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The Impact of Moderate Combination Exercise on HbA1c, IL-6, and TNF in Type 2 diabetic and Non-diabetic Subjects: an Interventional Non-randomized Clinical Trial

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Abstract— **Introduction:** The main causes of worldwide increase in prevalence of type 2 diabetes are the daily consumption of excessive number of calories and sedentary lifestyle. Diabetes is usually accompanied by hypertension, lipid disorders and obesity that are considered as risk factors for developing diabetes. This study is designed to assess the benefit of a combined exercise programme (cardio "aerobic" and resistance) on HbA1c and the inflammatory markers (IL-6, and TNF) in type 2 diabetic (T2D) and non-diabetic (ND) subjects. **Materials and methods:** This is an interventional non randomized clinical trial conducted from 2016 to 2019 at exercise physiology laboratory at De Montfort University (DMU). Our target volunteers are T2D (HbA1c > 6.4), and ND (HbA1c < 5.8) with age group from 18-60 years old who are fit and able to do exercise. No restriction on weight. The HbA1c, weight, BMI, waist and lung capacity were measured at baseline and at the 12th exercise session. In each exercise session the participant performed a combined exercise program consists of 30 min of resistance exercise followed by 20 min moderate cycling to be done twice a week for 6 weeks. **Results:** We enrolled 17 T2D subjects in the intervention group 4 females and 13 males and 8 ND in the control group 5 females and 3 males. In both groups there was a significant reduction in HbA1c level after 6 weeks (P= 0.000). In T2D group there was a significant weight reduction that decreased from (92.0± 4.3) to (90.0±4.5), (P< 0.001) and BMI reduction that decreased from (30.8± 1.0) to (30.2± 0.9), (P< 0.001). In ND, the changes in weight reduction and BMI level were not significant. In T2D group the changes in IL-6 level were only significant after the last exercise session. It was increased from 1.79±0.4 to 3.88±1.9 pg/ml (P=0.002), while it was not significant in ND group. In T2D and ND subjects, the changes in TNF level were insignificant. **Conclusion:** Development of combination exercise programs as a non-pharmacological intervention for diabetic and non-diabetic population are essential to decrease the prevalence of diabetes worldwide. In addition to conduction of public awareness events for proper implementation.

Keywords: Diabetes type 2, combined exercise, HbA1c, IL-6, TNF.

1. Introduction

Diabetes mellitus (DM) is a chronic disease characterized by chronic persistent hyperglycaemia [1,2]. This hyperglycaemia accompanied with metabolic disorder leads to organ damage and serious complications. Incidence of type 2 diabetes (T2D) increased globally with obesity and sedentary life style [2]. In 2040 the diabetic subjects are expected to be more than 642 million. Diabetes is mostly accompanied by hypertension, lipid disorders and obesity. Recent studies show that a reduction in HbA1c cause 35% relative risk reduction for fatal/nonfatal cardiovascular disease. Also 56% reduction in CVD when reduction of HbA1c is accompanied with decrease in systolic blood pressure (SBP). Blood glucose level might be controlled only by diet and exercise or it might need pharmacological intervention using oral anti-diabetic medication. The IL-6 and TNF are inflammatory markers that are linked to diabetes, obesity and insulin resistance [3-7]. In the UK, diabetes cost approximately 10% of NHS health expenditure, and expected to rise to 17% by 2035/2036 [4].

Inflammatory markers such as cytokines are protein molecules that play main roles in operating the body immune system [8]. They are secreted by different kind of cells into the circulation, the reticulo-endothelial, the adipose tissue and the musculoskeletal systems. It is released into circulation in response to different stimuli e.g. infections, antigens, mental stress and exercise [9]. Adipose tissue is the main site for storage of extra energy in the form of triglyceride (TG). It consists of multiple cell types such as pre-adipocytes, adipocytes, immune cells and endothelial cells. Obesity causes adipose tissue dysfunction which leads to metabolic complication [10].

In humans, IL-6 is a protein synthesized by T cells and macrophages at the sites of inflammation to stimulate immune response in case of infection, burn, trauma or tissue injury. The IL-6 receptors are found in the hypothalamus and is

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important in appetite regulation. On the other hand, IL-6 affects the function of pancreatic β-cells as well as interfering with insulin signalling and also, its reduction linked to increase high-density lipoprotein (HDL) [12,13]. High level of IL-6 associated with Metabolic syndrome, but the mechanisms by which IL-6 decrease HDL levels are unclear [11-14].

The anti-inflammatory effect of IL-6 inhibits tumor necrosis factor (TNF) from affecting insulin signalling which could prevent metabolic syndrome and hyperglycaemia [15]. The action of IL-6 is altered according to the secreting tissue and its action is controversial because it acts as anti-inflammatory and pro-inflammatory cytokine [9,15]. Dual action might be due to either individual variation of training status or methodological differences in exercise intensity or duration [15]. Therefore IL-6 secreted acutely after muscle contraction during exercise and this is useful in the metabolism process as it acts as anti-inflammatory cytokine by inhibition of TNF [16]. The IL-6 is increased with obesity and T2D, as it linked to insulin resistance (IR) [12-13]. TNF is a pro-inflammatory cytokine and produced mostly by macrophages and monocytes [12,17]. TNF enhances the production of CRP and is positively correlated with IR and T2D [12-13]. An increase in TNF is associated with elevated level of TG, LDL, body weight and IR as well as decrease HDL [12,17].

The aim of this study is to investigate the effect of a combined exercise programme cardio "aerobic" (AR) and resistance (RE) on HbA1c and the inflammatory markers (IL-6, and TNF) in T2D and ND subjects.

2. Materials and Methods

This is an interventional study conducted from 2016 till 2019 in the exercise physiology laboratory at DMU. Ethical and research committee approvals have been obtained in 2015. The researchers trained for first aid and had phlebotomy course at Nottingham university hospital. The advertisement was on DMU website and diabetes UK website to recruit volunteers. Before starting the programme, each subject had introduction visit to the gym equipment and signed the consent form. We offered an incentive of a subsidised gym membership at the De Montfort University's QEII Leisure Centre on completion of 100% of the dates agreed. This is considered as a present for the subjects for their participation and also to help them maintain the healthy exercise regimen until the following year's assessment.

2.1 Study design

This is an interventional non randomized clinical trial which consist of a combined exercise program. In each exercise session the participant performed 30 minutes of resistance exercise followed by 20 minutes moderate cycling. This is done twice a week for 6 weeks. At the beginning of each session the participants had to stretch-up for 11 steps of stretching, then he/she must cycle for five minutes to warm up. The RE consists of 3 sets, in each set the volunteer performed (squat, chest, back, biceps and triceps) 10 times. The HbA1c, weight, BMI, waist and lung capacity were measured at baseline and the 12th exercise session.

2.2 Intervention group

The intervention group is (n=17) T2D subjects, 4 females and 13 males. The control group is (n=8) ND subjects, 5 females and 3 males.

2.3 Selection criteria for volunteers

T2D subjects with HbA1c > 6.4 and ND subjects with HbA1c < 5.8, age group range from 18-60 years old who are fit and able to do exercise. No restriction on weight so obese subject could participate in the study. Any subject doesn't have any issue from exclusion criteria can join the programme. All T2D volunteers who are using oral hypoglycaemic agents or insulin or on life style modification are illegible to participate as well.

2.4 Exclusion criteria

People who had any of the following criteria were not allowed to participate such as heart disease, liver disease, kidney disease, uncontrolled and very high blood pressure > 160/95 mmHg, injury, bleeding, epilepsy, acute exacerbated bronchial asthma, osteoporosis, arthritis, mentally ill, had recent surgery, using medications that increase blood sugar e.g. steroids and using medications that mask hypoglycaemic symptom e.g. beta blockers.

2.5 Laboratory analysis

Que-Test A1c reagent kit is used to measure Glycated haemoglobin (HbA1c). By using finger pricking procedure (FPP) and squeeze a large drop of blood on the cartridge then place it into the analyser. In approximately 5 minutes the result will appear on the screen as well as a print of the result. Venous blood samples were taken by using aseptic technique via the vacutainer system. Venous blood samples collected from each volunteer (in combination exercise) total of 9 samples. In the first session 1 at base line before starting exercise, the 2nd after resistance exercise, and the 3rd one after aerobic exercise. In the 2nd exercise session only one sample after exercise and the same at 4th, 6th, 8th, 10th, and 12th exercise sessions. These samples centrifuge and refrigerate the plasma to be analysed later by Randox machine (Evidence Investigator™ Metabolic Syndrome). The Evidence Investigator™ Metabolic Syndrome Array I (METS I) is used to analyse blood sample for different test such as for IL-6 and TNF.

2.6 Statistical analysis

Data was analysed by using Excel 2010 and SPSS (version 22), values were expressed as mean with standard error of mean (SEM). Pre and post exercise samples were compared using a paired-samples t-test and the level of statistical significance was ($P \leq 0.05$).

3. Results

Data for all study groups are presented in **tables 1 and 2**. In T2D the weight reduction was significant which decreased from (92.0± 4.3) to (90.0±4.5), (P< 0.001) (**figure 1**). The BMI reduction was significant, it was (30.8± 1.0) and decreased to (30.2± 0.9), (P< 0.001), as demonstrated in **figure 2**. In ND as in **table 2**, the result of weight reduction improved from (58.86 ± 1.2) to (58.22 ± 1.2). It has no significant changes when comparing pre S1 and post S12; in pre S1 (58.86 ± 1.2) and post S12 (58.22 ± 1.2), (P value=0.490). BMI shows no significant reduction in pre S1 (29 ± 0.4) and decreased to (28.1 ± 0.2), (P value=0.382).

Table 1. T2D anthropometric variables

T2D	Pre 1st Se Ex	Post 12th Se Ex	P value
Age (years)	48.6 ± 2.6	-	-
Height (cm)	170.35 ± 4.8	-	-
Weight (kg)	92.0± 4.3	90.0± 4.5	0.001
BMI (kg/m²)	30.8± 1.0	30.2± 0.9	0.001
Data are expressed as mean ± SE and P value.			

Table 2. Anthropometric variables for ND on combination exercise.

ND	Pre 1st Se Ex	Post 12th Se Ex	P value
Age (years)	31.6 ± 4	-	-
Height (cm)	167.4 cm ± 4.4	-	-
Weight (kg)	58.86 ± 1.2	58.22 ± 1.2	0.490
BMI (kg/m²)	21.2 ± 1.2	20.9 ± 0.9	0.382
Data are expressed as mean ± SE and P value.			

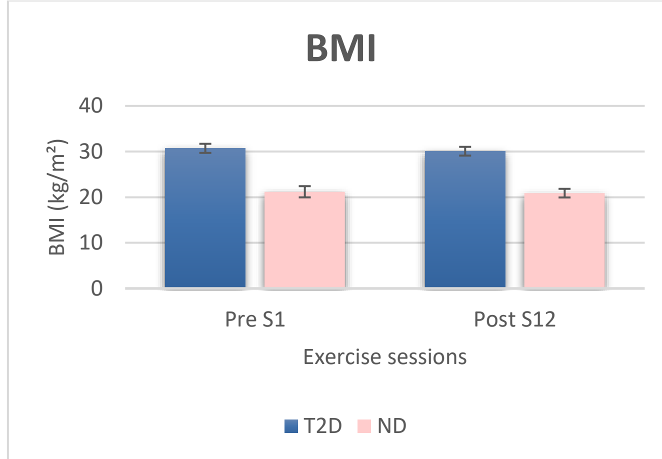

Figure 2. BMI changes across whole exercise sessions in both groups

In T2D and ND as in **table 3** and **figure 3**, there was significant reduction in the HbA1c level. These results demonstrate improvement in both study group. In T2D the reduction was (-6.8 mmol/mol "0.7 %") and in ND the reduction was (3.4 mmol/mol "0.4 %"). In the present study, HbA1c results in both T2D and ND has been significantly decreased after 12th sessions of combination exercise.

Table 3. HbA1c changes in T2D and ND exercise group.

	Pre S1	Post S12	P. value
HbA1c mmol/mol (T2D)	55.7± 2.7	48.9 ± 2.1	< 0.001
HbA1c mmol/mol (ND)	34.6 ± 0.6	31.2± 0.2	0.003
Data are expressed as means ± SE, % of differences, and P value.			

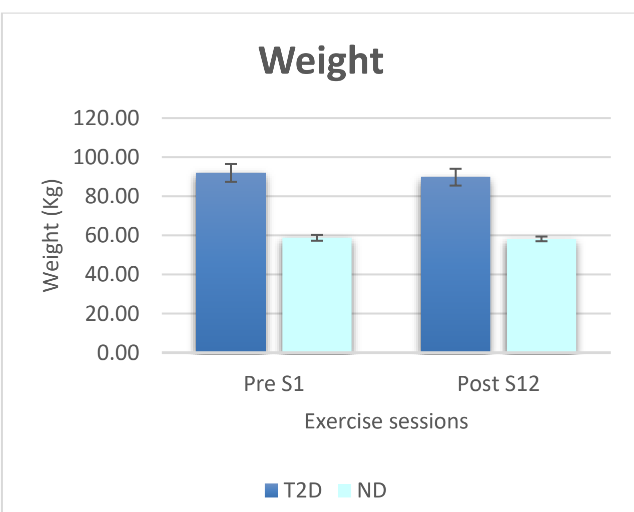

Figure 1. Weight changes across whole exercise sessions in both groups

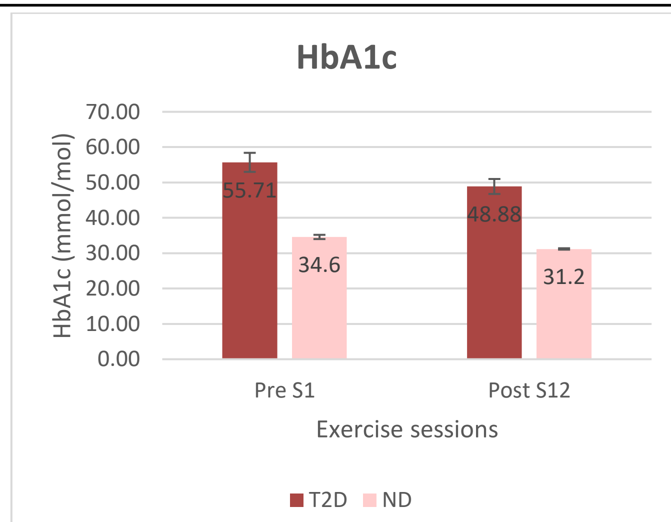

Figure 3. HbA1c changes across the exercise sessions in both group

The data obtained (in **figure 4** and **table 4**) for IL-6 shows an increment from 1.79±0.4 to 2.61±0.5 pg/ml (P=0.007) after the first exercise session which shows that the acute effect of combination exercise is significant. Moreover, IL-6 level was observed to increase with continuous performing regular exercise as demonstrated in **figure 5** and **table 5**, an increase from 1.79±0.4 to 3.88±1.9 pg/ml (P=0.002), this significant change suggests that chronic exercise increases the level of IL-6 higher than acute exercise.

In ND, the results for IL-6 show elevation after the 1st exercise session from 0.64±0.1 to 1.51±0.4 pg/ml, (P=0.074). Moreover, this level is found to remain high after 12th exercise session and a value of 1.10±0.5 pg/ml is obtained (P=0.126).

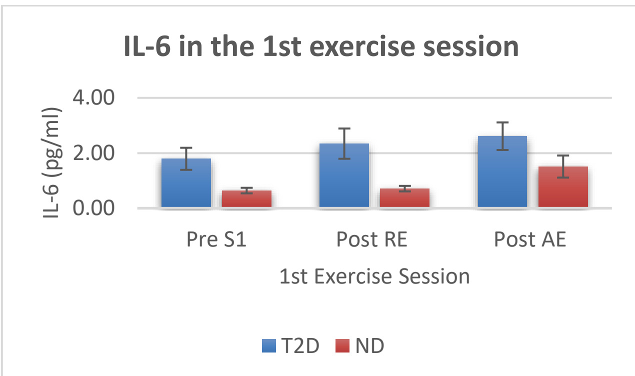

Figure 4. IL-6 level in T2D and ND across the 1st exercise session

Table 4. Changes in level of IL-6 was observed during the 1st exercise session (acute effect) in T2D and ND.

IL6 (pg/ml)	S1			P value
	Pre Ex	Post RE	Post AE	
T2D	1.79±0.4	2.34±0.4	2.61±0.5	0.007
ND	0.64±0.1	0.71±0.1	1.51±0.4	0.074
Data are expressed as mean ± SEM and P value for the effect Pre Ex (S1) and after S1 was obtained.				

In T2D arm, the value of TNF before exercise was recorded as 8.76±3.2 pg/ml and then decreased slightly to 8.06±2.7 pg/ml (P=0.489) after the acute effect of 1st exercise session (**figure 6** and **table 6**). Moreover, this level was slightly decreased after 6 weeks of exercise to 7.85±2.4 pg/ml (P=0.423) (**figure 7** and **table 7**). In ND group, there was increase in TNF level after 1st exercise session from 4.07±0.8 to 4.36±0.8 pg/ml (P=0.059). However, after 6 weeks of exercise a slight elevation of 4.11±0.5 pg/ml was observed (P=0.890).

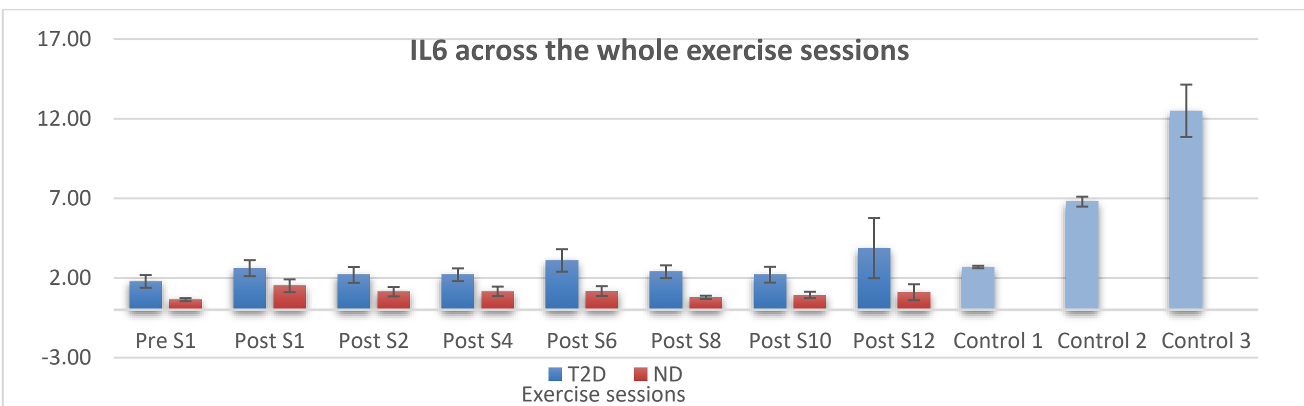

Figure 5. IL-6 level in T2D and ND across the whole exercise sessions

Table 5. Changes in IL-6 level was observed during the 12 exercise sessions (chronic effect) in T2D and ND.

IL6 (pg/ml)	Pre Ex	Post S1	S2	S4	S6	S8	S10	S12	P value
T2D	1.79±0.4	2.61±0.5	2.20±0.5	2.20±0.4	3.10±0.7	2.39±0.4	2.21±0.5	3.88±1.9	0.282
ND	0.64±0.1	1.51±0.4	1.14±0.3	1.16±0.3	1.18±0.3	0.79±0.1	0.94±0.2	1.10±0.5	0.126
Data are expressed as mean ± SEM and P value for the effect Pre Ex (S1) and after S12 was obtained.									

Table 6. Changes in TNF level was observed during the 1st exercise session (acute effect) in T2D and ND.

TNFA (pg/ml)	S1			P value
	Pre Ex	Post RE	Post AE	
T2D	8.76±3.2	8.20±2.6	8.06±2.7	0.489
ND	4.07±0.8	4.44±0.8	4.36±0.8	0.059

Data are expressed as mean ± SEM and P value for the effect Pre Ex (S1) and after S1 was obtained.

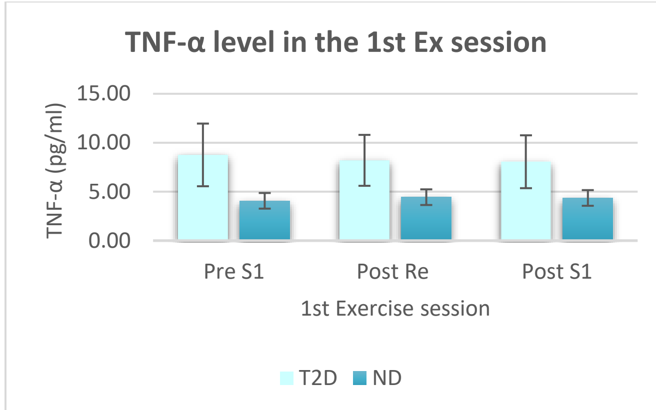

Figure 6. TNF level in T2D and ND in the 1st exercise session

Table 7. Changes in TNF level was observed during the 12 exercise sessions (chronic effect) in T2D and ND. Data is express as mean± SEM and P value for the effect Pre Ex (S1) and after S12 was obtained.

TNFA (pg/ml)	Pre Ex	S1	S2	S4	S6	S8	S10	S12	P value
T2D	8.76±3.2	8.06±2.7	5.97±0.7	8.37±2.7	8.55±2.7	7.05±2.1	5.82±0.79	7.85±2.4	0.423
ND	4.07±0.8	4.36±0.8	4.15±0.5	4.18±0.6	4.12±0.7	4.11±0.6	4.07±0.5	4.11±0.5	0.890

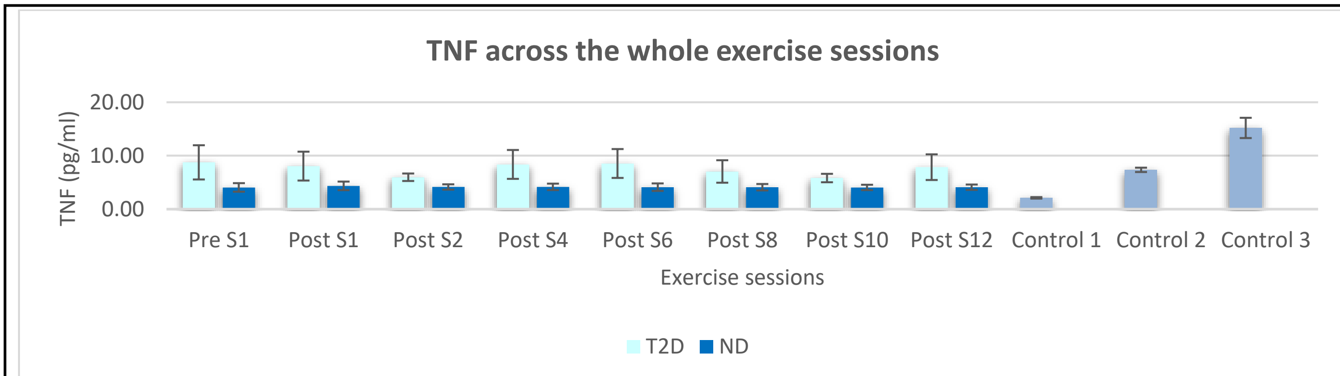

Figure 7. TNF level in T2D and ND across the whole exercise sessions

4. Discussion

Previous studies have shown the benefit of combination exercise on the improvement of HbA1c. Sigal et al., (2007) found that aerobic or resistance exercise training alone improved glycemic control, but the effects were more evident with both exercises combined [18]. Another study proved that in T2D subjects, only the combination exercise, but not aerobic or resistance training alone improved HbA1c level [19]. According to Yardley the order in which different type of exercise is carried out may be important, performing resistance exercise before aerobic exercise improved glycemic control and reduced the severity and duration of post-exercise hypoglycemia in diabetic patients. It has been found that performing RE then AE improve HbA1c and decrease post exercise hypoglycaemia [20]. Aguiar et al., 2014 concluded that such exercises and programs significantly improved the risk factors of T2D patients [6]. A combination of any two exercises led to a significant improvement in HbA1c [21]. We had the same results that combined exercises significantly improve HbA1c. Our results are similar to previous studies in significant reduction in weight and BMI among T2D subjects by using combined exercises [6-8] as well as significant elevation of IL-6 [31].

Moreover, high levels of IL-6 and TNF are associated with obesity and the progress of diabetes [22]. The value of exercise is closely linked to the anti-inflammatory effect. Physical exercise is linked to a decline in TNF and IL-6 [23-25]. However, evidence suggests that the intensity and duration of exercise and muscle damage after acute exercise could influence IL-6 response [26]. Physical exercise has a known impact in cytokines released by cells in the muscle. The production of TNF was directly inhibited by physical exercise via the production of IL-6 from the exercising muscles [27]. In this case, IL-6 is an anti-inflammatory factor whose concentration increases in the plasma after physical exercise which illustrates its dual action [27]. The anti-inflammatory impact of exercise in T2D volunteers is concerned with reducing levels of inflammatory cytokines and increasing the anti-inflammatory cytokines [23,28]. Some researchers suggested that regular exercise reduces inflammatory marker levels and protects against diseases caused by inflammation [29,30].

It was reported that IL-6 is linked to T2D and obesity [22], but in our study IL-6 is higher in T2D subjects with HTN. Our finding shows that most of our volunteers had HTN and higher BMI than ND which suggest that this might be the main reason for increasing IL-6 with exercise.

The function of IL-6 in insulin resistance in T2D has been emphasized in the field of research over the years [31-32], this is because pro-inflammatory cytokines, for example IL-6 were shown to be associated with certain metabolic disorders including T2D [22]. IL-6 plays a positive role in improving IS via exercise, consequently improving the functions of β-cells and the presence/circulation of GLP-1 [31]. In our study, both acute and chronic effect of exercise resulted in the elevation of IL-6 in both T2D and ND participants, however, the increment still insignificant. However, the study of Kim, (2016) reported a significant decrease in the level of IL-6 among participants exposed to circuit training when compared to aerobic exercise [31]. The difference in our results could be due to different reasons one of which is the type/mode of exercise used.

The intense exercise results in increased level of TNF in ND individuals [33-34]. However, in T2D the level of TNF is increased and some researches look into how this increased level can be decreased with exercise. In our study, there was an insignificant reduction in the level of TNF in T2D while in ND there was slight elevation. A study by Matthew Bouchonville shows similar finding to our results that indicate improvement of TNF after acute effect but the result is not significant as well [35].

Various studies reported that exercise lowers the levels of inflammatory markers. However, results are inconsistent, representing different modes, durations and intensities of exercise which might have different effects on inflammatory markers. Underlying chronic disease such as arthritis, hypertension or acute infection as well as obesity might interfere in the improvement of these markers. In addition to medication types might play a role in the changes of these inflammatory markers.

The limitations of this study are limited sample size included in both arms, no data for control group and no specific diet has been followed. While recruiting women is considered a strength as they are not usually involved in resistance training. This study is significant in clinical practice to emphasize the importance of life style modifications in both T2D and ND. For future work, it is planned to conduct another study with larger sample size and control group of both T2D and ND volunteers.

5. Conclusion

Combined exercise is beneficial for management of diabetes to control BG and improve HbA1c, weight and BMI to avoid further serious complication, in addition to decreasing the risk of having CVD or microvascular complications. Therefore, regular exercise should be a critical part of the various strategies used in managing T2D. This might be through development of specific programs and public education.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contributions: Taylor MJ, Sahota TS, Alsubaie NS and Alharbi BM started this project from 2015 till 2019. They submitted the proposal and soon received the ethical approval. Furthermore, Alsubaie NH and Alharbi BM started collecting data till 2019, searched via electronic data bases. Finally, Alsubaie NH analysed the results and completed the manuscript. Taylor MJ and Sahota TS reviewed the research and all the authors approved it.

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