A 12-week sports-based exercise program for inactive Indigenous Australian men improved clinical risk factors associated with type 2 diabetes mellitus.

Abstract

Objective: This study assessed the impact of a 12-week sports-based exercise intervention on glucose regulation, anthropometry and inflammatory markers associated with the prevalence of type 2 diabetes mellitus (T2DM) in Indigenous Australian men.

Methods: Twenty-six inactive Indigenous Australian men (48.6±6.6 y) were randomized into an exercise (n=16) or control (n=10) conditions. Training included ~2-3 days/week for 12 weeks of sports and gym exercises in a group environment, whilst control participants maintained normal activity and dietary patterns. Pre- and post-intervention testing included: anthropometry, peak aerobic capacity, fasting blood chemistry of inflammatory cytokines, adiponectin, leptin, cholesterol, glucose, insulin and C-peptide. An oral glucose tolerance test measured glucose, insulin and C-peptide 30, 60, 90 and 120 min post 75 g glucose ingestion.

Results: The exercise condition decreased insulin area under the curve (25±22%), increased estimated insulin sensitivity (35±62%) and decreased insulin resistance (9±35%; $p<0.05$), compared with control ($p>0.05$). The exercise condition decreased in body mass index, waist circumference and waist to hip ratio ($p<0.05$), compared to control ($p>0.05$). Leptin decreased in the exercise group, with no changes for adiponectin ($p>0.05$) or inflammatory markers ($p>0.05$) in either condition. Aerobic fitness variables showed significant increases in peak oxygen consumption for the exercise condition compared to no change in control ($p>0.05$).

Conclusion: Findings indicate positive clinical outcomes in metabolic, anthropometric and aerobic fitness variables. This study provides evidence for sport and group-based activities leading to improved clinical risk factors associated with T2DM development in clinically obese Indigenous Australian men.

Key Words: Aboriginal; Body composition; Insulin; Glucose; Inflammation; Cytokines

Introduction

An estimated 75% of Indigenous people living in non-remote areas report sedentary behaviour and low levels of physical activity [1]. In turn, Physical inactivity is reported to promote the development of obesity and is strongly associated with preventable chronic diseases such as type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). Of note, both disease states are disproportionately high in the Indigenous Australian population [1-3]. Increasing the levels of physical activity within high-risk Indigenous communities may assist in preventing the development of chronic diseases. Accordingly, given the prevalence for lifestyle-related chronic diseases in Indigenous populations, the need for evidence-based strategies to reduce physical inactivity and associated risk of non-communicable disease is essential [4]. However, to date there are very few published reports on exercise training as a primary prevention strategy for metabolic and cardiovascular disease within Indigenous people.

Of particular focus, glucose regulatory [5], chronic systemic inflammatory [6, 7] and anthropometric [8] indices are important risk-factors for metabolic disease and their interrelated effects on insulin resistance and atherosclerosis [7]. Specifically, training studies implemented within a range of Indigenous peoples report ameliorating metabolic disease through reductions in glycosylated haemoglobin (HbA1c), insulin action, body composition, blood lipids and blood pressure [9]. However, minimal evidence is available specific to the Indigenous Australian population [10, 11], with none in Indigenous Australian men regarding glucose regulatory, inflammatory and anthropometric variables.

Regardless of ancestry, sports-specific exercise training [12] or gym-based cardiovascular and resistance exercises [11] have been successful in improving glucose regulation, inflammatory and anthropometric outcomes [11, 12]. Evidence-based training programs may provide effective and sustainable opportunities to improve risk-factors associated with disease development in Indigenous Australian men. Moreover, based on the community and family-orientated culture embedded within Indigenous Australian communities [13], group and sports-specific exercise training sessions, particularly inclusive of small-sided games (SSG)

and boxing, may be an effective approach for increasing physical activity and improving clinical risk-factors associated with T2DM [11, 14]. The current study aimed to assess changes in clinical risk-factors following a 12-week exercise program. These include the assessment of primary glucose regulatory measures from oral glucose tolerance tests (OGTT) and secondary measures of inflammatory, anthropometric and aerobic capacity variables. It was hypothesized that a sports-specific exercise intervention will assist in improving these clinical risk-factors associated with the development of T2DM within Indigenous Australian men.

Methods

Over a 4 month period in 2012 participants volunteered from a regional New South Wales community through the support and guidance of the local Aboriginal Medical Centre and Men's group. Thirty-three men of Australian Indigenous ancestry were recruited and randomly (block randomization in groups of 4) assigned by the chief investigator to an exercise (n=17) or control (n=16) condition for pre-intervention testing. The extra participant was assigned to the exercise intervention based on anticipated drop-out and compliance rates [11]. Participant recruitment ensured a sample population representative of an inactive lifestyle (no regular planned or incidental activity of >60 min per week) and not diagnosed with pre-existing CVD or metabolic disorders. A 75 g oral glucose tolerance test (OGTT) at pre-intervention showed results indicative of diabetes for 6 participants who were then excluded from the study. Final sample size at post-intervention was 11 in exercise and 10 in control conditions (schematic overview of participant numbers shown in figure 1). Prior to participation, Institutional Human Ethics clearance was obtained and participants provided verbal and written consent for all testing procedures.

Participants attended two pre-intervention and two post-intervention testing sessions (Figure 1). The first testing session comprised of a PAR-Q, anthropometric measurements, blood pressure and an OGTT. The second testing session comprised of a graded exercise test (GXT). Anthropometric measures included stature, body mass, waist circumference (WC) and hip circumference using standard techniques [15].

Manual blood pressure was obtained with an aneroid sphygmomanometer and cuff (Welch-Alyn, Arden, North Carolina, USA) expressed as the mean of 3 measurements after the participant had been seated for 5 min.

Participants presented to the laboratory between 0600 and 0900 h following an overnight fast (10-12 h) and remained rested for a 2 h OGTT. Participants were cannulated for the collection of venous blood samples at fasting, 30, 60, 90 and 120 min post-glucose ingestion that was standardised for all participants at 75 g of glucose diluted in 300 mL of water, ingested within a 5 min period (Fronine Lomb's Scientific, Sydney, Australia).

A GXT determined peak oxygen consumption (VO_{2peak}) and maximal aerobic workload (W_{max}) and was performed on an electronically braked cycle ergometer (LODE Excalibur Sport, LODE BV, Groningen, The Netherlands). Prior to each test the metabolic gas analysis system (Parvo Medics, True2400, East Sandy, UT, USA) was calibrated. The test commenced at 25 W and increased by 25 W every min. Heart rate (HR) (Vantage NV, Polar, Kempele, Finland) was recorded each min with participants exercising until maximum heart rate ($HR_{max;}$ calculated as 220 - age) or volitional exhaustion prior to attainment of HR_{max}. Technicians were not blinded to group allocation and did not provide encouragement to the participants during pre and post-intervention testing.

Total exercise duration over the 12-weeks of training was maintained at 45 and 60 min sessions (including 5-10min of dynamic warm-up), with exercise intensity prescribed to maintain 70-85% HR_{max}. Training frequency progressed from an allocated 2 sessions (weeks 1-6) to 3 sessions per week (weeks 7-12). Heart rate (Vantage NV, Polar, Kempele, Finland) was recorded during all sessions at 5 min intervals for the calculation of mean HR, and a session-RPE (Borg's 6-20 scale) was obtained at the conclusion to calculate training load [16]. All participants were provided with positive reinforcement and transportation (if required) to all data collection and training sessions.

Supervised group-based cardiovascular and resistance exercises were performed at a local fitness centre (Weeks 1-12). Specifically, these sessions (45 min) altered between strength training (free weights i.e. chest press, squats, and lunges), core exercises (sit-ups with incorporation of medicine balls) and cardiovascular training of continuous stationary cycling, running and rowing ergometry. Resistance and/or speed (i.e. RPM or $km \cdot h^{-1}$) for individual participants was altered to maintain 70-85% HR_{max}. An additional session (60 min) comprised of boxing specific circuit training, including multiple stations of sparring, technique work using pads, speed ball, boxing bag, skipping, running and passive recovery. Throughout the program work to rest ratio progressed from 1:1 (weeks 1-3), 2:1 (weeks 4-6), 3:1 (weeks 7-9) and 4:1 (weeks 10-12).

The final weeks included a third weekly session of SSG (Weeks 7-12). All SSG training was conducted at an indoor multi-sports centre. Games included football (touch rugby, futsal), basketball and netball. Training duration consisted of 4 quarters, with 2-min passive recovery and court size of 15x28 m. The duration of each quarter progressed from 8 min (weeks 7-9) to 10 min (weeks 10-12). Depending on participant availability player numbers altered between 6 a-side (6v6) or 7v7.

The control condition completed pre and post-intervention testing sessions and were required to continue their usual inactive lifestyle (no regular planned or incidental activity of >60 min per week) and nutritional patterns for 12-weeks. Participants received both verbal and written instructions expressing the importance of maintaining these patterns. After the completion of the study, the control condition was provided with assistance to increase levels of physical activity.

Fasting venous samples were collected for analysis of lipid profile, C-reactive protein (CRP), insulin, glucose, C-peptide, glycosylated haemoglobin (HbA1c), total leukocyte count, interleukin (IL)-6, IL-1 receptor agonist (ra), IL-1β and tumor necrosis factor (TNF)-α. Venous blood from the OGTT was

analyzed for insulin, glucose and C-peptide. Following the clotting of the sample (SST) or immediately following collection (EDTA, FO), samples were centrifuged at 3500 rpm for 15 min at 4°C. Aliquots were frozen immediately at -80°C and -20°C for EDTA and SST, respectively. Whole blood was refrigerated (4°C) for a maximum of 6 h until analysis of total leukocyte count and HbA1c.

Fasting samples pre and post intervention were analysed for total cholesterol (Enzymatic method and polychromatic endpoint technique), high density lipoprotein (Accelerator selective detergent methodology), low density lipoprotein (Friedwald Equation), triglycerides (Enzymatic method and biochromatic endpoint technique; Dimension Xpand Plus, Siemens Healthcare Diagnostics, Sydney, Australia), total leukocyte count (Cell counter: Cell-Dyn 3200, Abbott Laboratories, Abbott Park, IL, USA) and HbA1c (High-performance liquid chromatography: Bio-Rad Variant, Bio-Rad Laboratories, Sydney, Australia). CRP (Particle enhanced turbidimetric immunoassay: Dimension Xpand Plus, Siemens Healthcare Diagnostics, Sydney, Australia), IL-6, IL-1β, IL-1ra and TNF-α were measured (Immunoassay ELISA: Quantikine, R & D Systems, Minneapolis, MN, USA), with intra and inter-assay coefficients of variation between 2.9-4.9%. Glucose (ABL825 Flex Analyzer, Radiometer Medical ApS, Bronshoj, Denmark), C-peptide and insulin (Solid-phase chemiluminescent enzyme immunometric assay: Immulite 2000, Siemens Healthcare Diagnostics, Los Angeles, CA, USA) showed intra and inter-assay coefficients of variation between 2.2-5.1%. Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) was calculated based on (fasting insulin x fasting glucose)/22.5 [17]. Area under the curve (AUC) was calculated using trapezoidal method [18]. The Matsuda index was calculated as an alternative measure to whole body insulin sensitivity [19].

All data are reported as mean ± SD. A one-way repeated measure ANOVA (pre-post intervention) was used to compare the effects of each intervention for all measured variables. A two-way repeated measures ANOVA (pre-post intervention x 5 time points of glucose load) was used to assess the effect of each intervention on glucose, insulin and C-peptide. Post-hoc paired sample t-tests were used to determine

where any difference lay pre- to post-intervention within each condition. Significance was accepted at $P<0.05$. All data not normally distributed were log transformed prior to analysis (variables included, all inflammatory cytokines, C-peptide, HbA1c, BMI and WHR). All statistical analyses were performed using PASW™ for MS-Windows version 20.0 (Statistical Package for the Social Sciences, Chicago, IL, USA).

Results

Mean training intensity (0-12 weeks) was 82.3 ±1.6% of age-predicted HR_{max} and Session-RPE of 14.2 ±4.3 AU. Attendance throughout the training study was 73 ±17% (weeks 1-6) and 65 ±16% (weeks 7-12), with a mean attendance rate of 69 ±16% (0-12 weeks).

Participant characteristics, anthropometry and VO_{2peak} pre and post 12 weeks of training are provided in Table 1. A significant decrease within the exercise condition was evident in BMI (p=0.001), WC (p=0.015) and WHR (p=0.018), while no significant difference was evident within the control condition (p>0.05). A significantly greater change was evident following the exercise program for body mass (p=0.042), BMI (p=0.013), WC (p=0.004) and WHR (p=0.041) compared to control???. Further, a significant increase in GXT duration (17.4 ±7.8%; p=0.0001) and W_{max} (14.2 ±6.5%; p=0.0001) was evident within the exercise condition compared to no change within the control condition (p>0.05). The pre to post change was significantly different between conditions for VO_{2peak} (p=0.021), GXT duration (p=0.002) and W_{max} (p=0.007).

Fasting blood chemistry, insulin sensitivity/resistance and inflammatory cytokines before and after training are provided in Table 2. Insulin AUC significantly decreased by 25±22% within the exercise condition (p=0.018), compared to no change within the control condition (p=0.702). The pre to post change in insulin AUC was significantly greater in the exercise compared to control condition (p=0.014). Matsuda ISI showed a significant increase of 35 ±62% within the exercise group (p=0.002), compared to

183 a 14 ±16% decrease within the control group (p=0.041). The pre to post change in Matsuda ISI was
184 significantly greater in the exercise compared to control condition (p=0.013). Leptin significantly
185 decreased in the exercise conditions (p=0.048), without changes in the control condition (p=0.674). The
186 pre to post change in leptin was significantly different between conditions (p=0.041). Adiponectin and all
187 inflammatory cytokines showed no significant changes within or between conditions (p>0.05).
188
189 **Discussion**
190 A novel finding from the present study is that 12-weeks of sports and group-based training improved
191 clinical risk-factors associated with the development of T2DM within previously inactive Indigenous
192 Australian men. Primary measures showed a decrease in insulin resistance, corresponding to decreased
193 insulin AUC and increased estimated insulin sensitivity. Moreover, positive changes also extended to the
194 secondary outcomes in anthropometry and VO_{2peak}. As such, improvements in these clinical risk-factors
195 through group and sports-based training may assist with ameliorating the future risk of developing T2DM
196 in this group of Indigenous Australian men.
197
198 Impaired insulin secretion and action are the two main pathophysiological disturbances leading to
199 abnormal glucose tolerance [20]. Early phase insulin resistance (>4 HOMA-IR) was present in the exercise
200 condition and was reduced to normal values after training. Pre-training results suggest the participants
201 were normoglyceamic but in an insulin resistant state. As further evidence, results of the OGTT indicated
202 that an increase in insulin secretion was required to compensate for decreased insulin sensitivity to
203 maintain normal glucose tolerance. Insulin AUC and estimated insulin sensitivity improved with training,
204 although was not normalized. Notably, it has been shown that changes in physical activity and dietary
205 patterns involved with reverting back to a hunter-gatherer lifestyle (ie. 12-weeks increased physical
206 activity and altered nutritional intake) in non-diabetic Indigenous Australians also improved, but also did
207 not normalize the insulin response to a glucose load [21]. We observed a similar response to exercise
208 training in the present investigation, although there were no changes in C-peptide, insulin AUC decreased

and estimated insulin sensitivity (Matsuda ISI) improved by 35%. These improvements suggest that a sustainable long term (>12-weeks) sports-based training approach may be required to normalize insulin sensitivity within clinically obese Indigenous Australian men.

The pathogenesis of metabolic syndrome is complex, with two main potential causative factors including insulin resistance and abdominal fat distribution (central obesity) [2, 22]. Following exercise training participants showed a decrease in abdominal obesity (WC and WHR) compared to the control condition. Waist circumference is a clinically useful measure that correlates with insulin resistance and is utilized as an indicator of central obesity and risk stratification of metabolic disease [2, 22]. Of note, Indigenous Australians are reported to have preferential central fat deposition in relation to their overall weight [23]. Furthermore, BMI significantly underestimates overweight and obesity as assessed by WC [23]. Accordingly, the difference in fat deposition within the Indigenous Australians affects the risk stratification for chronic disease development based off traditional anthropometric variables. Thus, care must be taken on generalising and interpreting these anthropometric measurements across Indigenous Australian communities [23] Importantly, the exercise program was successful at reducing WC, WHR and BMI, in conjunction with reduced insulin AUC and improved estimated insulin sensitivity/resistance.

Whilst causative factors of metabolic syndrome cannot be isolated to insulin resistance and central obesity, a myriad of other factors are also implicated including, a chronic systemic inflammatory state and hormonal dysregulation [2, 3, 8]. The present study showed no changes in anti- and pro-inflammatory cytokines in response to a 12-week exercise program. Pro-inflammatory cytokines TNF-α, IL-1β and IL-6 are released from adipose tissue and stimulate the hepatic synthesis of CRP [24, 25], a clinical marker predictive of cardiac complications associated with atherosclerosis and metabolic abnormalities [26]. In contrast, the anti-inflammatory cytokine IL-1ra acts as an agonist to IL-1β, whilst IL-10 inhibits the production of IL-1β and TNF-α; collectively contributing to the homeostatic control of the innate immune system [25]. Currently, there are no published exercise training interventions reporting inflammatory

cytokines in Indigenous Australian populations. Thus, it is difficult to draw firm conclusions about the clinical relevance of our findings.

Regardless of ancestry, previous literature shows both positive and equivocal results regarding the effects of aerobic and resistance training on inflammatory cytokines within sedentary populations [24]. Accordingly, reasons for the negligible inflammatory responses within the present study might extend to insufficient changes in body adiposity or dietary behaviours of the participants [24, 27]. Since European settlement, the traditional fibre-rich, high-protein, low saturated fat, low carbohydrate diet of many Indigenous communities has changed to high amounts of refined carbohydrates and saturated fats [1]. While we recognise the importance of changing the dietary habits within this select population [28], the focus of this study was to investigate the effectiveness of an exercise intervention alone. For this reason, we suggest that future research examining the inflammatory response to exercise training within Indigenous populations include dietary intervention/s specific to a fibre-rich, high-protein, low saturated fat, low carbohydrate diet within group and community settings.

Leptin and adiponectin are adipocytokines associated with the regulation of energy balance and insulin action [29]. Specifically, adiponectin stimulates food intake and decreases energy expenditure during a fasting state, whilst leptin decreases food intake and promotes a decrease in body mass [29]. As such, people who are obese and/or have T2DM show reduced concentrations of adiponectin and elevated concentrations of leptin [29]. Exercise is known to effectively reduce obesity and associated adiposity, thus, the response of leptin and adiponectin in conjunction with other compounding variables (i.e. glucose metabolism, insulin sensitivity, inflammation) may explain how exercise affects obesity. Aerobic exercise training reduces fat-mass and ideally this should occur with a concomitant decrease in leptin and an increase in adiponectin concentrations; however, as shown in a recent review this response is not consistent [29, 30]. Whilst fat-mass is not reported in the present study, the results of the exercise condition show improved VO_{2peak} and insulin sensitivity/resistance in conjunction with a decrease in leptin

concentration and no change in adiponectin. Collectively, these findings suggest that regular exercise can positively modify leptin concentrations; however, this change in leptin with relation to change in body composition (i.e. fat-mass and muscle mass) in Indigenous Australian men requires further investigation.

Conclusions

In conclusion, a 12-week exercise program within Indigenous Australian men shows improvements in metabolic, anthropometric and fitness variables. The current study was developed by members of the local Indigenous community, which shows great prospect for future programs to be extended to the wider community, including youth and women. Furthermore, these findings reiterate that the development and ownership of interventions by community members and organisations are an effective way at improving clinical health outcomes for primary disease prevention [10]. Indigenous populations are community focussed and therefore a group and sports-based intervention is more appropriate for collaboration and support than widespread individualized gym-based programs. Findings of the current study compliment a previous health and wellness program implemented within Indigenous Australian women [11] and highlights the potential for implementing sports-based training to improve clinical risk-factors associated with T2DM in normoglyceamic, but insulin resistant Indigenous Australian men.

Practical Implications

- Indigenous Australians are community focused and therefore a group and sports-based intervention is more appropriate than widespread individualized gym-based programs.
- Adherence is more likely with sport and group-based programs because it addresses individual and group needs for collaboration and support.
- Development and ownership of interventions by community members and organisations are effective at improving clinical health outcomes for primary disease prevention within Indigenous Australians.

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