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EFFECTS OF SINGLE BOUT AND SHORT TERM AEROBIC EXERCISE ON C-REACTIVE PROTEIN IN TYPE-2 DIABETES PATIENTS: A PILOT STUDY

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ABSTRACT

Type-2 diabetes is a leading risk for cardiovascular diseases and events due to ease of development of atherosclerosis in people with type-diabetes. Chronic inflammation is a major driver of atherosclerosis in type-2 diabetes and it has been linked to elevated C-reactive protein (CRP) level. The objective of this study was to determine whether CRP is amenable to aerobic exercise. A total of 40 adults diagnosed with type-2 diabetes patients were sampled randomly, and later, conveniently allocated into exercise and control groups. All the subjects were on the diabetes exchange diet as recommended by their Dieticians. Results show that the glucose level of the subjects of this study was fairly under control ((glycated haemoglobin (HbA1c) = 0.80±0.11% for each of the group)). A weak negative correlation was found between exercise-induced reductions in CRP and HbA1c (r = -0.345; p = 0.029). Significant ($p < 0.05$) difference in CRP was found between study and control groups following single bout (30 min) aerobic exercise, however, no significant ($p > 0.05$) difference in CRP was found between study and control groups after 8-weeks. Single bout or short-term aerobic exercises does not reduce CRP in people with fairly controlled type-2 diabetes mellitus.

Keywords: Diabetes, exercise, c-reactive protein, inflammation, physical activity.

Introduction

Patients with diabetes mellitus have about ten-fold risk for cardiovascular disease (Nathan *et al*., 2005). This is supported by the fact that cardiovascular disease accounts for more than 75% of all hospitalizations for diabetic complications in developed nations (Faxon *et al*., 2004). This could be attributed to the development of accelerated atherosclerosis (Watson *et al*. 2003), which accounts for 80% of all deaths among people living with diabetes (PLWD) in developing nation (*American Diabetes association, 1993*). In type-2 diabetes mellitus, hyperglycaemia induces endothelial injury thereby increasing endothelial permeability (Colwell *et al*., 1981). Increased endothelial permeability culminates in retention of low-density lipoproteins (LDL) which interact with underlying extracellular matrix. This interaction retains the LDL which further undergoes oxidation by reactive oxygen species (*Shrikhande & McKinsey, 2012*). The

oxidized LDL stimulates overlying endothelial cells leading to increased production of cellular adhesion molecules, chemotactic proteins, growth factors, while inhibiting nitric oxide production. This activates inflammatory events via activation of monocytes and macrophages activation (*Shrikhande & McKinsey, 2012*). Production of inflammatory cytokine by activated macrophages activates multiplication of smooth muscle cells of the containing vessel wall, thus resulting in fibrous plaque which may be destabilized, ruptured, or superimposed by thrombosis (Lusis, 2000). The consequence is vascular occlusion, which eventually precipitate cardiovascular event (Lusis, 2000).

It is discernible that chronic systemic inflammation is a major driver in the development of atherosclerosis and attendant cardiovascular disease (*Shrikhande & McKinsey, 2012; Nystrom, 2007; Sjoholm & Nystrom, 2006),* and this calls for the uncovering of the potential markers of systemic inflammation in type-2 diabetes patients particular CRP, and the possible ways of regulating them. CRP is a marker of systemic inflammation as well as an emerging independent predictor of cardiovascular disease in type-2 diabetes (Ridker *et al*., 1997). It is elevated in individuals with type-2 diabetes (*Sjoholm & Nystrom, 2006*) as a result of hepatocytic response to inflammatory cytokines (Wilson *et al*., 2006). Studies hold that elevated CRP is an independent predictor for cardiovascular events (Schulze *et al*., 2004), cerebrovascular disease mortality (Soinio *et al*., 2006), insulin resistance and late-onset complications in type-2 diabetes patients (Hayashino *et al*., 2006). CRP plays a direct pathologic role by promoting production of procoagulant tissue factor, leukocyte adhesion molecules, and chemotactic substances (Deanfield *et al*., 2005). It could impair vascular tone through inhibition of synthesis of nitric oxide, an anti-atherogenic agent (Deanfield *et al*., 2005). Overall, CRP increases the susceptibility of vascular walls to inflammation, atherosclerosis and eventually, cardiovascular events (Schulze *et al*. 2004). There is need for intervention targeting reduction in serum CRP. Physical activity remains one of the most important factors in the treatment of type-2 diabetes mellitus (Praet & Van loon, 2007), and studies have shown that exercise is effective for reducing insulin resistance and potential complications including atherosclerosis (Kadoglou *et al*., 2010). Exercise as the nature's medicine is believed to down-regulate the production of C-reactive protein and other inflammatory cytokines while up-regulating anti-inflammatory cytokines. Interventions directed towards reduction of CRP may optimize strategy aimed at combating atherosclerosis and cardiovascular events in type-2 diabetes patients. Aerobic fitness has been associated with decreased expression and release of CRP from hepatocyte (McGavock *et al*., 2004). This suggests that moderate to vigorous intensity aerobic exercise may be of benefit to individuals with type-2 diabetes (Balducci *et al.,* 2010). In addition, a high positive relationship has been found between C-reactive protein and tissue measurement indices amenable to exercise such as body mass, waist circumference, and the waist-hip ratio (Selvin *et al*., 2007). However, there exists paucity of literature on the effect of aerobic exercise intervention on CRP in type-2 diabetes patients CRP (Bijeh *et al*., 2012; Stewart *et al*., 2007; Hamedinia *et al*., 2007), especially in developing nations. This is a pilot study investigating effects of single bout and short-term aerobic exercises on C-reactive protein in type-2 diabetes patients.

Experimental

Subjects

The participants to this study comprised 40 (20 males and 20 females) adults diagnosed of type-2 diabetes mellitus, and who were attending the diabetes clinic of University of Nigeria Teaching Hospital (UNTH), Enugu. Their age ranged between 41 and 86 years. Subjects were fully informed about the experimental procedures, risk, and protocol, after which they gave their informed consent. Ethical approval was granted by the Health Research and Ethics Committee of the UNTH, Enugu.

Diet and Drug Characteristics of the Subjects

Subjects were on their hypoglycaemic drugs which were mainly sulfonylureas, in various dosages though. Dietary advice was a diabetes exchange diet that provides approximately 50 – 60% of calories from carbohydrates, approximately 10 – 20 % of calories from protein, and less than 30% of calories from fat as recommended by the Dieticians.

Research design

In this study, failed randomized controlled design was used to determine the effect of acute sub-maximal aerobic exercise on C-reactive protein. We used the word "failed" highlight a weakness in the design of this study, we started with random selection but later resorted to selection by convenience as participants were not forthcoming. Using large effect size (σ = 0.5) (Cohen, 1998), at degree of freedom of 1 and power (1-β) of 0.8, minimum sample size of 36 subjects was obtained. Subjects were conveniently sampled but randomly allocated into exercise group (A) and control (B) using simple random without replacement technique. They were asked to pick a number from a box which contained equal numbers allocated to two groups (A and B) as they presented for the study. The number they choose automatically assigned them to the groups where they participated. It is important to note that randomization process was interrupted towards the end of the study as the investigators resorted to convenience sampling to be able to recruit more participants into the study. The exercise group had a single bout aerobic exercise training lasting for 30 minutes while the control group had no structured form of exercise within the period. At the end of the exercise, a post-test procedure was administered to all subjects.

Inclusion criteria

Participants were recruited based on the following inclusion criteria: being medically and mentally stable, having no symptom of cardiac complication such as angina, referred to attending outpatient physiotherapy clinic, and blood pressure <140/90 mmHg.

Exclusion criteria

Subjects who were pregnant, on antidepressant, had chest pain or insufficient aerobic capacity following exercise testing were excluded. Those who were recently involved in vigorous physical activities were also excluded.

Pre-exercise Procedures

Cardiovascular Characteristics

Subjects resting heart rate (HR), Systolic blood pressure, (SBP) and diastolic blood pressure (DBP) were monitored from the right arm, using an automated digital electronic BP monitor (Omron digital BP monitor, Model 11 EM 403c; Tokyo Japan), as described by Musa *et al*. (2002).

Anthropometric measurement
The anthropometric characteristic such as weight (kg) and height (m), BMI (kg/m^2), waist circumference (cm), hip circumference (cm), and waist-hip ratio were measured following standardized anthropometric protocol (Praet *et al*. 2007).

Blood sample collection (venipuncture method)
Pre and post-treatment fasting blood samples were obtained between 8:00 am and 10:00 am after a minimum of 8-hour overnight fast. Five-milliliter syringes were used for blood sample collection. About 5 ml of blood was drawn from the antecubital vein of each subject under strict septic condition. Blood samples were allowed to coagulate at room temperature for one hour and centrifuged for serum. Serum samples were transferred into plastic containers sealed, and labeled. All samples were stored in a refrigerator at −80°C until analysis.

Glycated haemoglobin (HbA1c) test
Glycated haemoglobin as a gold standard test in monitoring long-term control of diabetes mellitus (World Health Organization, 2011) was used to assess the subjects' blood glucose level. HbA1c reflects the average blood glucose level over the past three months (World Health Organization, 2011), and it can be performed at any time of the day and does not require any special preparation (Rahlenbeck, 1998). HbA1c has been used as an index of glycaemia control in handful Nigerian studies (Emeribe *et al*., 1998; Adewolu & Idogun, 2014; Adebisi *et al*., 2009). In this study, HbA1c was measured using standard laboratory procedure (American Diabetes Association, 2014; Nathan *et al*., 2008; Tiez, 2009; Wu, 2009).

C - reactive protein
In this study CRP test was performed as thus: five microlitre capillary was filled with patient sample and dropped into the tube with R_1 dilution liquid, with tube closed and mixed well for 10 secs. 50 microlitre diluted sample was applied to the TD/Test device using automatic pipette. The sample was allowed to soak into the membrane for approximately 30 secs. Thereafter, 50 microlitre of the R_2 (solution of monoclonal anti CRP labeled with ultra-small gold particles) were added and allowed to soak into the membrane for 20 secs. 50 microlitre of R_3 washing solution (phosphate buffered NaCl PH 7.4) to the TD/Test device was applied and the reagent was allowed to soak into the membrane for approx 20 secs. All test precautions were observed, and result was read off within 5minutes using Nycocard READER II (Tietz, 2009; Wu, 2009).

Pre-exercise stress test
In this study, the Young Men Christian Association sub-maximal cycle ergometry test protocol was used to assess subjects' aerobic power (VO_2 max) as described by Heyward (2002) and Brook *et al*. (1996). After warm-up (five minute zero resistance exercise), the first three minutes work rate was set at between 100 and 150 kg.m.min^{-1} (17 – 25 watts), (1 watt = 6 kilogram meter per minute (kg.m.min^{-1})). The pedal speed was set at 50rpm (revolution per minute) by setting the metronome between 68 and 100 bpm (beat per minute). Heart Rate (HR) and BP were measured within the last minute of each stage. If a HR of above 110 bpm was obtained in the first three minutes, then only one additional three minute stage was performed by increasing the workload by either 25 watts or 150 kg.m.$^{min-1}$. If the second stage HR was less than 110 bpm, then 3rd or

4th stages three minutes was performed at additional workload of 25 watts or 150 kg.m.min^{-1} up to 300 kg.m.min^{-1} in order to obtain two HR between 110 and 150 bpm. These two HR did not differ by more than 5 bpm, and where they did, the test was extended by another minute until a stable value was obtained. At the end of the test, five minute recovery period (cool down) at zero resistance was administered.

The Intervention

The experiment constituted cycle ergometer at a moderate intensity of between 50 − 60% of subjects' HR-max which was estimated from age of subject subtracted from 220, at a work/rest ratio of 1:1 (American College of Sports Medicine, 2008; Nieman, 2011). The subjects pedaled at a slow speed and zero resistance for five minutes as warm up exercise. The workload was 100 kg.m.min^{-1}, which was increased at a pedal speed of 50rpm to obtain a HR max of 60%. The training session was concluded with a cool-down exercise which was slow speed pedaled at zero resistance for five minutes. The exercise duration was five 6 minutes (30 min) work interspaced with six minute rest. At the rest intervals, subjects pedaled at zero resistance. The workload that gave the HR max was noted and recorded for subsequent training sessions. The trainings were done in the morning hours between 8:00 am and 11:00 am. Post-training C-reactive protein and HbA1c were measured after the first 30 mins exercise bout. At the end of 8-weeks exercise intervention, post-training C-reactive protein, HbA1c, body composition and blood pressure were measured following earlier described protocols, techniques and methods.

Data analysis

All data was analyzed using the statistical package for social sciences (SPSS) version 23 was used, with α set at 0.05. Following outcome of exploratory statistics, log-transformation was performed for CRP and HbA1c. Independent t-test was used to compare continuous baseline characteristics between the groups, and a chi-squared test (χ^2) was used to compare dichotomous variables between groups. Correlations between baseline CRP and each of age, body composition measures and blood pressure were analyzed with spearman correlations instead Pearson's coefficient, considering the distributions of other continuous variables. The influence of sex on baseline CRP was ascertained with aid of Median test. Additionally, correlations of the changes in CRP following exercise training with each of change in body composition indices and HbA1c were evaluated in the study group only (n = 20).

Results

Result showed that the control group is significantly (p = 0.022) older than the study group. No significant difference (p > 0.05) in body composition measures, blood pressure between groups. A significant median difference in baseline CRP was observed (p = 0.002) between groups, with the control group having higher CRP value. Sex distribution of the subjects was same (male ─ 20, female ─ 20; p = 1.000) in both groups.

TABLE 1

Baseline characteristics of the subjects (age, body composition measure, blood pressure, HbA1c, C-reactive protein and Sex)

	Mean±SD/Median(IQR)			
Characteristics	Control group	Study group	Overall	p value
Age (years)	58.80±6.6	53.20±8.17	56.00±7.86	0.022*
Weight (kg)	72.80±10.43	76.00±12.05	74.40±11.24	0.373
Height (meters)	1.69±0.12	1.68±0.07	1.69±0.10	0.671
Body Mass Index	25.64±4.37	26.67±3.43	26.15±3.911	0.410
Waist Circumf (cm)	101.05±12.55	95.65±10.78	98.35±11.87	0.153
Hip Circumf (cm)	102.20±5.09	105.25±10.35	103.73±8.20	0.244
Systolic BP (mmHg)	131.3±15.12	125.10±18.6	128.20±17.07	0.256
Diastolic BP (mmHg)	80.05±7.92	82.45±8.15	81.25±8.02	0.35
HbAcI (%)	0.80±0.11	0.80±0.11	0.80±0.11	0.922
CRP (mgL^{-1})	4.8(3.7-7.4)	1.3(0.8-2.7)	3.6(1.1-6.8)	0.002*

IQR: interquartile range

Analysis of correlation showed there was significant correlation between baseline CRP and each of age (R = 0.348; p = 0.028) and diastolic blood pressure (R = -0.386; p = 0.014). No significant correlation was found between pre-exercise CRP and each of weight, height, body mass index, waist circumference, hip circumference, waist-hip ratio, systolic and blood pressure (all $p > 0.05$). There was significant relationship between baseline CRP and HbA1c (p = 0.003) (Table 2). Participants' sex had no significant influence on baseline CRP (t = -1.307; p = 0.199).

TABLE 2

Relationship between baseline CRP and each of age, body composition, blood pressure and HbA1c

	CRP (µg/mL)	
Characteristics	R	p value
Age (years)	0.348	0.028*
Weight (kg)	-0.087	0.594
Height (meters)	-0.088	0.588
Body Mass Index	-0.021	0.897
Waist Circumf (cm)	0.104	0.523
Hip Circumf (cm)	0.140	0.391
Systolic BP (mmHg)	-0.293	0.066
Diastolic BP (mmHg)	-0.386	0.014*
HbAcI (mmol/L)	-0.335	0.035*

Result showed there were significant differences ($p < 0.05$) in CRP between study and control groups following acute/single bout (30min) ($p < 0.05$) and 8-weeks aerobic exercise sessions ($p < 0.05$). However, controlling for the baseline differences in CRP and age, we resorted to comparison of post-exercise changes in CRP. Result showed that there was no significant difference in CRP reduction between exercise and control groups, following acute (30 minutes) aerobic exercise ($p > 0.05$). However, after 8-weeks (24 sessions) of aerobic exercise, the study group recorded a significantly greater reduction in CRP than the control ($p < 0.05$) (Table 3).

TABLE 3

Between-group comparison of CRP using Median Test

	Median (IQR)		
Characteristics	Study group	Control group	p value
CRP (µg/mL)			
Acute (30min post)	4.0 (2.9 to 6.6)	1.1 (0.9 to 2.95)	0.004*
Short term (8-weeks post-baseline)	3.7 (1.9 to 5.8)	1.0 (0.7 to 2.0)	0.011*
ΔCRP (30min post-baseline)	-0.2 (-1.2 to 1.0)	-0.15 (-0.7 to 0.2)	1.000
ΔCRP (8-weeks post-baseline)	-1.0 (-1.8 to -0.1)	-0.2 (-0.6 to -0.03)	0.027*

Δ: change

Post-exercise analysis showed that there was no significant correlation between CRP and each of BMI, blood pressure, waist and hip circumference (All *ps* > 0.05) (Table 4). After exercise, a weak negative correlation was found reductions in CRP and HbA1c ($r = -0.345$; $p = 0.029$).

TABLE 4

Correlations between change in CRP and change in each of body compositions, blood pressure and HbA1c in exercisers

	ΔCRP (µg/mL)	
Characteristics	R	p value
Body Composition		
ΔWeight (kg)	0.169	0.476
ΔBody Mass Index	-0.294	0.208
ΔWaist Circumf (cm)	0.061	0.797
ΔHip Circumf (cm)	-0.002	0.992
Blood Pressure		
ΔSystolic BP (mmHg)	-0.253	0.281
ΔDiastolic BP (mmHg)	0.067	0.780
Δ**HbAcl** (mmol/L)	-0.345	0.029*

Discussion

The key finding in this study is that both single bout and short-term (8 weeks) aerobic exercises reduced CRP in people living with type-2 diabetes mellitus. This finding is supported by results obtained in larger studies (Balducci *et al.,* 2010; Kamal *et al.,* 2012), in which there was no significant reduction in CRP following six months' aerobic exercise performed for 60 minutes, three sessions per week at 55 – 65% of maximum heart rate reserve resulted in no significant reduction in CRP (Bijeh *et al.,* 2012). Also, Murtagh *et al*. (2005) reported no significant reduction in CRP following to 45 minutes walking program performed at 60 − 70% of heart rate maximum in overweight, healthy and inactive men. Different levels of exercise intensities (65%, 85% and 100% of VO2max) have been found to lead to no significant change in the levels of CRP (Tsao *et al*., 2009). Alas, one of the largest and well controlled trials on this subject reported no significant reduction in CRP level following a nine month exercise training of different modalities (Swift *et al*., 2012). However, this finding of

the present study is consistent with Kamal & Ragy (2012), in which 12 weeks (three times per week) aerobic exercise reduced body weight, body mass index (BMI), and CRP levels. Similarly, Balducci *et al.* (2010) found that long-term high-intensity (preferably mixed) training, in addition to daytime physical activity, is required to obtain significant reductions in inflammatory cytokines including CRP. Contrary to the result obtained in Swift *et al.* (2012) where the control group who had higher baseline CRP, howbeit non-significant, ended up having higher post exercise reduction in CRP, in our study, the study group ended up with greater reduction in CRP despite having significantly lesser CRP value than the control group. Similar to Swift *et al*. (2012), some studies hold that individual with higher metabolic burden respond more to exercises (Bohm *et al*., 2016; Alvarez *et al*., 2013; Hansen *et al*., 2015) and lifestyle intervention (Borel *et al*., 2012; Schafer *et al*., 2007; Kantartzis *et al*., 2011), than their counterparts with lower metabolic burden. Nonetheless, our study casts doubt on the postulation of Swift *et al.* (2012) that CRP regulatory mechanism is subject to a ceiling effect in the non-exercising control, and a floor effect in exercisers. More so, higher metabolic burden may limit burden's response to exercise instead of facilitating as previously opined. However, the fact that the study group were significantly younger than the control group may contribute to the greater reduction in CRP found in the exerciser.

The aforementioned discrepancy between this present study and previous ones portray the level of heterogeneity that characterizes the subject of this study. It is important to note that the intensity, type, and the length of the exercise along with muscular vulnerability, and the number of the used muscles, previous physical activity level and baseline CRP level are influential on CRP response to exercises (Balducci *et al*., 2010; Bijeh *et al*., 2012). Late reduction in CRP has been reported in high intensity exercise of short duration, in which the use of different muscular tissues is almost rare (Kasapis & Thompson, 2005). Exercises containing largely resistance component proved to be more effective in reducing CRP through improved glucose metabolism (American College of Sports Medicine, 2010). However, there is need for further studies to unravel the mechanisms of CRP response to exercise. Reduction in body composition and leptin level is one of the proposed mechanisms of CRP response to exercise (Balducci *et al*., 2010). In this study, there was no significant reduction in body composition following aerobic exercises, however, reduction in CRP levels has been reported independent of weight loss (Balducci *et al*., 2010), and a scenario in which aerobic exercise did not reduce CRP levels in adults but improved measures of body composition and physical fitness has also been reported (Kelley & Kelley, 2006). Another proposed mechanism of CRP response to exercise is through HbA1c regulation. Consistently, our study showed there was significant correlation between reduction in CRP and HbA1c in exercisers. This supports the postulation that CRP regulation is dependent on HbA1c (Swift *et al*., 2012). However, what reduction in HbA1c is necessary to bring about a significant reduction in CRP is not known. The third but not the least proposed mechanism is through the regulation of other inflammatory cytokines. CRP is believed to be released by hepatocyte in response as to inflammatory cytokines such as interleukin 6, interleukin 4, and tumor necrosis factor alpha (Wilson *et al*., 2006). Our study neither support nor reject this postulation as inflammatory cytokines such as interleukin 6, interleukin 4, and tumor necrosis factor alpha were not included in this present study.

The fact that information about participant medications especially anti-inflammatory agents was no collected, categorized and

appropriate adjusted for in the statistically analysis constituted a limitation to this study. Furthermore, the study is limited by baseline difference in age between groups as this could not be adjusted using non-parametric median test.

Conclusion

Both single bout and short-term aerobic exercises of 8weeks duration reduce CRP in people with fairly controlled type-2 diabetes mellitus. There is need for randomized controlled trial including variables on anti-inflammatory medications, previous but recent physical activity history, and other inflammatory cytokines. There is also need for a robust meta-analytic synthesis of study effects on the subject of this study.

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Competing interest

Authors declare there was no competing interest.

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