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Short Communication

Exercise An Important Component in The Treatment and Prevention of Obesity

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Dietary intervention can use either calorie dilution or calorie restriction and both have been an important arm in the management of obesity, with calorie restriction having the additional advantage of increasing longevity [1]. In general, in humans' dietary intervention has been partially successful in the short term but most participants regain significant weight after 12 -18 months. Exercise has therefore been added as an extra arm in the management of obesity in an attempt to prevent the weight gain [1,2]. Calorie dilution has been a successful dietary intervention causing greater weight loss than calorie restriction but does not have the other benefits of calorie restriction such as increasing longevity [1]. Weight loss results in bodily adaptations that include increasing appetite and decreasing energy expenditure [2] adding to the problem of maintaining weight loss long term and treatment requires continued attention and long-term maintenance visits [2]. Exercise alone has not been successful in achieving weight loss in the overweight/obese but needs to be an integral part of their management program because it provides significant benefits in aerobic fitness, preservation of lean body mass, improved cardiovascular fitness, insulin sensitivity, control of type 2 diabetes and blood pressure [3] even though it does not cause more than minimal weight loss [3]. It appears that once established weight gain is difficult to reverse long term with either exercise or diet or a combination of both.

The question that has only recently been adequately addressed is what happens when exercise is initiated before the weight gain is induced by a high fat diet. To answer this question, we took C57BL/6J mice and had 2 control groups of no exercise on chow or high fat diet (HFD) and 2 groups on chow and HFD that were undergoing moderate-intensity endurance exercise (END) and high intensity interval training (HIIT) for 10 weeks [4]. In order not to confound the situation by adding caloric restriction all animals were fed ad libitum [4]. The main findings are that both exercise programs significantly and similarly prevented the increase in body weight and adiposity, increased lean mass proportionally to body weight, and improved insulin sensitivity in the HFD-fed mice. These findings were accompanied by decreased markers of adipogenesis, inflammation and extracellular matrix accumulation in SAT and EPI fat depots [4]. There appeared to be a difference in the response of fat pads to the different form of exercise with epididymal fat pads weight and size reduced by END, but HIIT reduced both subcutaneous adipose tissue and epididymal adipose tissue weight and size [4]. In a similar study of only 10 weeks, it was

shown that quadriceps muscle adiponectin was increased more by END than it was by HIIT exercise. Indicating that there might be differences in the response to types of exercise. Specifically, END in HFD mice increased quadriceps muscle adiponectin mRNA (20-fold; $p<0.05$) and increased protein content of high molecular weight (HMW) adiponectin (3.3-fold), whereas HIIT induced a milder increase (2.4-fold) [5]. Interestingly, HFD induced an up-regulation of muscle adiponectin mRNA levels in untrained mice (~10-fold) [5]. The maximal running capacity and the grip strength of exercised mice was maintained. Fat infiltration and an increase in muscle triglyceride was prevented by both exercise programs [5]. GLUT 4 mRNA and protein were decreased by HFD, however, END and HIIT prevented this change in heart [6]. The previous were physiologically reflected in the reduction in the blood glucose area under the curve during an insulin tolerance test (ITT) after both END and HITT in HFD mice [5]. Interestingly in another experiment where exercise was started after a completion of 10 weeks of HFD, only HIIT was able to increase GLUT4 protein in the heart [6]. In summary, it was when diet and exercise commenced together that END and HIIT were able to maintain the GLUT4 protein, insulin, and the area under the ITT curve [6]. Moreover, heart and skeletal muscle HMW adiponectin was more responsive to increase after END in HFD mice [5,6].

In an excellent review Santoro, et al. [7] address the question of what happens when adipocytes become dysfunctional. After overloading with lipid, the dysfunctional adipocytes reduce muscle and liver insulin sensitivity [7]. A similar response to that seen when knockout of GLUT4 or CHREBP in adipocytes decreased glucose transport in skeletal and cardiac muscle [7]. Maintenance of the ability of adipocytes to undergo changes in hypertrophy and hyperplasia are normal functions in the transition from the fasted to fed state [7]. It is when this process becomes challenged and adipocyte depots can no longer receive more lipid that the lipid becomes deposited in other tissues and insulin resistance occurs along with decreased secretion of adipokines. We see this with adiponectin, resist in and leptin levels in the HFD state [4-6,8] but these changes were prevented in mice that had started exercise and HFD at the same time but not in mice that were delayed in starting the exercise program till after 10 weeks of HFD [6]. It was after the appearance of crown cells in the adipocyte depots that the ectopic lipid appeared in the liver of long-term fat fed mice [8]. Weight loss is an important first step in reversing the effects of overloaded adipocytes in the obese [2] and exercise has a role in weight maintenance and in reducing the level of lipid in the liver [9].

The feeling of hunger itself may be a key player in the effect of calorie restriction as this does not lose more fat tissue than calorie dilution [1] but does result in animals being more active in the dark hours (1.5 times) compared with controls and calorie diluted diet mice, presumably they were seeking food with its associated increased activity [1] In long term high fat feeding experiments we have shown the early stages are when the adipocytes are able to handle the caloric load but as time and calories ingested increased this produced a problem where the fat tissue could no longer store lipid and the peripheral tissues started to accumulate fat especially in the liver and muscles [5-8]. The problem is to be able to predict when exercise should start to prevent the effects of obesity. Alternatively, a program with long term exercise goals may need to be coordinated with the changes in nutrition of the community.

Most exercise training studies in which intra hepatic lipid content is decreased, however, do not show significant changes in body mass or fat and fat free mass [9,10-12]. Indicating that individual tissues can respond but the overall effect was not a decrease in weight or fat content [9]. This may be able to correct liver fat changes, but it does not seem to correct the changes in fat depots and these may continue to offload their excess lipid to other tissues in the long term [1]. In complement, a recent plasma proteomics study from our group indicated that exercise was able to partially normalise HFD-derived disturbances, where a more significant effect was seen when exercise started at the same time as the dietary intervention. However, whether the changes in liver insulin signalling or in the handling of excess nutrients contributes to hepatic lipid deposition remains to be elucidated [12, 13].

The difficulty in maintaining weight reduction with diet and exercise has resulted in the use of GLP-1 agonists for weight loss in the obese as well as in the treatment of diabetes [14]. It has even been touted as an alternative for bariatric surgery described in a recent blog [14] and reports have indicated that about 4.8 to 7.2kg weight loss can occur. Metformin can usually only achieve modest weight loos of about 2.3 kilos. Another alternative for morbid obese to lose weight is bariatric surgery [15,16] and a review of procedures from 2005 to 2015 showed that patients with severe obesity with a bypass lost more weight than those with a sleeve or a band. Early complications however were more common in patients who had a bypass. The recommendation of the review was that "people with severe obesity who are considering bariatric surgery should think about these tradeoffs in the benefits and risks of the procedures and discuss them with their doctor so that they can choose the procedure that best suits their personal preferences". Because of the previous and the metabolic benefits from exercise during obesity, one of the recent modifications in the management of candidates to undergo bariatric surgery of a mandatory physical exercise program (along with a multidisciplinary approach), to prepare the patient for the physical stress that the surgery involved [17]. Another suggested approach to this problem is to pharmacologically inducing beiging of white adipose tissue or increasing brown adipose tissue depots as a means of weight control [16]. It is early in the investigation and

therapeutic agents are being investigated [16]. The process relies on the induction of thermogenic processes in the white or brown adipose tissue. UCP-1 and more recently the creatine cycle have been implicated as mechanisms of the futile cycle [18].

It is clear that we have not found the final solution to restoring healthy weight to a population that has consumed excess calories. There are many partial solutions and a number of different approaches have been taken to find the solution to the problem. Surgical intervention can find the solution for some. Pharmaceutical intervention looks hopeful with the GLP-1 agonists the best option so far. Dietary control started early in life can coupled with a planned exercise program may be a solution for a number, but this universal problem has not found a universal solution at this stage.

Conflict of interest

No Conflict of interest.

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