was sample size. The target number of volunteer was to recruit 60 subjects: 20 T1D, 20 ND, 20 T2T and 20 T2I. However, fewer were recruited in all groups and because T2I were rarer who fulfilled the exclusion criteria.

Several were rejected in this process. Greater volunteer numbers and even sized groups would have improved the confidence in the comparison of the study groups (ND, T1D, T2T and T2I). On reflection, NHS ethical approval would have increased the pool of possible recruits and although NHS ethical approval can take more than a year, it would have been worth doing.

Future work

This project has opened the door to the objective assessment of combined exercise as a prescribable programme to treat diabetes without necessitating extra pharmacological input. Several variables were studied but others have become attractive targets that can improve and extend the study area. For example, the period of exercise was short (6 weeks with 12 sessions) but could be extended to 12 weeks so that meaningful HbA1c changes could be monitored. In addition, the changes in the resting, fasted metabolic rate (the resting energy expenditure, REE) were not assessed in this study as a baseline where the reading is taken for 20 minutes in the recumbent position at the start and finish of the study. Measurement of insulin sensitivity by Oral Glucose tolerance test OGTT would be useful to drill down on calorie use, with calculations using suitable indices such as the Matsuda Index.

The team is interested in performing the exercise programme with AE prior to RE to assess any differences within the study groups and could also look at the variation in the intensity of exercise performed. In this connection, as the study is expanded, the more extended screening of cytokines and other inflammatory and metabolic markers could be undertaken economically (in terms of cost and time), using suitable multi-array immunoassay equipment as at the latter part of this PhD project. Many projects

could be built on the basis of this one, but the re assessment of volunteers throughout a three year period to study physiological and immunological over the long term is particularly important as it is known that continuing support is needed for diabetic people.

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Appendices

(Appendix 1)

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DE MONTFORT UNIVERSITY
LEICESTER

Leicester School of Pharmacy

Faculty of Health & Life Sciences

De Montfort University Diabetes and Exercise _Survey 2011

DMU University Diabetes and Exercise Survey 2011

Dear Participant

Our research group in the School of Pharmacy are working to produce a medical device that might help people with diabetes maintain the right level of glucose in their blood. We would like to invite you to take part in this survey because you have either **Type 1 or Type 2 diabetes**. It is an opportunity for you to discuss your experience with various aspects of your diabetes and your attitudes with exercise. The information we get from this survey will be combined with a practical study we will also be conducting which may lead to recommendations to improve the lifestyle of people with diabetes in the future. The information could also help research toward a suitable exercise regime for people with diabetes.

All information collected about you during the course of the survey will be strictly confidential and we will not ask for any personal details.

If you have any questions then please contact us.

Thank you very much for your time.
Yours sincerely

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Return to:

FREEPOST RSAT-ZSRT-RRGG

INsmart Diabetes Survey

Faculty of Health & Life Sciences

Section A: About you

Q1. Are you?

1. ☐ Female
2. ☐ Male

Q2. How would you best describe your occupation?

1. ☐ Professional
2. ☐ Skilled
3. ☐ Semi-skilled
4. ☐ Manual labour
5. ☐ Student

6. □ Retired
7. □ Other, please state…….

Q3. How old are you?

1. □ Between 1 - 10 years
2. □ Between 11 - 20 years
3. □ Between 21 - 30 years
4. □ Between 31 - 40 years
5. □ Between 41 - 50 years
6. □ Between 51 - 60 years
7. □ Between 61 - 80 years
8. □ Over 80 years

Q4. How old were you when your diabetes was first diagnosed?

1. □ Between 1 - 10 years
2. □ Between 11 - 20 years
3. □ Between 21 - 30 years
4. □ Between 31 - 40 years
5. □ Between 41 - 50 years
6. □ Between 51 - 60 years
7. □ Between 61 - 80 years
8. □ Over 80 years

Q5. What is your highest level of education?

1. □ I am still in full time education
2. □ I underwent some form of educational training (e.g. vocational or college)
3. □ I am in or have had a higher education (e.g. university)
4. □ I am still in full time education as a mature student
5. □ I have not had any further education after leaving school

Q6. What is your ethnic group? (Please tick one box from section A to E)

A. WHITE

1. □ British
2. □ Irish
3. □ Any other White background (Please write in_____)

B. MIXED

4. □ White and Black Caribbean
5. □ White and Black African
6. □ White and Asian
7. □ Any other mixed background (Please write in_____)

B. ASIAN OR ASIAN BRITISH

8. □ Indian
9. □ Pakistani
10. □ Bangladeshi

11. □ Any other Asian background (Please write here _____)

B. BLACK OR BLACK BRITISH

12. □ Caribbean
13. □ African
14. □ Any other Black background (Please write in_____)

B. CHINESE OR OTHER ETHNIC GROUP

15. □ Chinese
16. □ Any other ethnic group (Please write in_____)

Q7. Which country do you live in?

……

Section B: Your diabetes

Q8. How was your diabetes diagnosed?

1. □ By your GP (General Practitioner)
2. □ By hospital clinic
3. □ By friend/ family
4. □ By ambulance/Accident and Emergency
5. □ By yourself
6. □ By medical check-up (eg. work, insurance)
7. □ Other, please state**…….**

Q9. What type of diabetes do you have?

1. □ Type 1
2. □ Type 2
3. □ I don't know
4. □ Other, please state**…….**

Q10. Please state your height, weight

1. Height**……** (cm or feet and inches)
2. Weight**……** (kg or stones and pounds)

Q11. Is there a history of diabetes in your immediate family?

1. □ No
2. □ Yes, please state who**……..**

Q12. What do you find most difficult about your diabetes?

1. □ Healthy diet
2. □ Exercising
3. □ Testing blood glucose levels
4. □ Other, please state**……**

Q13. Do you use insulin?

1. □ Yes

2. □ No. Please go to Q19

Q14. What type of insulin(s) do you use?

1. □ Humalog® (Lispro)
2. □ Novorapid® or Novolog® (Aspart)
3. □ Actrapid® (regular or soluble insulin)
4. □ Humulin S® (regular or soluble insulin)
5. □ Humulin I® (Isophane)
6. □ Insulatard® (Isophane)
7. □ Mixtard®
8. □ Humulin M3®
9. □ Levemir® (detemir)
10. □ Lantus® (Glargine)
11. □ Other (list) _____

Q15. How many insulin injections do you give yourself in a normal day?

1. □ 1 - 2
2. □ 2 - 4
3. □ 4 or more

Q16. How long have you been injecting this number of injections each day?

1. □ Ever since I started taking insulin
2. □ Less than one year
3. □ 1 – less than 2 years
4. □ 2 – less than 5 years
5. □ longer than 5 years

Q17. What was the total amount of insulin you used yesterday (over 24 hours)?

1. □ Between 20 - 39 Units
2. □ Between 40 - 79 Units
3. □ Between 80 - 100 Units
4. □ Other, please state**……**

Q18. What is the typical total amount of insulin you use each day?

1. □ Between 20 - 39 Units
2. □ Between 40 - 79 Units
3. □ Between 80 - 100 Units
4. □ Other, please state**……**

Q19. What was your HbA1c when you were diagnosed with diabetes? (if known)

1. □ Don't know
2. □ Below 5 % (31)
3. □ Between 5 and 6 % (31 and 42)
4. □ Between 6.1 and 7 % (43 and 53)

5. □ Between 7.1 and 8 % (54 and 64)
6. □ Between 8.1 and 9 % (65 and 75)
7. □ Between 9.1 and 10 % (76 and 86)
8. □ Over 10% (86). Please state**……**

Q20. How often is your HbA1c measured?

1. □ Every 3 months
2. □ Every 6 months
3. □ Every year
4. □ Other, please state**……**

Q21. What is your recent measured HbA1c result?

1. □ Don't know
2. □ Below 5 % (31)
3. □ Between 5 and 6 % (31 and 42)
4. □ Between 6.1 and 7 % (43 and 53)
5. □ Between 7.1 and 8 % (54 and 64)
6. □ Between 8.1 and 9 % (65 and 75)
7. □ Between 9.1 and 10 % (76 and 86)
8. □ Over 10% (86). Please state**……**

Q22. Was your HbA1c taken in the last 3 months?

1. □ Yes
2. □ No. Please state when**……**

Q23. What do you think your HbA1c should be?

1. □ Don't know
2. □ Below 5 % (31)
3. □ Between 5 and 6 % (31 and 42)
4. □ Between 6.1 and 7 % (43 and 53)
5. □ Between 7.1 and 8 % (54 and 64)
6. □ Between 8.1 and 9 % (65 and 75)
7. □ Between 9.1 and 10 % (76 and 86)
8. □ Over 10% (86). Please state**……**

Q24. In the last 12 months, have you had any of the following tests?

	Yes	No	Don't know
1. Your blood pressure taken by a doctor or nurse			
2. A cholesterol test by a doctor or nurse			
3. An eye test where a photograph of the back of your eyes was taken			
4. Your bare feet were examined			
5. You have had your weight checked by a doctor or nurse			

Q25. For each question please tick yes, no or don't know

	Yes	No	Don't know
1. Has your eyesight suffered as a consequence of your diabetes?			
2. Do you have diabetic kidney disease?			
3. Do you require dialysis?			
4. Have you had a kidney transplant?			
5. Is your usual blood pressure normal?			
6. Do you take any medication to control your blood pressure?			
7. Are you on lipid lowering medication (for high cholesterol or triglycerides)?			
8. Have you ever had a heart attack?			
9. Do you ever have chest pain due to angina?			
10. Have you ever had heart bypass surgery (coronary artery bypass)?			
11. Have you ever had a balloon angioplasty or a coronary stent placed?			
12. Have you ever had, or suspected that you had a stroke?			

Q26. Please tell us what your cholesterol levels are, if known?

1. Total cholesterol level**……**
2. High-density lipoprotein (HDL)**…….**
3. Low-density lipoprotein (LDL)**……**

Q27. Have you ever had a low blood glucose 'hypoglycaemia'?

1. □ Yes
2. □ No. Please go to Q37

Q28. What symptoms do you experience when you have a 'hypoglycaemia'? Tick all that apply to you

1. □ Pale skin
2. □ Trembling
3. □ Sweating
4. □ A feeling of weakness/fatigue
5. □ Rapid heartbeat
6. □ Hunger
7. □ Agitation/irritability
8. □ Poor concentration
9. □ Blurred vision
10. □ Loss of coherence
11. □ Black out
12. □ Convulsions/Fit

13. □ Coma
14. □ Other, please state**……**

Q29. How low does your blood sugar get before you feel these symptoms?

1. □ Don't know
2. □ Between 4 and 5 mmol/L (72 and 90 mg/dl)
3. □ Between 3.5 and 3.9 mmol/L (63 and 70 mg/dl)
4. □ Between 3 and 3.4 mmol/L (54 and 61 mg/dl)
5. □ Below 3 mmol/L (54 mg/dl), please give a value _____mmol/L

Q30. What time(s) of day do you have hypoglycaemia? (Tick all that apply)

1. □ Morning
2. □ Afternoon
3. □ Evening
4. □ During night
5. □ Any additional comments**……..**

Q31. Does hypoglycaemia affect your day-to-day activities?

1. □ A great deal
2. □ Quite a lot
3. □ A little
4. □ Not at all

Q32. Do you respond to a low blood sugar by taking a sugary food or drink immediately?

1. □ Yes
2. □ No, please state what you do**……**

Q33. Has problems with hypoglycaemia stopped you permanently from being able to drive?

1. □ Yes
2. □ No

Q34. During the past 12 months have you had "severe" hypoglycaemia where you passed out or had a seizure that required help from others?

1. □ No, please go to Q36
2. □ Yes, Please state what happened**……..**

Q35. If yes, how many times has this occurred?

1. □ 1 - 2
2. □ 3 - 5
3. □ 6 or more

Q36. How many times have you had to go to hospital because of hypoglycaemia in the past 12 months?

1. □ None
2. □ 1 – 2
3. □ 3 – 5
4. □ More than 5

Q37. How many times per week is your measured fasting blood glucose 10 mmol/L (180 mg/dl) or above?

1. □ Once
2. □ Twice
3. □ More than twice
4. □ Never

Q38. Has your blood sugar ever been above 20 mmol/L (360 mg/dl)?

1. □ Yes
2. □ No

Q39. Have you ever been in diabetic ketoacidosis (DKA)?

1. □ Yes
2. □ No. Please go to Q41

Q40. Do you know what caused your diabetic ketoacidosis (DKA)?

1. □ Because you were unwell
2. □ Missed taking insulin
3. □ Because you were stressed
4. □ Diet
5. □ Other, please state**…….**

Q41. Have you ever been in a coma because of "high" blood glucose?

1. □ Yes
2. □ No

<u>Section C: Your diet</u>

Q42. How would you describe your diet approach?

1. □ You are eating healthily.
2. □ You too busy to find healthy foods or meals.
3. □ You don't know enough about good nutrition or how to eat healthily.
4. □ Sometimes, you try to eat healthy food
5. □ You can't resist junk food.
6. □ Your eating habits are poor.

Q43. Have you been given any dietary advice to help control your diabetes?

1. □ Yes
2. □ No

Q44. Do you follow a medically approved dietary programme to help control your diabetes?

1. □ No
2. □ Yes, please state**……**

Q45. Do you count carbohydrates regularly in order to help you to control your diabetes?

1. □ Yes
2. □ No

Q46. How many calories do you think you eat and drink in a typical day?

1. □ 1500 or fewer
2. □ Over 1500 up to 2000
3. □ Over 2000 up to 2500
4. □ Over 2500 up to 3000
5. □ Over 3000 up to 3500
6. □ 3500 or more
7. □ I don't know

Q47. Do you eat special diabetic food/drink?

1. □ No
2. □ Yes, please list and state why**……..**

Q48.Do you drink alcohol?

1. □ No
2. □ Yes. How many units per week**……**

Q49. Do you smoke?

1. □ No
2. □ Yes, please state how many per day…….

Section D: Your attitude to exercise

Q50. How important is doing exercise to you?

1. □ Important
2. □ No view
3. □ Not important

Q51. Do you exercise regularly?

1. □ Yes

2. □ No, you do not exercise at all. For the rest of the survey answer only questions 52, 53 and 54. Thank you for your participation in this survey

Q52. Are there any barriers preventing you from taking part in more exercise and sport? (Please tick all that apply)

1. □ Health reasons
2. □ Lack of motivation
3. □ Embarrassment about how you look. eg overweight or lack of fitness
4. □ You doubt it will lead to weight control
5. □ Lack of time
6. □ It does not interest me
7. □ It is too expensive
8. □ Lack of transport
9. □ Fear of Injury
10. □ Don't know
11. □ Other, please state……

Q53. Which of the following factors influenced your decision to participate in exercise and sport? (Please tick all that apply)

1. □ To keep well with your diabetes
2. □ Better control of your blood glucose
3. □ Better for HbA1c value
4. □ To improve health and fitness
5. □ Loss weight
6. □ Family participate in sport
7. □ Because friends do it
8. □ Because you enjoy it
9. □ To relieve stress

Q54. What frustrates you MOST about exercise? Tick all that apply

1. □ Finding time to exercise every day
2. □ Having to change your diet
3. □ Motivating yourself
4. □ Pain after exercise
5. □ Other, please state……

Q55. What effect did exercise have on your life after you became diabetic?

1. □ No effect on your diabetes
2. □ Positive effect on your diabetes

3. □ Negative effect on your diabetes

Q56. How effective has exercise been on each of the following

	Effective	No change	Detrimental	Comments
1. Better general Health				
2. Low HbA1c				
3. Poor blood glucose control				
4. Fewer Hypoglycaemia events				
5. Fewer Hyperglycaemia events				

Q57. Where do you typically exercise?

1. □ At school/college/ work/ university
2. □ In a sports team (e.g. football, netball)
3. □ In a class or club (e.g. aerobics, dance, etc)
4. □ At a gym
5. □ On your journey home (eg. walking or cycling)
6. □ Elsewhere, please state**……**

Q58. Do you have a membership in any sport centre or physical activity group?

1. □ Yes
2. □ No

Q59. What type of exercise do you do? (Please tick all that apply)

1. □ Walking
2. □ Cycling
3. □ Weight training (resistance exercise)
4. □ Swimming
5. □ Team sports basketball/football
6. □ Running
7. □ Other, please state**……**

Q60. Typically what is your blood glucose value pre-exercise?

1. □ Below 5 mmol/l (90 mg/dl)
2. □ Between 5 and 6 mmol/l (91 and 108 mg/dl)
3. □ Between 6.1 and 7 mmol/l (109 and 126 mg/dl)
4. □ Between 7.1 and 8 mmol/l (127 and 144 mg/dl)
5. □ Between 8.1 and 9 mmol/l (145 and 162 mg/dl)
6. □ Between 9.1 and 10 mmol/l (163 and 180 mg/dl)
7. □ Over 10 mmol/l (180 mg/dl). Please state**……**

Q61. At what level of intensity do you exercise?

1. □ **Low** (Easy, does not induce sweating unless it's a hot, humid day, no noticeable change in breathing patterns)
2. □ **Moderate** (Somewhat hard, sweat after about 10 minutes of exercise. Breathing becomes deeper and more frequent)
3. □ **High** (Hard, sweat after 3-5 minutes. Breathing is deep and rapid)
4. □ Combination between low and moderate
5. □ Combination between low and high
6. □ Combination between high and moderate

Q62. Typically, how many days of the week do you undertake physical activity and exercise?

1. □ Every day
2. □ 1 - 2 days
3. □ 3 - 5 days
4. □ 6 days

Q63. How many times do you exercise per day?

1. □ Once
2. □ Twice
3. □ Three times
4. □ More than 3 times

Q64. When do you do your exercise? Tick all that apply

1. □ Morning
2. □ Afternoon
3. □ Evening
4. □ After a meal
5. □ Before a meal

Q65. In a typical exercise day how long do you spend participating in sport or exercise?

1. □ Less than 30 minutes
2. □ From 30 minutes to less than 1 hour
3. □ From 1 to less than 2 hours
4. □ From 2 to less than 3 hours
5. □ From 3 to less than 4 hours
6. □ More than 4 hours

Q66. How many times do you test your blood glucose in normal day (24 hr)?

1. □ Once
2. □ Two – four times
3. □ More than 4 times

Q67. Does this change on an exercise day?

1. □ Test more
2. □ Test less
3. □ No change

Q68. Do you change the number of insulin injections on exercise day?

1. □ More
2. □ Less
3. □ No change

Q69. Does your insulin dose change in exercise day?

1. □ More, how much**…….**
2. □ Less, how much**…….**
3. □ No change
4. □ Dependent on type of exercise. Please state**…….**

Q70. Do you inject insulin pre-exercise?

1. □ No
2. □ Yes, please state how much……

Q71. During the exercise day, for each question please tick all that apply

	Before exercise	**During exercise**	**After exercise**
1. When do you test your blood glucose?			
2. When do you take your insulin dose?			
3. When do you take carbohydrate?			

Q72. If your blood sugar was less than 4mmol/L (72mg/dl) pre-exercises, what would you do?

1. □ Miss out your pre- exercise bolus
2. □ Reduce your pre- exercise bolus
3. □ Leave the exercises today
4. □ Take some carbohydrate then exercise
5. □ Nothing
6. □ Other, please state**……**

Q73. Do you experience hypoglycaemia while exercising?

1. □ Always
2. □ Frequently

3. □ Rarely
4. □ Never

Q74. How many times in the last month has your blood glucose been below 4mmol/L (72mg/dl) after exercise?

1. □ Once
2. □ Between 1 - 3 times
3. □ More than 3 times
4. □ None, go to Q77

Q75. If you experience a hypoglycaemia after exercise what action do you take?

1. □ Re-check your blood glucose
2. □ Eat or drink carbohydrate
3. □ Other, please state**……**

Q76. If you have hypoglycaemia associated after exercise, when would be your major risk period?

1. □ 0 - 1 hour
2. □ 1 - 2 hours
3. □ 3 - 6 hours
4. □ More than 6 hours

Q77. How many times in the last month has your blood sugar been above 10mmol/L (180mg/dl) after exercises?

1. □ Once
2. □ Between 1 - 3 times
3. □ More than 3 times
4. □ None, go to Q79

Q78. If you experienced hyperglycaemia (high blood glucose) after exercise what action do you take?

1. □ Inject insulin dose
2. □ Re-check your blood glucose
3. □ Drink water or any drink with no calories
4. □ Seek medical help
5. □ Eat some thing (eg.carbohydrate)

Q79. Have you experienced any of the following symptoms during or after exercise? (Please tick all that apply)

1. □ Bleeding
2. □ Chafing
3. □ Flushing
4. □ Hives

5. □ Hyperthermia
6. □ Muscle cramps
7. □ Red face
8. □ Shortness of breath
9. □ Urinary (colour, blood, pain)
10. □ Other
11. □ None

Q80. Would you like to add any comments?

(Appendix 2)

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DE MONTFORT UNIVERSITY
LEICESTER

HLS FREC Ref: 855

17th November 2012

Joan Taylor
Pharmacy
HLS

Dear Joan,

Re: Ethics application – Use of exercise-based physiological monitoring to compare calorie turnover in the two main types of diabetes and where different therapies are used (ref: 855

I am writing regarding your application for ethical approval for a research project titled to the above project. This project has been reviewed in accordance with the Operational Procedures for De Montfort University Faculty of Health and Life Sciences Research Ethics Committee. These procedures are available from the Faculty Research and Commercial Office upon your request.

I am pleased to inform you that ethical approval has been granted by Chair's Action for your application. This will be reported at the next Faculty Research Committee, which is being held in January 2012.

Should there be any amendments to the research methods or persons involved with this project you must notify the Chair of the Faculty Research Ethics Committee immediately in writing. Serious or adverse events related to the conduct of the study need to be reported immediately to your Supervisor and the Chair of this Committee.

The Faculty Research Ethics Committee should be notified by e-mail to HLSFRO@dmu.ac.uk when your research project has been completed.

Yours sincerely,

Professor Paul Whiting
Chair
Faculty of Health and Life Sciences
Research Ethics Committee

(Appendix 3)

Leicester School of Pharmacy

Faculty of Health & Life Sciences

Volunteer Information Sheet

Title of Project: The effects of aerobic and resistance exercise on diabetes

Name of Principal Investigators: Prof MJ Taylor, Mr.Ahmed Alsabih and Mr.Mohamd Alblihed

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. If you do wish to take part please complete the slip at the end of this sheet.

What is the purpose of the study?

As part of the growing research work into diabetes, School of Pharmacy, De Montfort University (DMU) are working to investigate the effects of combined exercise programme (aerobic and resistance) on blood glucose, metabolic parameters that could help people with the management of their diabetes.

This research involves a combination of two types of exercises and this is where we need your help. We would like to invite you to take part in this study which will help us to understand the role of exercise and how it can help people with diabetes to maintain a healthy body weight and to possibly manage better their blood glucose level.

We will keep your information strictly confidential and nobody other than the research team will have access to your personal information.

Before any research goes ahead it has to be checked by De Montfort University Research Ethics Committee. They make sure that the research is fair.

Why have I been invited?

You have been invited to take part in this study because you are a healthy male, or have either Type 1 or Type 2 diabetes and your age is between (18 – 55).

Do I have to take part?

It is up to you to decide. We will answer any questions you have about the study and go through this information sheet. We will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive from your doctor or hospital.

What will happen to me if I take part?

Preliminary procedures

Before enrolling in the study you will be asked to attend a screening visit where we will:

- discuss and complete confidential questionnaires regarding your health, family history and physical activity level.
- measure your blood pressure and heart rate.
- measure your height and weight

- provide an opportunity for you to ask questions.
- familiarise you with equipment to be used in the study and teach you how to use the recumbent ergometer bike and how to lift the weights safely in the multigym machine.
- This session will also be used to determine the intensity of exercise during cycling on the recumbent ergometer bike using Heart Rate Reserve (HRR). Also, in this orientation session we will use predicted one repetition maximum (1RM) to determine how much weight for different muscles you should lift in the resistance exercise session later.

These preliminary procedures will enable us to determine whether you are suitable to safely participate in the study or not.

Main experimental trials

The main experimental trials will involve 2 x 2 hour exercise sessions a week for a 6-week period, (exercise session includes rest + final observation of volunteer for hypos etc…).

Blood glucose levels will be monitored before, during and after each session, using a standard finger prick test. By using the Radiometer, Blood gases, Albumin, Lactate, and Electrolytes will be tested before, and after exercise programme. In addition, Cholesterol, High density lipoprotein, low density lipoprotein and Triglyceride will be monitored before, and after exercise programme using a finger prick test.

Each exercise session will consist of a combined exercise protocol of 35 min of resistance exercise (3 sets of 8 -10 repetitions at 50 – 60% of predicted one-repetition maximum strength 1-RM) using upper and lower muscle groups followed by 20 min moderate cycling at 50 – 60% of predetermined heart rate reserve (HRR). Heart rate (HR) and rate of perceived exertion (RPE) will be taken in a different time points throughout the exercise trial.

Expenses and payments

We would like to pay expenses and to offer an incentive of £120 each on completion of 100% of the dates agreed to.

What are the possible benefits of taking part?

There may be no benefits to you but as a result of being involved in this study may will receive health and fitness information about yourself including fitness tests and body measurement. The findings of this study will be published in scientific journals so that understanding about how exercise can help people with diabetes to improve their health and control their weight and blood glucose levels. This information may contribute towards improved exercise guidelines for the diabetic patients.

We will provide you with feedback about the main study findings and also about your own results and would be delighted to explain our findings and discuss possible implications with you.

What if there is a problem?

The chance of something going wrong is small. All of the procedures involved in this study are low risk and our screening tests are designed to ensure that you will only participate if it is safe for you to do so. However, if you have any concerns at any time about any aspect of the way you have been approached or treated during the course of this study, you should ask to speak to the researchers who will do their best to answer your questions (contact details below), and the normal De Montfort University complaints mechanisms will be available to you.

Will my taking part in the study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you, which leaves the University, will have your name and address removed so that you cannot be recognised from it.

What will happen if I don't want to carry on with the study?

While we do not expect the programme to cause you to become upset if this does happen then you will have the option to pause or stop your participation immediately, you may continue only if you wanted to. If you withdraw from the study, we will destroy all your identifiable data, but may use the data collected up to your withdrawal

Who has reviewed the study?

This study has been reviewed and approved by the Faculty of Health and Life Sciences Ethics Committee at De Montfort University. Approval does not guarantee that you will not come to any harm if you take part. However, approval means that the Committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits and that you have been given sufficient information on which to make an informed decision.

You will be given a copy of this information sheet and a signed consent form to keep for your records.

Contact for Further Information

Any questions about the procedures used in this study are encouraged. If you have any doubts or questions, please ask for further explanations by contacting Ahmed Alsabih on p09053155@myemail.dmu.ac.uk or Mohamd Alblihed on p06004947@myemail.dmu.ac.uk or Prof.Taylor on 01162506317 or mjt@dmu.ac.uk

Thank you for taking the time to read this Volunteer Information Sheet

(Appendix 4)

Leicester School of Pharmacy **Faculty of Health & Life Sciences**

Standard Operation Procedure (SOP)

Title of Project: The effects of aerobic and resistance exercise on diabetes

Name of Principal Investigators: Prof MJ Taylor, Mr.Ahmed Alsabih and Mr.Mohamd Alblihed

Preliminary procedures

Before enrolling in the study the volunteer will be asked to attend a screening visit where we will:

- discuss and complete confidential questionnaires regarding his health, family history and physical activity level.
- measure his blood pressure.
- measure his height and weight
- provide an opportunity for him to ask questions
- familiarise him with equipment to be used in the study and teach him how to use the recumbent ergometer bike and how to lift the weights safely in the multigym machine.

- This session will also be used to determine the intensity of exercise (moderate intensity) on the recumbent ergometer bike and how much weight he should lift in the resistance exercise session later.

These preliminary procedures will enable us to determine whether the volunteer suitable to safely participate in the study or not.

Main experimental trials

The main experimental trials will involve 2 x 2 hour exercise sessions a week for a 6-week period,(exercise session includes rest + final observation of volunteer for hypos etc…).

Blood glucose levels will be monitored before, during and after each session, using a standard finger prick test. Total Cholesterol, High density lipoprotein, Low density lipoprotein and Triglyceride will be monitored before, during and after exercise programme and after the second session in each week of 6 weeks of exercise programme using a finger prick test. There may be occasions when the volunteer may not be allowed to participate if that or another health issue is deemed to threaten wellbeing.

Each exercise session will consist of a combined exercise protocol of 35 min of resistance exercise (3 sets of 8 -10 repetitions at 50 – 60% of one-repetition maximum strength 1-RM) using upper and lower muscle groups followed by 20 min moderate cycling at 50 – 60% of predetermined heart rate reserve (HRR)or ratings of perceived exertion (RPE).

The exercise session will include the following 6 phases:

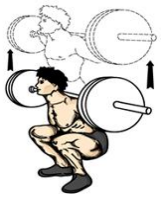
1. Stretching: stretch lower and upper muscle groups for 5 min

2. Warm-up: start with cycling for 10min on the recumbent ergometer bike at low to moderate intensity (30 to 40% of HRR). Warm-up is an essential part of the exercise session and designed to prepare the body for exercise, increase body

temperature and to reduce the potential post-exercise injury or pain (muscle stiffness).

3. Resistance exercise: this phase will include 35 min of five different exercises working upper and lower muscle groups (3 sets of 8 -10 repetitions at 50 – 60% of one-repetition maximum strength 1-RM) and using the Multigym machine

Working muscle groups as follows: (3 sets of 8 -10 repetitions each exercise)

 a. Squat	 b. Incline bench press	 c. lat curl pull down	 d. Triceps	 e. Biceps

4. Cycling

The volunteer will do moderate cycling at 50 – 60% of predetermined heart rate reserve (HRR) or ratings of perceived exertion (RPE) for 20 min. The volunteer and the bike will be attached to monitoring equipment that can produce instant graphical representation of performance linked to work done and produce different metabolic parameters such as Oxygen consumption (VO_2), Carbon Dioxide Production (VCO_2), Respiratory Exchange Ratio (RER), Heart rate (HR) etc. The volunteer attachment will be via a breathing mask and by ECG stick-on electrodes.

5. Cool-down: cycling for 5 - 10min on the recumbent ergometer bike at low to moderate intensity (30 to 40% of HRR). The purpose of the cool-down phase is reducing the risk of injury and brings the body physiological responses back to normal such as heart rate and blood pressure.

6. Stretching: stretch lower and upper muscle groups for 5 min.

I ……(NAME AND ADDRESS OF PARTICIPANT) would like to participate in a focus group/interview in the DMU research study 'Investigating views on acceptable methods for controlling blood sugar'.

_____

_____

Signed by Participant date

Name ……..Address……..

Postcode…….. Telephone number ……

(Appendix 5)

Leicester School of Pharmacy

Faculty of Health & Life Sciences

Study Number:

Patient Identification Number for this trial:

Consent Form

Title of Project: The effects of aerobic and resistance exercise on diabetes

Name of Principal Investigator: Prof MJ Taylor, Mr.Ahmed Alsabih and Mr.Mohamd Alblihed

Please initial at the end of each point

1. I confirm that I have read and understand the Participant Information Sheet dated. (05/10/2011) (Version 2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. I understand that agreeing to take part means that I am willing to undertake some exercise and giving samples in the above study.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my legal rights being affected.

3. I understand that any information I provide is confidential, and that no information that could lead to the identification of any individual will be disclosed in any reports on the project, or to any other party. No identifiable personal data will be published. The identifiable data will not be shared with any other organisation.

4. I understand that confidentiality can be guaranteed for information which I might disclose in any session or visit I attend. I understand that this information will be used only for the purpose(s) set out in this statement and my consent is conditional on the

University complying with its duties and obligations under the Data Protection Act 1998.

5. I agree to take part in the above study.

Participant Name…….. Signature…….Date…….

Person Taking consent……...Signature……Date……..

When completed, copy for patient; copy for researcher site file.

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(Appendix 6)

Leicester School of Pharmacy

Faculty of Health & Life Sciences

Volunteers Health Screen for Study Volunteers

Name: …… Volunteer Identification Number…….

It is important that volunteers participating in research studies are currently in good health and have had no significant medical problems in the past. This is to ensure (i) their own continuing well-being and (ii) to avoid the possibility of individual health issues confounding study outcomes.

Please complete this brief questionnaire to confirm fitness to participate:

At present, do you have any health problem for which you are:

(a) On diabetes medication, prescribed or otherwise yes [ ] no [ ]

(b) Other medication yes [ ] no [ ]

(c) Attending your general practitioner yes [ ] no [ ]

(d) On a hospital waiting list yes [ ] no [ ]

In the past two years, have you had any illness which required you to:

(a) consult your GP yes [ ] no [ ]

(b) was this related to diabetes yes [ ] no [ ]

(c) attend a hospital outpatient department yes [ ] no [ ]

(d) be admitted to hospital yes [ ] no [ ]

Have you ever had any of the following:

(a) Convulsions/epilepsy yes [ ] no [ ]

(b) Asthma yes [ ] no [ ]

(c) Eczema yes [ ] no [ ]

(d)	Heart problems	yes [ ]	no [ ]
(e)	A blood disorder	yes [ ]	no [ ]
(f)	Head injury	yes [ ]	no [ ]
(g)	Digestive problems	yes [ ]	no [ ]
(h)	Hearing problems	yes [ ]	no [ ]
(i)	Problems with bones or joints	yes [ ]	no [ ]
(j)	Disturbance of balance/co-ordination	yes [ ]	no [ ]
(k)	Numbness in hands or feet	yes [ ]	no [ ]
(l)	Disturbance of vision	yes [ ]	no [ ]
(m)	Thyroid problems	yes [ ]	no [ ]
(n)	Kidney or liver problems	yes [ ]	no [ ]
(o)	Chest pain	yes [ ]	no [ ]
(p)	Any other health problems	yes [ ]	no [ ]
Do you currently smoke		yes [ ]	no [ ]
	Have you ever smoked	yes [ ]	no [ ]

If so, for how long did you smoke and when did you stop? ……

How many units of alcohol do you typically drink in a week? …….

If YES to any question, please describe briefly if you wish (e.g. to confirm whether problem was short-lived, insignificant or well controlled.) (Use a separate sheet if necessary)

…….

Name and address of your GP ……

Letter received from GP ☐

(Appendix 7)

Private and confidential

Volunteer Record Sheet

Volunteer Identification Number:

TITLE…… FIRST NAME…… SURNAME……
DATE OF BIRTH…….. AGE……MALE / FEMALE …
CORRESPONDENCE ADDRESS……..
…… POSTCODE: ……
HOME TELEPHONE: …….. MOBILE: ……..
WORK TELEPHONE ……
EMAIL ADDRESS: ……
Please tick ☐ I am happy for De Montfort University Diabetes and Exercise Group to contact me by email
(We may will be sending key information via emails, so please include an up to date email address that you will check on a regular basis)
PERSON TO CONTACT IN CASE OF EMERGNCY……
RELATION TO YOU……
HOME TELEPHONE: …….. MOBILE: ……
EMAIL ADDRESS: ……..

Type of diabetes? Healthy ☐ Type 1 ☐ Type 2 ☐ Other ☐
Number of years with DM duration……..
Do you have any other medical conditions? Yes/ No
If yes, please state: ……
Do you have any specific dietary requirements? Yes/ No
If yes, please state: ……
Name of your GP…… Tel……
Address ……Post Code……
Do you have any existing medical conditions Yes / No
If yes, please state……
Any infectious diseases Yes / No
If yes, please state ……

Have you been in hospitalised the past year Yes / No

If yes, why ……

History of acute diabetic complications

Number of Hypoglycaemia (low blood sugar) event in last month……..

Number of Hyperglycaemia (high blood sugar) event in last month …….

Number of Diabetic ketoacidosis event in last month……

Are you taking any medications, pills or drugs…….. If yes, please list and state dose

……..

Do you have any of the following?

	Yes	No		Yes	No
Heart Disease			Liver Disease		
High Blood Pressure			Kidney Disease		
Rheumatic arthritis			Hepatitis		
Heart Murmur			Asthma		
HIV Positive /Aids			Tuberculosis (TB)		
Any allergy			Stroke		
Tumour (Cancer) History			Epilepsy		
Terminally or mentally ill			Any recent surgery		
Restriction in physical activity because of disease			Had an active infection		
Participation in exercise (aerobic or resistance) 2 times or more weekly for 20 minutes or longer per session during the previous 6 months					

Diabetes mellitus DM

Type of insulin……

Units / day……

Injections / day……

Blood glucose testes / day …….

PLEASE RETURN THIS FORM TO: De Montfort University Diabetes and Exercise Group 2012

Participant Name…….. Signature…….Date…….

(Appendix 8)

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (October 2002)

LONG LAST 7 DAYS SELF-ADMINISTERED FORMAT

FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS (15-69 years)

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health–related physical activity.

Background on IPAQ

The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

Using IPAQ

Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

Translation from English and Cultural Adaptation

Translation from English is encouraged to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

Further Developments of IPAQ

International collaboration on IPAQ is on-going and an ***International Physical Activity Prevalence Study*** is in progress. For further information see the IPAQ website.

More Information

More detailed information on the IPAQ process and the research methods used in the development of IPAQ instruments is available at www.ipaq.ki.se and Booth, M.L. (2000). *Assessment of Physical Activity: An International Perspective.* Research Quarterly for Exercise and Sport, 71 (2): s114-20. Other scientific publications and presentations on the use of IPAQ are summarized on the website

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** and **moderate** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

PART 1: JOB-RELATED PHYSICAL ACTIVITY

The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?

☐ Yes

☐ No → ***Skip to PART 2: TRANSPORTATION***

The next questions are about all the physical activity you did in the **last 7 days** as part of your paid or unpaid work. This does not include traveling to and from work.

2. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, heavy construction, or climbing up stairs **as part of your work**? Think about only those physical activities that you did for at least 10 minutes at a time.

_____ **days per week**

☐ No vigorous job-related physical activity → ***Skip to question 4***

3. How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?

_____ **hours per day**
_____ **minutes per day**

4. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads **as part of your work**? Please do not include walking.

_____ **days per week**

☐ No moderate job-related physical activity → ***Skip to question 6***

5. How much time did you usually spend on one of those days doing **moderate** physical activities as part of your work?

_____ **hours per day**
_____ **minutes per day**

6. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **as part of your work**? Please do not count any walking you did to travel to or from work.

_____ **days per week**

☐ No job-related walking → ***Skip to PART 2: TRANSPORTATION***

7. How much time did you usually spend on one of those days **walking** as part of your work?

_____ **hours per day**
_____ **minutes per day**

PART 2: TRANSPORTATION PHYSICAL ACTIVITY

These questions are about how you traveled from place to place, including to places like work, stores, movies, and so on.

8. During the **last 7 days**, on how many days did you **travel in a motor vehicle** like a train, bus, car, or tram?

_____ **days per week**

☐ No traveling in a motor vehicle → ***Skip to question 10***

9. How much time did you usually spend on one of those days **traveling** in a train, bus, car, tram, or other kind of motor vehicle?

_____ **hours per day**
_____ **minutes per day**

Now think only about the **bicycling** and **walking** you might have done to travel to and from work, to do errands, or to go from place to place.

10. During the **last 7 days**, on how many days did you **bicycle** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐ No bicycling from place to place → ***Skip to question 12***

11. How much time did you usually spend on one of those days to **bicycle** from place to place?

_____ **hours per day**
_____ **minutes per day**

12. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐ No walking from place to place → ***Skip to PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY***

13. How much time did you usually spend on one of those days **walking** from place to place?

_____ **hours per day**
_____ **minutes per day**

PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

This section is about some of the physical activities you might have done in the **last 7 days** in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family.

14. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, chopping wood, shoveling snow, or digging **in the garden or yard**?

_____ **days per week**

☐ No vigorous activity in garden or yard → ***Skip to question 16***

15. How much time did you usually spend on one of those days doing **vigorous** physical activities in the garden or yard?

_____ **hours per day**
_____ **minutes per day**

16. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?

_____ **days per week**

☐ No moderate activity in garden or yard → ***Skip to question 18***

17. How much time did you usually spend on one of those days doing **moderate** physical activities in the garden or yard?

_____ **hours per day**
_____ **minutes per day**

18. Once again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, washing windows, scrubbing floors and sweeping **inside your home**?

_____ **days per week**

☐ No moderate activity inside home → ***Skip to PART 4: RECREATION, SPORT AND LEISURE-TIME PHYSICAL ACTIVITY***

19. How much time did you usually spend on one of those days doing **moderate** physical activities inside your home?

_____ **hours per day**
_____ **minutes per day**

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY

This section is about all the physical activities that you did in the **last 7 days** solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **in your leisure time**?

_____ **days per week**

☐ No walking in leisure time → ***Skip to question 22***

21. How much time did you usually spend on one of those days **walking** in your leisure time?

_____ **hours per day**
_____ **minutes per day**

22. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like aerobics, running, fast bicycling, or fast swimming **in your leisure time**?

_____ **days per week**

☐ No vigorous activity in leisure time → ***Skip to question 24***

23. How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?

_____ **hours per day**
_____ **minutes per day**

24. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis **in your leisure time**?

_____ **days per week**

☐ No moderate activity in leisure time → ***Skip to PART 5: TIME SPENT SITTING***

25. How much time did you usually spend on one of those days doing **moderate** physical activities in your leisure time?
_____ **hours per day**
_____ **minutes per day**

PART 5: TIME SPENT SITTING

The last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekday**?

_____ **hours per day**
_____ **minutes per day**

27. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekend day**?
_____ **hours per day**
_____ **minutes per day**

This is the end of the questionnaire, thank you for participating.

(Appendix 9)

Visit Measurements sheet

	TRIAL 1						TRIAL 2					
Sessions number	**1**	**3**	**5**	**7**	**9**	**11**	**2**	**4**	**6**	**8**	**10**	**12**
1. Subject name/Ref	**Name**						**Ref:**					
2. Date	/ /						/ /					
3. Food inventory sheet												
4. Temperature of the lab												
5. ADI calibration												
6. Zero all input												
7. Chest polar Attached												
8. RER at rest 5 min on (ADI)												
9. BP & HR at rest	/ mm Hg				bpm		/ mm Hg				bpm	
10. BG before exercise	mmol/L						mmol/L					
11. Stretching for 5 min												
12. Warm up on the bike for 5 min (at 50-55 % HRR)												
Resistance Sets	**1st**		**2nd**		**3rd**		**1st**		**2nd**		**3rd**	
13. Exercise 1 Squat												
14. Exercise 2 Chest												
15. Exercise 3 Back												
16. Exercise 4 Triceps												
17. Exercise 5 Bicep												
	RPE			**HR**			**RPE**			**HR**		
18. After 1st set of Resistance												
19. After 2nd set of Resistance												
20. After 3rd set of Resistance												
21. BG after Resistance	mmol/L						mmol/L					
22. BP & HR after	/ mm Hg				bpm		/ mm Hg				bpm	

Resistance						
23. 5 minute break (attach the 3 leads ECG, pulse rate and mouth piece)						
24. Start cardio exercise cycling						
	RPE	**HR**	**BG**	**RPE**	**HR**	**BG**
25. At 10 min of Cycling						
26. At 20 min of Cycling						
27. Stretching for 5 min						
28. BP & HR after Cycling	/ mm Hg		bpm	/ mm Hg		bpm
29. BG after Cycling	mmol/L			mmol/L		

	Visits		
	1st	**6th**	**12th**
1. Height			
2. Weight			
3. Body water %			
4. Body Fat %			
5. BMI			
6. Blood Gases			
A. Blood pH			
B. pCO2 mmHg			
C. pO2 mmHg			
7. Electrolytes			
A. K+ mmol/L			
B. Na+ mmol/L			
C. Ca+ mmol/L			
D. Cl- mmol/L			
E. Lactate mmol/L			
8. Lipids profile			
A. LDL mmol/L			

B. HDL mmol/L								
C. Total cholesterol mmol/L								
D. Triglyceride mmol/L								
9. HbA1c	**1st**			**12th**				
10. Waist (cm):	**1st**			**12th**				
11. Hip (cm):	**1st**			**12th**				
12. Waist/HIP Ratio:	**1st**			**12th**				
13. Blood samples for Immuno assay, Insulin, C-peptide	**Acute exercise**			**Chronic exercise**				
	Before Exercise	**After Resistance**	**After Cycling**	**2nd**	**4th**	**6th**	**8th**	**12th**

(Appendix 10)

Assessment of caloric intake

FOOD INVENTORY INSTRUCTIONS

It is important that you weigh and record everything that you eat and drink except water for the day prior to each main experimental trial. Please do not take any alcohol on these days.

Please

- start a separate page for each day.
- start a separate line for each item
- for the day before exercise, try to eat same food as similar as you can.

<u>Column 1</u>

Record meal and time and place of eating.

<u>Column 2</u>

Describe each item as accurately as possible, stating where relevant:

(i) Type and brand

(ii) Whether food is fresh, dried, canned, frozen, salted, smoked, etc.

(iii) Whether food is cooked, if so give method of cooking e.g. fried, baked, etc.

<u>Column 3</u>

Record the weight of each item after cooking:

(i) Place scales on a level surface

(ii) place plate or container on top of scales

(iii) press 'ON/Reset' button to turn on scales

(iv) once zero appears, add first item of food

(v) record weight displayed

(vi) press reset button before weighing next item

Wherever possible, record weights in grams. If this is not possible, record weights in household measures (e.g. sugar or jam in teaspoons, stating whether level, rounded, or heaped).

Column 4

Record the weight of any leftovers, such as food remaining on plate, weight of container in which food has been weighed, apple cores, etc.

If food consists of several items, please list each on a separate line i.e. instead of writing 'one cheese sandwich', record separately the weights of bread margarine, cheese, etc.

Please remember to record all drinks, as well as food, giving weights where possible, or volumes if these are known. Record separately the weight of added milk and sugar.

An example is shown below.

Food Inventory - Example

Name:.....Date:.....

1	2	3	4
Time/Place	**Description of food/drink**	**Weight of food/drink (g)**	**Weight of container/ leftovers (g)**
Breakfast	Cornflakes (Kelloggs)	28	
8:30am	Milk (Sainsbury's virtually fat-free)	48	
Home	Bread (Mothers Pride, large white	76	
	sliced, toasted)		
	Flora margarine	7	
	Robinsons lemon marmalade	12	
	Coffee (instant)	2	
	Milk (whole pasteurised)	10	
Lunch	Cheese (Cheddar)	55	
1:00pm	Bread (white, crusty)	76	
Pub	Butter	4	
	Chutney (2 teaspoons)		
Snack	Coffee (instant)	2	
3:30pm	Coffee-mate	6	
Office	Mars Bar	35	
	Apple	76	8 (core)
Dinner	Turkey Fillet (frozen, grilled)	102	
6:30pm	Potatoes, old, boiled	320	74
Home			(leftover)
	Peas (Birds Eye, frozen, boiled)	50	
	Heinz tomato ketchup	14	
	Yoghurt (Ski strawberry thick and	162	10
	creamy)		(carton)
	Coffee, filter	148	
	Milk (Sainsbury's virtually fat-free)	8	