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Six Weeks High Intensity Interval Training (HIIT) Improves a Variety of Different Diabetes Mellitus Type 2 Risk Markers

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Abstract

Background: It is estimated that 1 in 11 of the world's adult population suffers from type 2 diabetes. Novel exercise regimes such as high intensity interval training (HIIT) programme are gaining attention as an alternative treatment for managing type 2 diabetes (DM2). This study assesses the effects of a 6-week HIIT programme on DM2 risk markers.

Method: Eighteen participants aged 20-24 years were divided into test (n=9) and control (n=9) group. Each session consisted of 3 × 1 minute maximal effort cycling sprint followed by a 2-minute resting period. Physiological measurements were taken at pre HIIT (week 0) and after HIIT programme (week 6).

Results: After 6 weeks HIIT, mean test subjects' systolic blood pressure significantly decreased by 4.4% (p=0.004), diastolic blood pressure decreased by 7.2% (p=0.049) and body fat index decreased by 0.94% (p=0.033). There were also improvements in the test subjects' weight, VO_2max and glucose AUC, although these were not statistically significant. Genetic analysis revealed that an individual with +45T/G SNP had worsened glucose area under the curve (AUC) following the HIIT programme.

Conclusion: 6 weeks of HIIT has the capacity to significantly improve blood pressure and body fat index, whilst also improving other DM2 risk markers. Individuals with +45T/G SNP demonstrate worse glucose AUC after HIIT. Patient selection using genetic information is therefore critical in order to correctly identify which patients will benefit most from HIIT. HIIT could represent a feasible effective treatment for a life limiting disease.

Keywords: HIIT; Physical activity; Obesity; Diabetes mellitus; Adiponectin; Exercise; Anaerobic exercise

Introduction

For many years now, genetics has been linked with the onset and development of obesity and DM2 [1]. More recently, single nucleotide polymorphisms (SNP) have been identified and linked with conditions such as obesity and DM2 [2,3]. Previous literature has demonstrated that different single nucleotide polymorphisms (SNP) may contribute to an increased risk of developing DM2. One SNP identified was +45T/G polymorphism in the adiponectin (ADIPOQ) gene and how this increases an individual's risk of DM2 [3]. A meta-analysis was performed using 45 publications with 9986 DM2 patients and 16,222 controls for analysis of ADIPOQ +45T/G SNP. Results displayed that individuals with the +45T >G polymorphism were associated with an overall significant increased risk of developing DM2 [3]. Current guidelines suggest 150 minutes of moderate intensity aerobic exercise per week or 75 minutes of hard intensity aerobic activity [4]. Despite the large source of literature highlighting the fact that exercise has positive health benefits, exercise is on the decrease. One of the reasons for this trend is that the cost of a fitness club membership is too expensive. The main reason for individuals however is due to a lack of time in the day to exercise regularly [5]. To overcome this time issue, HIIT has been developed as a novel low volume high intensity programme which is an efficient way to potentially reduce the risk of DM2 and other cardiometabolic diseases [6]. HIIT is much more physically demanding than the 75 minutes of hard intensity aerobic exercise, therefore a shorter amount of time is needed to complete this programme. HIIT has been shown to produce greater physiological and biochemical changes than conventional exercise [7], making it an ideal, feasible programme to incorporate into people's lives potentially playing a part in the prevention, treatment and management of DM2 (Figure 1).

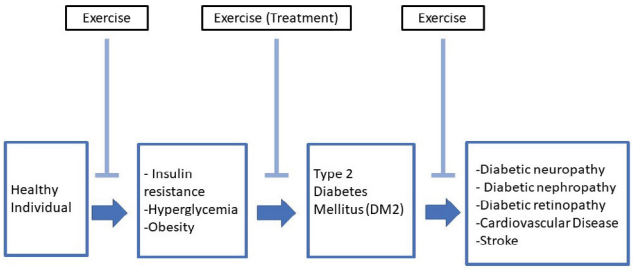

Figure 1: Arrow chart displaying how physical activity could be used to prevent, manage and treat DM2. Exercise may be able to improve conditions of insulin resistance by enhancing insulin sensitivity and improving GLUT 4 translocation, which would result in improved glucose uptake throughout the body. HIIT could also slow progression of neuropathies and retinopathies by avoiding chronic periods of hyperglycemia and at the same time decreasing blood pressure and elevating circulating levels of HDL cholesterol.

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Aims and objectives

An alarming increase in the population of type 2 diabetics is putting an enormous burden on health services worldwide, with current management plans unfeasible. It is very important that we investigate an alternative realistic plan which would cater for the mass population. HIIT has the potential to become a cost-effective way of doing this. Not only would HIIT save an enormous amount of revenue for health services, but it may also improve the general health and wellbeing of patients, ultimately leading to a decrease in the number of lifestyle-related diseases. This study's main aim is to assess whether HIIT could stimulate a positive improvement in cardiorespiratory markers and improve glucose area under curve in our exercise group cohort. Future work to build on this study would be to assess how many HIIT sessions are needed per year in order to maintain risk factors within normal physiological range. Alongside this, it may be worth assessing how long the effects of HIIT have on the body, and so by introducing a period of "detraining", investigate if a period of not performing HIIT would reverse or even worsen any changes that the 6-week HIIT programme potentially caused in the first place.

The study also investigates whether SNP in various genes would predispose individuals to developing DM2 by possessing +45T/G SNP. It will assess whether some individuals with SNP may benefit more or less from HIIT training. This study could then be taken further by assessing whether HIIT improves cardiorespiratory fitness markers without the need for dietary supplementation or drug treatment.

Finally, our study needed to ensure that the working parameters of the programme were safe. This was vital in our study as numerous bodies criticise and condemn this type of activity commenting that HIIT is unsuitable for the majority of the population due to the high intensity of the exercise sessions. It is important to educate individuals therefore by reiterating the fact that HIIT programmes do not come in just a single training plan protocol. Obese diabetic patients looking to improve their insulin sensitivity would not be able to complete the same plan as a healthy athlete looking to complete a HIIT programme in order to improve their VO_2max. It is important therefore to tailor the exercise programme to the individual and this could be done by performing an exhaustive incremental cycling test. This would introduce the concept of personalised medicine to DM2 management. If our study could prove that a 6-week HIIT programme could cause weight loss and improve cardiorespiratory risk markers in a safe manner, it would contribute to the growing body of literature supporting HIIT as a novel method which helps to reduce the risk of developing a lifestyle related disease such as obesity and DM2.

Materials and Method

Subjects

Eighteen healthy young male and female students were asked to participate in our study. Nine subjects were allocated to the test group which underwent 6 weeks of HIIT, and the remaining nine subjects were allocated to the control group. The control group did not undertake the HIIT and continued with their normal lifestyle. All subjects involved in the HIIT successfully completed the programme. They were asked to read a document explaining what the study involved prior to the start of the study. Individuals were informed of the experimental protocol prior to giving informed written consent (see appendix). Ethical approval was given by the Cardiff University School of Bioscience Committee (see appendix for documentation). Subjects were informed that they could withdraw from the study at any time, without having to provide a reason. The experimental procedures for the study was carried out at week 0 and 6 for both the test and control group, but the control group were not subjected to polymorphism analysis.

Physiological measurements

Weight and body fat index (BFI) were measured using a weighing scale (Tanita 2001, US). Body mass index (BMI) was calculated by dividing the subject weight (Kg) with the mean height $(m)^2$. BFI was also calculated using skin calipers (Accu-measure, US) (measured at four points: bicep, tricep, waist (suprailiac) and subscapular area). The body fat index was then calculated using the sum of the four skinfold measurements, along with the body density (calculated from standard age and gender matched charts). The systolic and diastolic blood pressure alongside resting heart rate were recorded using an automated clinically validated blood pressure monitor (Boots Pharmaceuticals, Nottingham, U.K). Four measurements were gathered for each blood pressure reading and then the mean value used in analysis.

Oral Glucose Tolerance Test (OGTT)

Subjects were required to abstain from intense physical activity the day prior to the OGTT and to have fasted overnight. Fasting blood glucose levels were quantified using a glucometer (Benecheck plus), and then a bolus of 75 g glucose powder 99% CHO, (Pure Series™ Dextrose, Colchester, UK) was ingested at time (t=0). Blood glucose levels were continually measured every 30 minutes until 120 minutes had passed. Blood sampling was gathered by skin puncture using a single use safety lancet (Owen Mumford, UK). Results of the OGGT allowed us to plot blood [glucose] *vs.* time, therefore enabling us to measure area under glucose concentration-time-curve (AUC).

VO_2max and Wmax test

Subjects performed an exhaustive incremental cycling test (Monark Ergomedic E, Sweden) in order to calculate maximal oxygen uptake capacity (VO_2max) using a gas analyser system (AD instruments, Oxford, UK). This was performed on a different day to the OGTT and subjects were asked to abstain from exercise and intense physical activity for 24 hours prior to the test. Subjects cycled for 5 minutes initially as a warm up period at 30 watts whilst 60 revolutions per minute (RPM) or above was to be maintained throughout the test. Following 5 minutes, the wattage increased by 30 watts (W) every 2 minutes until the subject was exhausted and unable to continue. Wmax was recorded as the wattage where the subject broke and was unable to continue with the test due to exhaustion. Maximal aerobic power (in watts) achieved before exhaustion (breaking wattage) was then used as the initial starting wattage for the HIIT training. VO_2max was calculated as the highest value achieved which was sustained for ~30 seconds using LabChart.

HIIT programme

The HIIT programme consisted of 3 sessions per week with no more than 2 rest days between each session and lasted a period of 6 weeks. Each session entailed the same structure with subjects having to perform 3 x 1-minute sprints set at a specific wattage (the breaking wattage of VO_2max test), with the pace kept at 120 RPM or above. Subjects were asked to increase their working wattage by 10% if they managed to complete 3 intervals maintaining >120 rpm on 2 consecutive sessions. On the contrary those unable to maintain the 120 rpm were required to decrease the wattage by 10%. By applying a progressive increase in working wattage, this allowed us to personalise HIIT protocol to the individual and help minimise the plateau effect,

therefore not allowing participants to acclimatise to the working conditions. Each session began with a 2-minute warm up period with no added weight whilst cadence was maintained at ~60 RPM. This was thought to be an important part of the protocol as studies have shown that an adequate warm up result in improved intermittent stunt performance and helps to reduce injuries sustained during intense exercise [8,9]. Following warm up, 3 × 1-minute sprints were done. After each minute of sprint, a 2-minute rest period was provided where the subject remained on the bike but cycled at a low cadence (50-60 RPM) with no resistance. The total time spent on the exercise bike was ~12 minutes. The subjects were asked to utilise the 2-minute cool down period correctly in order to help remove lactate acid build up from the legs and to reduce delayed onset muscle soreness (DOMS) so that they could perform optimally during the next session.

DNA isolation

During a different day to the OGTT and VO_2max test, the test subjects' DNA was extracted and isolated in order to locate and identify single nucleotide polymorphisms. DNA was gathered from the subjects' saliva using a QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). Subjects were required not to eat at least 30 minutes before collecting saliva and up to 5ml was collected in a 50ml Falcon Tube. The QIAGEN supplementary protocol [10] was followed apart from the last step where the DNA was eluted with 100µl of distilled water rather than 150µl. The remaining DNA was stored at 4°c.

Gel electrophoresis

Gel electrophoresis was carried out throughout in order to visualise the separate DNA mixtures. Agarose gels were used and once the gel was lukewarm, 5µl of SYBR® Safe DNA Gel Stain (Life Technologies, Invitrogen, Paisley, UK) was added and the gel was allowed to cool and set in a mould. 10X diluted TBE (40ml TBE+360ml distilled water) was used as a running buffer in a horizontal gel electrophoresis tank (Jencon, Leicestershire, UK) connected to a MP-250N voltage box (Major Science Power, California, USA). The DNA samples were run next to either a Quickload 2 log DNA ladder (New England Biolabs, Massachusetts, USA) or next to a 25-base pair DNA Ladder (Life Technologies, Invitrogen, Paisley, UK) to determine the size of the DNA fragments. Gels were visualised and photographed using an ultraviolet transilluminator.

PCR protocol

The polymerase chain reaction-restriction length polymorphism method was used to determine the distribution and genotype frequencies of the SNP45 T/G polymorphism in exon 2 of the adiponectin gene. The DNA fragments containing the SNP45 was amplified from genomic DNA using the forward primers 5'-GCA GCT CCT AGA AGT AGA CTC TGC TG-3' and the reverse primer 5'GCA GGT CTG TGA TGA AAG AGG CC-3' such as in Li et al. [11] and Tu et al. [12]. Primers were ordered from Invitrogen (Life Technologies, Paisley, UK) and were made up to 100µmol primer stock solution by adding the recommended amount of distilled water to the primers according to the instructions on the certificate of analysis received from Invitrogen (see appendix for certificate). Polymerase chain reaction was carried out on samples of genomic DNA from exercise group using a thermal cycler (Techne, Staffordshire, UK) with conditions taken from the study by Li et al. [11] study. Conditions for the primers consisted of 35 cycles of; denaturation at 94°c for 30 s followed by annealing at 60°c for 30 s and then extension at 72°c for 30 s. The PCR products were then kept in incubation at 25°c by applying a final hold of 25°c on the thermal cycler. 5µl of each PCR product from each subject was run on a 2% agarose gel at 120V for 60 minutes and then 100v for 20 minutes alongside a Quick-Load 2 Log DNA Ladder (New England Biolabs, Massachusetts, USA) to assess fragments size.

Restriction digest

After PCR was completed, 10µl of the product was mixed with 2 µl of Sma1 (New England Biolabs, Hertfordshire, UK) 5 µl of buffer and 33 µl of distilled water. This was then incubated in the thermal cycler at 25°c for 12 hours.

Statistics

Statistical analysis was performed using Excel and R statistical software. All parameters were compared between baseline (week 0) and post HIIT (week 6) by using the paired t-test. The data was checked for normality by using the Shapiro-Wilk normality test. The data was deemed normal if the p value exceeded 0.05. All measurements were assessed to see whether there was a significant difference between pre-HIIT and post-HIIT by using the 2 tailed t-test. Area under glucose curve was calculated using the standard trapezoid rule on Excel.

Results

Mean physiological and biochemical measurements at baseline week 0 (pre-HIIT) and week 6 (post-HIIT) are recorded in Table 1. Statistical analysis revealed that there was no significant difference between initial measurements (t=0) of the test and control group. Although controls did not participate in the HIIT programme during the 6-week period, the nomenclature "pre-HIIT" will be used to refer to both test and control subjects' measurements prior to the beginning of the HIIT protocol. On the contrary, "post-HIIT" will be used to test and control subjects' physiological measurements recorded after the 6-week HIIT period. We can see from Table 1. that there was a tendency for some of the measurements to change. During the data collection, many of the control failed to provide data for pre and post HIIT therefore it was decided to exclude 3 as there was only one part of data rather than two, giving us a sample of 6 for the control VO_2max. It is important to note test subjects were allocated a number with the letter A, whilst controls were categorised as a number and a B letter. Early on in the HIIT, test subject 48A suffered a tibial fracture and as a result was not able to complete the HIIT programme. 48A therefore moved to the control group and did not partake in the exercise, only the physiological testing at 0 and 6 weeks. The mean weight of the test group decreased by 0.27 kg following the HIIT programme (p=0.349) whilst the control group's weight also decreased but only by 0.12 kg (p=0.849). The mean BMI also decreased in the test subjects by 0.08 Kg/m^2 (p=0.4387) whilst there was no change in the control group with the BMI staying the same at 24.14 Kg/m^2 (p=1). A decrease of 1.07% was seen in the test subject's body fat index (BFI) using the callipers with p value of 0.314, whilst an increase of 0.2% was seen in the control subjects (p=0.9054). A statistically significant result was seen however when the BFI was calculated using the electronic scales. The test subjects BFI decrease by 0.94% (p=0.03312). On the contrary, this significant change was not seen in the control group which showed an actual increase of 1.8% (p=0.368).

VO_2max response to HIIT can differ extensively

Statistical analysis of the test group VO_2max following HIIT revealed no significant change. After the HIIT programme, the test subjects' VO_2max decreased by 0.35 ml/min/kg (p=0.849) from baseline to week 6 compared to the control group which actually increased by

4.62 ml/min/kg although this was not statistically significant (p=0.490). When only looking at the positive responders in the test group (subject 40A, 49A, 50A, 51A and 52A) the mean increase in VO_2max was 3.72 ml/min/kg ± 0.72. (p=0.711). It is interesting to see that the VO_2max post HIIT decreased by 16.16% in subject 44A (Figure 2).

Tolerance to a bolus of glucose is highly variable

From looking at the test group in Figure 3, we can see a decrease in the glucose AUC in 6/9 (66.7%) of the test subjects. The remaining 3 test subjects (40A, 44A, and 49A) AUC increased 1.52%, 4.29% and 10.61% respectively. The largest improvement in glucose AUC was test subject 50A with a 16.7% decrease from 972.75 to 810.3 arbitrary units. The positive responders (41A, 46A, 47A, 50A, 51A, 52A) had a mean decrease of 51.11 arbitrary units ± 23.43 (p=0.233). Subject 49A exhibited a 10.61% increase in glucose AUC from 805.5 to 891 arbitrary units (Figure 3).

HIIT can influence blood pressure significantly

There was a significant decrease in the mean test subjects' systolic blood pressure of 5.32 (p=0.004579). The mean systolic blood pressure within the control group also decreased by 3.81 but this was not statistically significant (p=0.178). 8/9 (89%) of the test subjects responded positively resulting in improvement in systolic pressure, with only test subject 46A increasing 0.6% from 120.25 mmHg to 121 mmHg. Following the HIIT programme, there was a mean decrease of 5.6 mmHg (p=0.049) in the test subjects' mean diastolic blood pressure, compared to a decrease of 5 mmHg (p=0.151) in the control. It is interesting to see the variety of different changes occurring, with subject 44A's diastolic blood pressure decreasing by 23.1%, whilst subject 47A's diastolic blood pressure increased by 8.9%. The control subjects' diastolic blood pressure also changed variably with some individual improving significantly (42B, 43B, 44B, 54B and X) whilst other control subjects' diastolic blood pressure worsened (48B and 59B) (Figures 4 and 5).

Detection of Adiponectin 45T/G SNP

Polymerase chain reaction-restriction fragment length polymorphism method was utilised to identify adiponectin 45T/G SNP. Figures 6 and 7 illustrates the genomic DNA of each test subject. Control subject 48A was included also due to 48A originally being a test subject but who had had to withdraw from the test. It is evidently clear that extraction of genomic DNA from each test subject was successful and that the restriction enzymes could now be applied to investigate the distribution of allele and genotype frequencies of 45T/G SNP in exon 2 of the Adiponectin gene. Restriction enzyme digest of the test subjects' DNA using *Sma1* revealed that subject 49A was a heterozygous T/G individual with the SNP producing fragments of 372, 209 and 163 base pairs. The remaining test subjects were all deemed wild type T/T without the SNP, producing 1 fragment at 372 base pairs.

Table 2 displays the individual changes which occurred in each test subject following the 6-week HIIT programme. We can see that the majority of the changes post HIIT are beneficial and that there are fewer worse results compared to improvements. It clearly shows the heterogenous response to personalised HIIT with some subjects responding very well improving each cardiovascular risk marker (subject 52A) whilst others do not do so well only improving half of the parameters (subject 49A). From looking at subject 49A who displayed the +45T/G SNP, we can conclude that HIIT improved blood pressure, BFI% (scales) and VO_2max, whilst increasing the glucose AUC 10.61% and increasing the subject's weight by 0.3 kg.

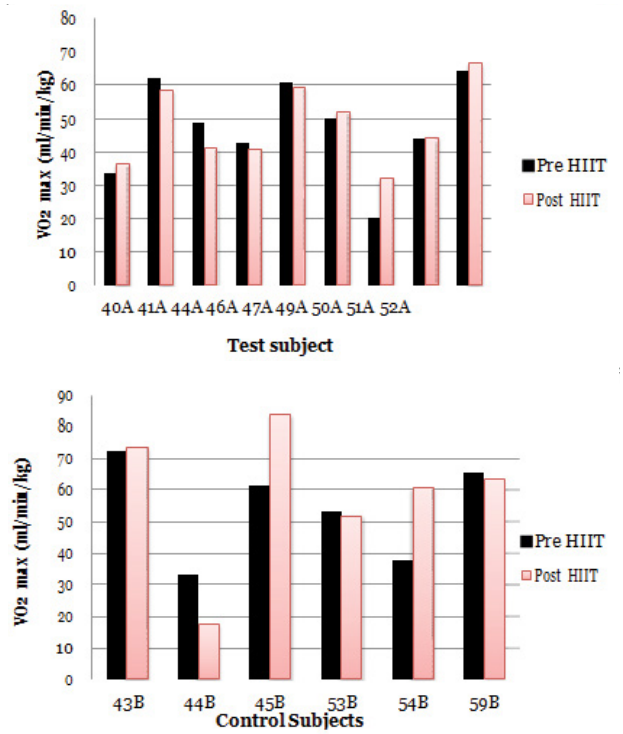

Figure 2: Column charts displaying the VO_2 max results of the test and control subjects pre- HIIT and post-HIIT. These charts illustrate the varied response to the programme with some individuals improving dramatically (45B), whilst some individuals remain with the same VO_2 max (51A) post HIIT, and others VO_2 max decreased following HIIT (44A).

Discussion

Findings

The main findings of this study are that individuals who took part in a 6-week HIIT protocol induced greater positive changes in systolic blood pressure, diastolic blood pressure and body fat index compared to control group. These changes were statistically significant and therefore strengthen the potential for HIIT to be utilised in a clinical setting. This was complemented also by a variety of improvements in other parameters including VO_2max and glucose AUC, although not significant. From contextualising the data with previous literature on HIIT, this will assist in the critical evaluation of the results and strengthen the argument for utilising HIIT in clinical practice. We can see in Table 3 various HIIT studies which we can evaluate alongside our study design.

From comparing our results and findings with pre-existing literature which evaluates HIIT, we can hypothesise that in order to induce greater positive physiological and biochemical changes within individuals, such risk markers need to reside outside normal working ranges initially before starting HIIT. Numerous studies have analysed HIIT for its beneficial use as a low-cost treatment option. Babraj et al. [13] conducted a study on sixteen young healthy men in order to assess whether HIIT would have beneficial results in healthy individuals. From as little as 2 weeks, HIIT induced significant changes in glucose AUC, insulin sensitivity and NEFA concentration-time curve (12%, 37%, 26% respectively, all p <0.001). This supports the argument that if HIIT can cause significant positive changes in individuals who are

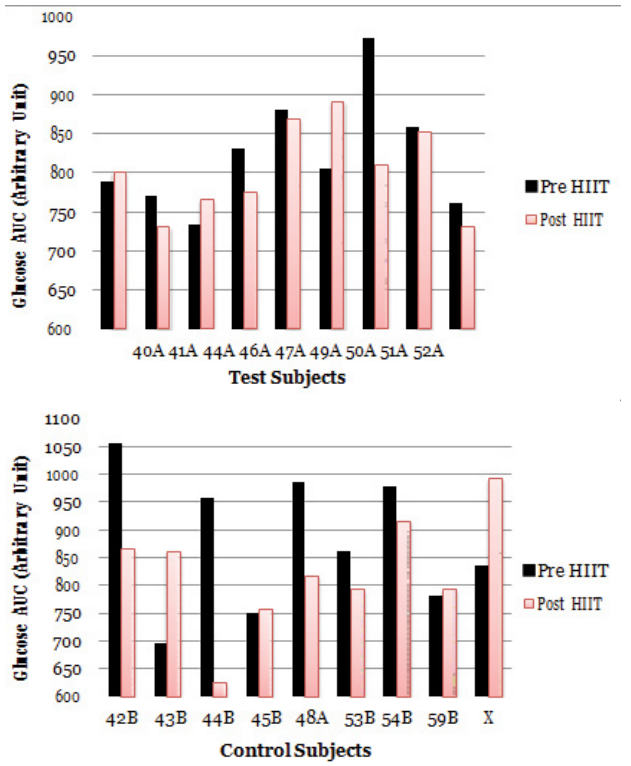

Figure 3: Glucose AUC charts for test and control subjects. Results show that the majority of test subjects (66.7%) glucose AUC improved. The mean AUC of the test subject decreased by 19.745 ($p = 0.409$) whilst the control group mean AUC decreased by 54.52 ($p = 0.341$).

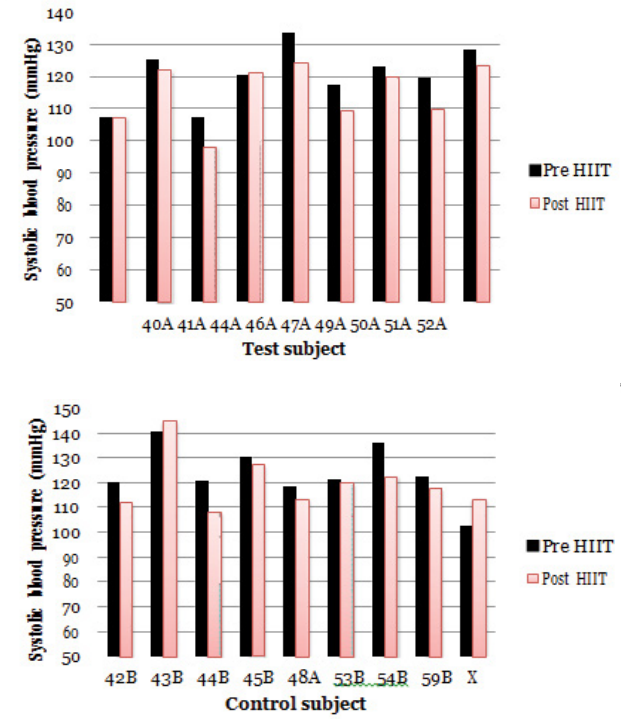

Figure 4: Systolic blood pressure results for pre and post HIIT in test and control groups. There were large decreases seen by 44A and 54B whilst subject X's systolic blood pressure significantly increased by 10.5%

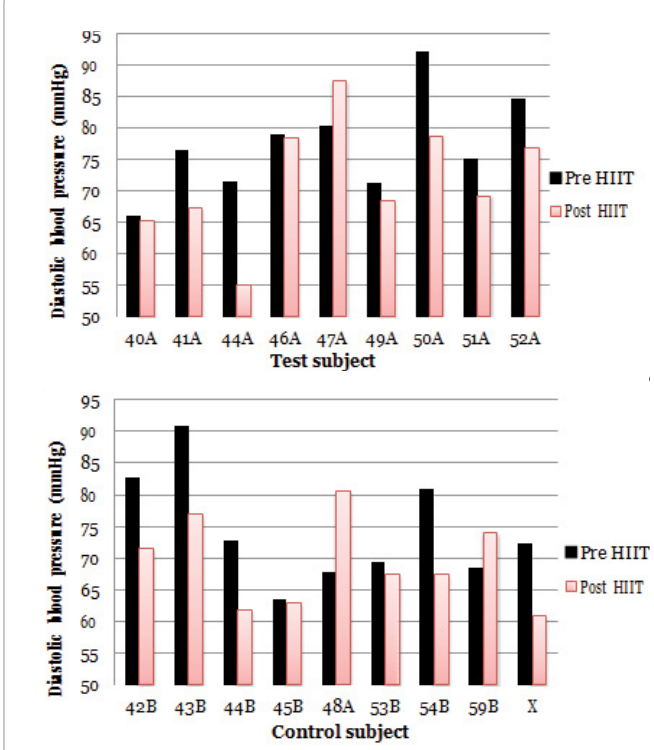

Figure 5: Effects of HIIT on diastolic blood pressure in test and control subjects. Results from both sets of data seem to have a much more varied nature compared with other parameters with large increases in 47A, and 48A, and large decreases in subjects 44A, 50A, 43B and 54B.

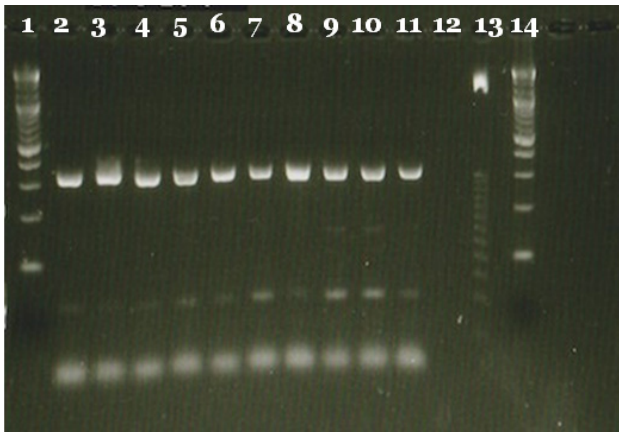

Figure 6: Gel electrophoresis of genomic DNA of test subject and control subject 48A. From left to right; Lane 1- Log2 ladder, Lane 2- 40A, Lane 3- 41A, Lane 4- 44A , Lane 5- 46A, Lane 6- 47A, Lane 7- 48A, Lane 8- 49A, Lane 9- 50A, Lane 10- 51A, Lane 11-52A, Lane 12- empty , Lane 13- 25 bp ladder, Lane 14- Log2 ladder. Lane 7 (subject 48A) is a control and was included in the restriction enzyme digest.

already healthy in as little as 2 weeks, then the area for improvements in individuals whose risk markers lie outside normal range could improve dramatically. Another study conducted by Whyte et al. [14] displayed that 2 weeks of HIIT training in 10 overweight/obese males resulted in significant improvements in systolic and diastolic blood pressure, whilst also decreasing glucose AUC although there was no change in Insulin sensitivity. Many of our findings are consistent with

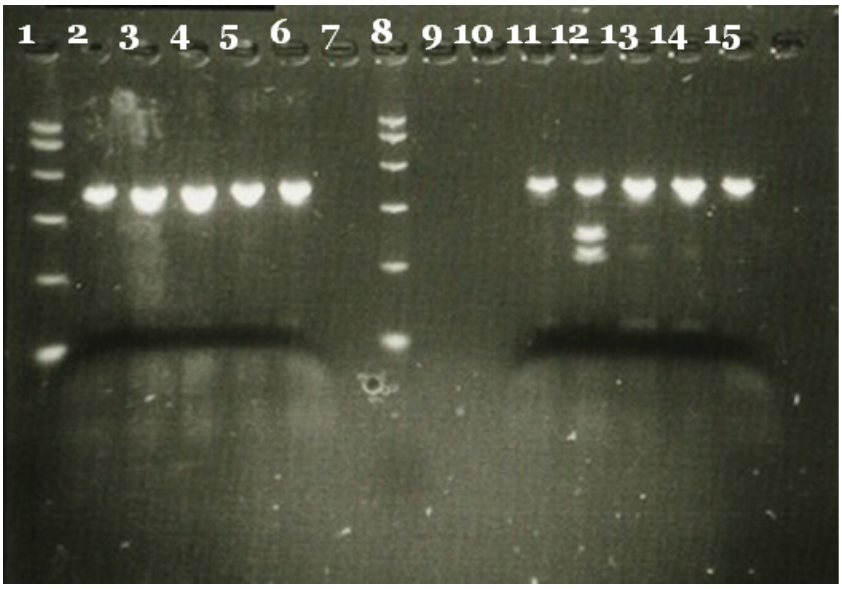

Figure 7: Ultraviolet image of restriction enzyme digest of all test subjects. From left to right, Lane 1- Log2 ladder, Lane 2- 40A, Lane 3- 41A, Lane 4- 44A, Lane 5- 46A, Lane 6- 47A, Lane 7- empty, Lane 8- Log2 ladder, Lane 9- empty, Lane 10- empty, Lane 11- 48A, Lane 12- 49A, Lane 13- 50A, Lane 14- 51A, Lane 15- 52A. 48A is illustrated in this image but it is important to note that this is a control subject and 48A did not take part in HIIT. Test subject 49A appears to be Heterozygous TG producing fragments at 372, 209 and 163 base pairs (bp). All other subjects are wild type TT producing 1 fragment at 372 bp.

Physiological Measurements	Control Week 0 (9)	Control Week 6 (9)	P value	Subject Week 0 (9)	Subject Week 6 (9)	P value
Weight (kg)	75.04 ± 5.46	74.92 ± 5.64	0.8499	68.88 ± 6.92	68.61 ± 6.91	0.3491
BMI (kg/m2)	24.14 ± 0.82	24.14 ± 0.77	1	24.11 ± 1.76	24.03 ± 1.76	0.4387
Systolic blood pressure (mmHg)	123.67 ± 3.70	119.86 ± 3.70	0.1789	120.26 ± 2.90	114.94 ± 3.05	0.004579
Diastolic blood pressure (mmHg)	74.31 ± 2.91	69.31 ± 2.31	0.1519	77.49 ± 2.63	71.89 ± 3.18	0.04909
Pulse pressure (mmHg)	49.36 ± 3.22	50.56 ± 3.73	0.8223	45.22 ± 2.66	43.06 ± 1.70	0.9174
% BFI (calipers)	18.67 ± 2.80	18.87 ± 2.68	0.9054	19.89 ± 2.04	18.82 ± 2.10	0.314
% BFI (scales)	20.98 ± 2.70	22.78 ± 2.75	0.3688	24.72 ± 3.53	23.78 ± 3.36	0.03312
Waist cir (cm)	77.66 ± 3.06	77.11 ± 3.10	0.2755	76.16 ± 4.28	76.50 ± 3.78	0.8296
Hip cir (cm)	90.64 ± 3.00	92.11 ± 3.35	0.3512	92.5 ± 4.36	91.94 ± 4.28	0.4198
VO2 max (ml/min/kg)	53.85 ± 6.34 (6)	58.47 ± 9.37 (6)	0.4903	47.48 ± 4.81	48.83 ± 3.93	0.8495
Glucose AUC	878.45 ± 43.51	823.93 ± 36.52	0.3416	822.425 ± 24.46	802.68 ± 19.46	0.4097

Table 1: Mean physiological measurements of the test and control subjects at week 0 and 6. The sample size is 9 for both test and control unless otherwise stated in brackets.

Test Subjects	Weight (kg)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	% BFI (scales)	% BFI (calipers)	BMI	VO2 max (ml/min/kg)	Glucose AUC
40A	-0.35	0.25	0.75	0	0	-0.15	-2.8	-12
41A	-0.7	3.125	9.375	0	2.35	-0.05	3.6	39.75
44A	0.1	9.5	16.5	2.5	5.45	0.05	7.9	-31.5
46A	0.5	-0.72	0.625	2	-0.2	0.15	2.3	54.75
47A	1	9.375	-7.125	2	0.85	0.2	1.6	12.6
49A	-0.3	8.25	2.875	1.5	-4.4	-0.1	-1.6	-85.5
50A	-0.1	3.375	13.625	0	-0.45	0	-11.8	162.45
51A	0.3	9.8	6	-0.5	5.05	-0.15	-0.1	5.7
52A	2	4.875	7.75	1	1	0.7	-2.3	31.425

Table 2: Table to show changes occurring post HIIT in test subjects. Physiological measurements were calculated by gathering the value at week 0 and subtracting the value at week 6 from it. If the resulting number was negative, then this would mean that there is an increase since the initial value pre HIIT. Positive numbers indicated a beneficial change in the parameter apart from VO2 max, where a positive number actually indicated a decrease in VO2 max. For ease of use, numbers highlighted in yellow represent a beneficial improvement in the parameter, whilst numbers in red actually represent a worse results post HIIT.

the growing body of literature that HIIT can improve cardiorespiratory fitness markers associated with obesity and DM2. These studies in Table 3 alongside our study, therefore, support HIIT as a potential cost effective, primary intervention that may delay and potentially prevent health burdens associated with lifestyle related diseases.

VO_2max

Following the HIIT programme, our test group saw an average increase of 2.8% in VO_2max and from contextualising these results with other studies, this would be in agreement with pre-existing literature

Author and publish date	Sample size	Working conditions	Physiological and biochemical changes post HIIT
Dall CH et al. [16]	17 participants (all heart transplant recipients (mean age= 52 years; 75% male)	12 weeks- 2 x 4 min; 2 x 2 min; 4 x 1 min; All >80% of VO2 peak; 2 min recovery between each set	↑ in VO2 peak (17%) ↓ in systolic bp (p= 0.037) ↑ in Heart Rate by 4.3 beats per minute
Mancilla et al. [30]	18 participants which are overweight or obesity and glucose intolerance	12 weeks- 10 x 60s with 2 min rest in between sets speed maintained at 30-40 km/h	↑ in VO2 max (24.6%) ↓ in 2-hour OGTT (-33.7 ± 47.9 mg/dL or -12.5%) ↓ in body fat (-4.3 ± 5.6 Kg)
Kuehnbaum [31]	11 female participants	6 weeks-10x60s at 90% maximal Heart rate 1 min rest between sets at 50W	↑ in VO2 max (4.7 ± 3.4 ml/min/kg ↑ in Wmax (26 ± 15 W) - No overall improvement in glucose AUC
Bouchard et al. [15]	89 participants (64M 25F) Mean age- 16.7 years	7 weeks -4x30s with 30s rest (3x week for 2 weeks) - 5x30s with 30s rest (3x week for 2 weeks) - 6x30s with 30s rest (3x a week for 2 weeks) - 6x30s with 20s recover (3x a week for 1 week) Running Maximal effort	↓ in systolic bp from 119 to 114 - Cardio respiratory function improved from 79 to 84 - No change in diastolic bp, HDL, LDL, total cholesterol and triglycerides
Racil et al. 2013 [17]	34 females (11 in HIIT group) mean age 15.9 years Obese	12 weeks -6x30s with 30s rest (100% maximal effort/50%) for 4 weeks -8 x 30s with 30 s rest (105% effort) for 4 weeks - 8x30s with 30s rest (110% effort) for 4 weeks	-Weight 83.5 ↓ 80.3 cm - Waist cir 93.7 ↓ 90.3 cm - Body fat % 37.2 ↓ 34.3 -VO2 max 36.9 ↑ 39.7 ml/min/kg
Hood et al. [26]	7 participants (4M 3F) 45 years sedentary, healthy	10x60s with 60 s recovery; 60% of peak power 3x week, 2 weeks	↑ 260% Glut 4 transporter ↓ fasting insulin - ↑Insulin sensitivity of 35% by the insulin sensitivity index
Whyte et al. [14]	10 males, untrained, mean age- 32 overweight/obese	4x30s x 2 session; 5x30s x 2 session; 6x30x 2 session; max effort 2 weeks	Glucose AUC 15.6 ↓ 14.9 (not significant) -VO2 max 32.8 ↑ 35.9 ml/min/kg - systolic 127 ↓121 mmHg - diastolic 80 ↓ 71 mmHg -Fat oxidation 0.11 ↑ 0.13 g/min -No change in Insulin sensitivity
Babraj et al. [13]	16 males 21 years healthy recreationally active	2 weeks; 4x 30s cycle twice; 5x30s cycle twice; 6x30s cycle twice; Max effort	Glucose AUC 664 ↓ 585 Insulin sensitivity 80 ↑ 98 (Cederholm index) - Plasma Non-Esterified Fatty Acid (NEFA) AUC decreased 31584 ↓ 23370 - Work done in 250 kJ time trial increased by 6%
Tjønna et al. [23]	32 participants - Metabolic syndrome patients - 52.3 years	16 weeks- 4x 240s (90% maximal effort) with 180s rest (70% effort) - 3x week	Insulin sensitivity 62.2 ↑ 72.2 - Adiponectin 7.8 ↑9.4 - Weight 91.8 ↓ 89.5 - Systolic bp 144 ↓ 135 mmHg - Diastolic bp 95 ↓ 89 mmHg - VO2 max 33.6 ↑ 45.3 ml/min/kg

Table 3: Numerous HIIT studies with working conditions and findings summarised.

that HIIT could serve as a low-cost treatment option for individuals who are at risk of developing a lifestyle related disease.

When comparing the findings of our study with recent literature on HIIT, it is important to consider the length and intensity of the HIIT protocol alongside the type of subjects gathered to complete the training programme. Our study consisted of 9 working minutes per week. Although our results showed that 6 weeks of HIIT induced a positive change in VO_2, other studies have demonstrated that as little as 2 weeks is enough to induce these changes. Whyte et al. [14] displayed that 2 working weeks was enough to cause significant improvements in VO_2max (32.8 ml/min/kg - >35.9 ml/min/kg p=0.015) whilst Tremblay et al. [15] conducted a 15 week study to assess whether HIIT caused beneficial changes in healthy individuals who were not obese, and results from this study demonstrated that HIIT induced greater losses in subcutaneous fat than endurance training.

Another factor which is important to consider when evaluating the results is the varying levels of intensity related to HIIT. Our study calculated the working wattage for each individual by an exhaustive incremental cycling test and using the breaking wattage as the working wattage for the subject. Our study proved that HIIT is a safe method of physical activity since no injuries were reported. The rigorous nature of HIIT meant that our study involved 1-minute repetitions of full out maximal effort, whilst other studies such as Tremblay et al. [15], consisted of short sharp 15 second bursts, working up towards 30 seconds in the latter stages of the protocol. Dall et al. [16] adopted a longer working set involving 4-minute repetitions at working efforts greater than 80% of VO_2 peak. Our study involved healthy young individuals who were within normal parameters for most of the physiological measurements. It is interesting to see that when we look at individual results, a variety of different outcomes post HIIT occur. Subject 50A was the heaviest test subject but was the individual whose VO_2 improved the most from 20.1 to 31.9 ml/min/kg. This shows that individuals who are already fit and healthy may find it harder to improve their VO_2max whilst someone who is not so athletic and perhaps overweight may be prone to greater physiological improvements. Racil et al. [17] investigated the effects of a 12-week HIIT programme on young obese females. Results displayed an average significant increase of 7.6% in VO_2max whilst our study only displayed an average of 2.8%. However, from looking at subject 50A, perhaps the individual most at risk of developing a lifestyle related disease, their VO_2max increased 58.7% thereby strengthening the argument that individuals who are at an increased risk of developing a lifestyle related disease will have greater positive changes from HIIT. As VO_2max improved in both

test and control group, it is difficult to suggest that HIIT was solely responsible for the improvement in physiological fitness since the control group did not undertake HIIT.

Currently, although the exact mechanism is unknown, low VO_2max levels seems to correlate with reduced insulin sensitivity, and as a result can be used as a predictive marker to identify individuals at risk of developing DM2 [18]. If we can therefore improve VO_2max in individuals who are beginning to develop insulin resistance, not only would this be of clinical relevance from an improved insulin sensitivity point of view but also decrease the risk of developing coronary heart disease in later life [19]. A large study conducted by Aspenes et al. [20] revealed that women with a VO_2max <35.1 ml/min/kg were five times higher to have a cluster of cardiovascular risk factors compared to those who had VO_2max levels higher than these parameters.

Systolic and diastolic blood pressure

Current guidelines defined by the European Society of Hypertension define optimal systolic blood pressure as <120 and normal as between 120-129 mmHg, whilst optimal diastolic is <80 and normal between 80-84mmHg [21]. Numerous studies have reported that HIIT is effective in reducing systolic and diastolic blood pressure [22]. Our study also supports this hypothesis and results show that test subjects mean systolic and diastolic blood pressure pre HIIT was 120.26 mmHg and 77.49 mmHg respectively. Measurements were repeated post HIIT and systolic blood pressures had decreased by 5.32 mmHg whilst diastolic was reduced was also reduced by 5.6 mmHg. It was initially thought that it would be very difficult to induce significant positive changes in blood pressure when the current blood pressures were already in healthy normal parameters. The findings from our study proved that 6-week HIIT programme yielded statistically significant improvements in blood pressure of young healthy individuals. One could craft an argument therefore over the clinical benefits of HIIT as a potential low-cost therapy for individuals who are DM2 or obese and at risk of developing secondary macrovascular complications. Current research yields varied results as to the benefits that are achievable from HIIT, with some studies unable to show an improvement in blood pressure.

Whyte et al. [14] conducted a short 2-week HIIT study in overweight and obese men, and results showed a 4.7% reduction in systolic blood pressure after 24 hours post training- but this beneficial change was not sustained at 72 hours post exercise. The authors suggested the positive changes failed to last post HIIT due to a reduction in sympathetic nervous activity and enhanced nitric oxide-mediated vasodilation. This was in agreement with Tjønna et al. [23], who proved that 16 weeks of HIIT resulted in a 6.25% and 6.32% decrease in systolic and diastolic blood pressure respectively. Contrary to this, Gormley et al. [24] investigated a 6-week HIIT programme and results showed no significant decline in systolic and diastolic blood pressure when subjects exercised at 50%VO_2R (difference between resting and maximal VO_2), 75% VO_2R and 95% VO_2R. From analysing their findings, they concluded that there was no significant changes in blood pressure. This may be due to the fact that subjects already had very low blood pressures pre HIIT (108/65 mmHg) and would be difficult to improve blood pressure readings further.

Glucose and insulin sensitivity

Results from our study displayed that between week 0 and 6, there was a mean decrease of 19.745 arbitary units in the test group compared to a mean decrease of 54.52 in the control group. Although the change was not statistically significant, it does agree with the pre-existing literature on how HIIT improves glucose control and was consistent with the work of Babraj et. al [15] which showed that 2 weeks of HIIT caused a 12%, 37% and 26% decrease in the glucose AUC, insulin and non-esterified fatty acid (NEFA) concentration respectively. A reduction in NEFA is clinically important as NEFA regulates insulin sensitivity throughout the body (Ndlovu 2013).

Reduced plasma NEFA levels has been shown to positively regulate insulin sensitivity during an oral glucose tolerance test (OGTT) [25]. As there was a large decrease in glucose AUC in the control group, it is difficult for us to say that HIIT was solely responsible for the improvement as the control group did not participate in the HIIT programme. Hood et al. [26] reported a 260% increase in GLUT 4 transporter expression following a 2-week HIIT programme, and subsequently a 35% increase in insulin sensitivity at 72 hours post HIIT. This study shows the potency of a short HIIT programme and its ability to improve the uptake of glucose, thus preventing the development of DM2. Future research may be worth assessing whether HIIT increases the expression of GLUT4 transporters. All this evidence therefore displays the efficacy of HIIT as an effective strategy to promote good health.

Body fat index

Obesity has long been known to be a major risk factor in the development of prediabetes and DM2 [27]. This study demonstrated that a 6-week HIIT programme caused a significant decrease in test subject body fat index by 3.8%. This result correlates with Racil et al. [17] who demonstrated that a 12-week HIIT programme caused a 7.8% reduction in body fat index. Although our study supports the concept of HIIT as a beneficial intervention to decrease BFI, it is important to note however that the measurement of BFI on the calipers did not yield a significant change.

Although the caliper measurement yielded an average 5.4% decrease in BFI, this failed to give a significant result and it is important to consider the strengths and limitations of each measurement. The fat calipers provide a realistic measurement of subcutaneous fat and minimal technical skill is needed in order to master this method. Disadvantages however include the human technical source of error [28]. It was agreed that a selected individual would carry out all BFI measurements in order to decrease the human technical error but due to time constraints, it was not possible and therefore every test subject had a different person performing the procedure This would decrease the reliability of the procedure due to some individuals being much stricter with their location of the measurement site, whilst other individuals may be more lenient and collect a smaller reading in order to please their fellow test subjects. Another limitation of using fat calipers is that the equation used to calculate body fat percentages from skinfold thickness measurements was derived from data of healthy individuals. Any result from our study which lay outside normal parameters will therefore give poor precision and accuracy. When calculating an individual BFI, any error will be magnified by the use of prediction equations not derived from a comparable (obese/overweight) population. The use of a bioelectrical impedance analysis scale to measure BFI in our study provided an alternative method which may be more relevant in this type of research. As this programme investigated whether any changes would occur as a result of HIIT, although the scales may not be as accurate as calipers, they would provide more consistency throughout the study.

Adiponectin 45T/G SNP

From genomic analysis of the test subjects, subject 49A was a heterozygous T/G individual with 3 fragments cleaved as a result.

From looking at the individual changes in Table 2. we can see that 49A's glucose AUC increased by 10.61% and this is in agreement with pre-existing literature. A meta-analysis conducted by Li et al. [29] revealed that individuals with SNP+45G allele displayed an increased risk of developing DM2. This would agree with our findings since test subject 49A glucose AUC has got worse following HIIT indicating a worsened glucose/insulin sensitivity and the subject had also gained 0.3 Kg (0.5% increase). Li et al. [11] commented that individuals with the +45 SNP were associated with obesity and insulin resistance. From contextualising this theory with our data, it would be in agreement that individual 49A who possesses the SNP is at an increased risk of developingDM2 and that this polymorphism is associated with lower plasma adiponectin compared to individuals with the T allele. Li et. al [11] argues that 45T/GSNP affects insulin resistance by possible altering the stability of mRNA, modifying circulating levels of adiponectin and eventually decreasing plasma adiponectin concentration. It may be beneficial to investigate whether if an individual has 45T/G SNP, how would this affect adiponectin levels and whether HIIT would cause any changes in levels of Adiponectin and TNF-α.

Conclusion and Future Research

The main research aim of this study was to assess the effects of a 6-week HIIT programme on physiological and biochemical markers associated with DM2. Our findings found tendencies for body fat index, systolic and diastolic blood pressure to significantly change after 6 weeks of HIIT. Although these were not significant, there was also a tendency for weight, BMI, glucose AUC and VO_2max to also improve, demonstrating the heterogenous responses individuals can have as a result of HIIT. This study therefore highlights that 54 minutes of intense physical activity over a 6-week period has the ability to significantly improve risk markers associated with DM2. This is important since obesity and the development of DM2 have become a worldwide epidemic, and One of the solutions to prevent this is a loss of fat mass. Not only would this improve risk markers, enhance quality of life and decrease the amount of mortalities associated with DM2, but would also have enormous economic benefits to health care systems worldwide. As this was a pilot study, it was decided to recruit a small number of individuals initially, as the aim of this was to primarily test safety and feasibility. Upon showing this, we would like to continue the study and expand to increase sample size. Another factor which we would like to build upon was dietary monitoring. We asked patients to keep a nutritional diary and to maintain their current eating regimes whilst part of the study and for the follow up. As the patients were all healthy young individuals, we found it difficult to monitor physical activity levels outside of the programme. To account for this during the next study, we would ask all participants to complete an International Physical Activity Questionnaire to document daily activity levels. A growing body of literature supports the concept of a novel low-volume HIIT programme as an effective low-cost treatment plan for inducing central (cardiovascular) and peripheral (skeletal muscle) adaptations which are linked to improving an individual's physical health. Our study involved healthy young individuals who were not at risk of developing a lifestyle related disease such as DM2, but there is minimal literature on the effects of HIIT in individuals who are diabetics or who are pre-diabetic, thus the effects of HIIT on these types of individuals are not truly understood. Future studies, therefore, should investigate long term (months-years) HIIT interventions in a range of clinical cohorts such as individuals with insulin resistance, obesity and DM2. Further research into HIIT would be to identify the genes which may pre dispose individuals to respond better to HIIT than conventional exercise, and screen genetic makeups in order to determine which individuals would benefit from HIIT and which would require medical intervention and screen genetic makeups in order to determine which individuals would benefit from HIIT and which would require medical intervention. Extensive further research is therefore needed for the vision of HIIT as a form of personalised medicine to become a reality in everyday life.

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