A tepary bean diet and exercise delays indices of type 2 diabetes in female fa/fa rats

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Abstract

Legumes have been shown to protect against the development of type 2 diabetes (T2D). Previous work has focused on the impact of legumes on the glycemic index with little attention given to other physiological changes. Considerable evidence also demonstrates that exercise is beneficial for diabetic individuals. This study sought to determine the individual and synergistic effects of a legume diet and exercise on indices of T2D and tested the hypothesis that the synergy of these factors would protect against typical changes in glycemic hormones and lipids across the weight gain and insulin resistant stage of development in genetically obese rats. Fatty Zucker (fa/fa) rats, 6-7 wks of age were assigned to one of four treatment groups (*n* = 10/group); 1) tepary bean diet and exercise [TE], 2) tepary bean diet [T], 3) control diet and exercise [CE], 4) control diet [C]. A legume diet and exercise [TE] resulted in significantly less weight gain (126 g vs. 222 g in [C]) and lower body mass compared to animals in other treatment groups. The interaction of [TE] also resulted in significantly lower serum insulin compared to [C] animals across the study period. Diet [T] alone, significantly decreased serum triglycerides and cholesterol relative to [C] animals. Our results indicate that a tepary bean diet, with exercise, can decrease typical changes in weight gain, glycemia and lipid profile in fa/fa rats. The adoption of such a program in individuals showing signs of T2D would also likely serve to protect against these physiological changes. (Int J Diabetes Metab 15: 38-45, 2007)

Keywords: *Tepary bean, carbohydrate metabolism, lipids, exercise, Type 2 diabetes*

Introduction

Diets high in fiber are effective for improving glucose control,[1-10] lowering plasma insulin concentration [6, 7, 10] and decreasing serum triglyceride and cholesterol concentrations [1,9,11,12] in individuals with Type 2 diabetes. In humans, regular physical exercise enhances insulin sensitivity, improves glucose tolerance and decreases serum triglyceride and cholesterol concentrations in both non-diabetic [13-16] and non-insulin dependent diabetic individuals (NIDDM).[17] Considerable evidence also exists that demonstrates that when regular physical training is used in conjunction with dietary manipulation there is an even greater improvement in glucose tolerance than with diet alone in individuals with Type 2 diabetes.[18] While we have shown previously that exercise, together with the incorporation of tepary bean into a high fat diet, attenuated weight gain, subcutaneous and visceral fat gain compared to untreated controls, [19] we have yet to report the effects of this diet and exercise program on glucose and lipid metabolism.

Exercise training has been shown to be associated with improved insulin stimulated muscle glucose uptake, [20-23] decreased insulin and glucose response to an oral glucose tolerance test, [23,24] improved total body glucose disposal [25] and decreased glycated hemoglobin.[26] Also, exercise training has been shown to yield a decrease in basal blood glucose, insulin, cholesterol and triglyceride in fa/fa rats.[27]

To date there are no studies which have looked at the combined effect of a leguminous diet and exercise on changes in plasma insulin, glucose and lipid concentration across both the rapid weight gain phase and the insulin resistance stage of development in genetically obese rats, an animal model of human obesity and type 2 diabetes. Such an investigation is warranted since much of the rising incidence of Type 2 diabetes and obesity in many of today's population groups has also been accompanied by an increase in urbanization and a move away from the traditional active farming lifestyle; lifestyle changes that often result in a decrease in both physical activity and the consumption of traditional foods such as legumes. In many native groups, such as the Pima Indians of Arizona, who demonstrate an exceptionally high incidence of Type 2 diabetes, this change in activity pattern has also been coupled to a shift away from the traditional diet high in wild foods and fiber (wolfberries, tepary beans, prickly pears, mesquite pods, mustard seeds etc.) towards a more high-fat, fast food diet. In a recent study comparing the effect of a diet rich in traditional desert foods with a high-fat mixed diet on diabetes incidence rates and the risk of developing diabetes in this particular population, it was noted that those Pima Indians who consumed the mixed diet had a greater risk (2.5 times), and a greater crude incidence rate (63 cases per 1000 person years) of developing diabetes than those individuals who consumed the more traditional Indian diet.[28] Several investigators have also proposed that these more traditional legume foods have acted as protective

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agents against the development of diabetes in these, and other genetically prone populations.[29,30] The progressive change to a diet that is low in fiber and high in fat, particularly in these more susceptible populations, may in fact be a major contributing factor to the dramatic rise in prevalence of NIDDM over the last century.[31]

The hypothesis tested in this study was that the combined effect of a leguminous diet with or without exercise, compared with a purified control diet, would protect against changes in plasma insulin, glucose and lipid concentrations which are typical across both the rapid weight gain phase and the insulin resistance stage of development in genetically obese rats. The Fatty Zucker rat was chosen as the animal model for this study since it is genetically predisposed to characteristics such as hyperinsulinemia, hyperlipidemia, obesity, and insulin resistance that simulate the type 2 diabetic state in humans. Moreover, the development of these characteristics occurs in an age-dependent fashion, similar to that which is observed in humans.

Materials and Methods

Experimental protocols of this study were approved by the All University Committee on Animal Use and Care, Michigan State University, USA.

Animals

Forty female Fatty Zucker (fa/fa) rats, (6 to 7 wk of age; 153 to 242 g) (Charles River Laboratories, Kingston, NY, USA) were randomly assigned to one of four treatment groups (n=10/group): 1) tepary bean diet and exercise (TE), 2) tepary bean diet (T), 3) purified control diet and exercise (CE), 4) purified control diet (C) (Dietary information to follow). Rats were housed individually in stainless steel suspended cages and had access to food and water *ad libitum*. Prior to initiating experimental procedures, animals underwent a 4-day familiarization period in which regular rat chow was consumed. Animals were housed on a 12h light-dark cycle at a constant temperature of 22 $\pm$ 1°C with a relative humidity of 45-55%.

Dietary Information and Food Intake

Dietary composition details are described in Table 1, with the constituent components of the tepary beans, which were purchased from a local grocery store in Sacatan, AZ having been described elsewhere.[32] Control and tepary bean diets were designed so that 37% of kcals came from fat, so as to approximate the fat content of an average American[33] and Pima Indian[29] diet. Although a 37% fat component would not typically be recommended in conjunction with legumes this was necessary to control for fat composition of the diet across the two groups. It is also consistent with the findings of Boyce and Swinburn [29] who indicated that 35% of the Pima's dietary energy was derived from fat.

Food intake was determined weekly for all animals by calculating the difference between the weight of pre- and post-consumption volumes. Food consumption was monitored every 24-48 h with the food weight (in dish and cage) noted and additional food distribution volumes recorded.

Exercise Protocol

Rats in the TE and CE groups were exercised five consecutive days per week on a motor driven treadmill between the hours of 1-4 pm. Rats were nudged if they did not run and no electric shock was used. Running speed and duration were gradually increased over a 5-week period to a training level of 20m min^{-1}, 0% grade for 60 min d^{-1}. Animals were trained at maximal running speed and duration for 8-weeks, a training protocol that has been shown previously to elicit a significant training effect in fa/fa rats. [34]

Table 1: Composition of Tepary bean and Control diets

Ingredients (g/100 g diet)	Tepary Bean Diet	Control Diet
Tepary bean[1]	56.4	----------
Casein[2,3]	5.0	21.26
DL – methionine[3]	0.4	0.25
Corn oil[4]	3.0	3.0
Hydrogenated fat[4,5]	15.0	15.0
Non-nutritive fiber[3,6]	------	3.64
Corn starch[4]	10.0	25.83
Sucrose[4]	5.0	25.83
Choline bitartrate[3]	0.2	0.2
Mineral mix, AIN76™ [3,7]	4.0	4.0
Vitamin mix, AOAC[3,8]	1.0	1.0
Protein	18.9	18.9
Fat	18.5	18.0
Carbohydrate (excluding fiber)	52.4	52.4
Energy[9] (kJ/100g diet)	1888	1857

1. Based on data from Handbook #8-16, pinto beans contain 25% protein, 64% carbohydrate (4.3% fiber), 1.2% fat and 9.8% moisture. For calculations of dietary fat, fiber and carbohydrate, values for pinto beans were used for tepary beans. 2. High protein casein, 87.5% protein. 3. Purchased from Teklad Test Diets, Madison Wisconsin 4. Obtained from Food Stores, Michigan State University 5. Crisco. Manufactured by Procter and Gamble, Cincinnati, Ohio. Product is composed on partially hydrogenated soybean and palm oils. 6. Cellulose-type. 7. J. Nutr. 107:1340-1348, 1977 8. Association of Official Agricultural Chemists, Washington, D.C. Official Methods of Analyses of The Association of Official Agricultural Chemists, 9th ed., 1960, p.680, paragraph 39.133 .

Blood Sampling and Analyses

Tail artery blood samples (1mL/animal) were obtained at 0, 4, 6, 8 and 13 weeks from methoxyflurane-anesthetized fa/fa rats. Rats were fasted for 12-15 h and exercise was completed at least 41-45 h prior to blood collection. Upon sampling, serum was separated, collected, stored at -20°C and assayed following completion of the study protocol.

Blood samples were placed on ice until completion of remaining withdrawals and then centrifuged for 25 min at 1500 x g. The serum was removed with a Pasteur pipette and stored in small plastic vials at -20°C until analyzed. To prevent sample differences due either to differences in standards within the diagnostic kit or day to day technical variation samples were measured for all groups from the same kit and on the same day. Glucose was analyzed via glucose oxidase assay (Sigma Diagnostics Kit 510, Sigma Chemical, St. Louis, MO, USA), insulin was determined by enzyme-immunoassay (WAKO Insulin test kit, Wako, Richmond, VA, USA), triglycerides were analyzed by colorimetric procedure (Sigma Diagnostics Procedure No. 336, Sigma, St. Louis, MO), and cholesterol was measured using a modification of the enzymatic colorimetric method of Allain et al. [35] (Sigma Diagnostics Procedure No. 352, Sigma, St. Louis, MO).

Tissue dissection and Muscle analysis

Upon study completion (week 13), to assess the effectiveness of the exercise training program, the heart and right soleus muscle were surgically removed and weighed. The soleus muscle was flash frozen in liquid nitrogen and stored at -80°C prior to detection of succinate dehydrogenase (SDH) activity according to the method of Cooperstein et al.[36]

Statistical analyses

Means (± SEMs) were used to describe the data unless indicated otherwise. Mean body mass, serum glucose, insulin, triglyceride and cholesterol concentrations among experimental groups were statistically compared using a repeated measures analysis of variance (STATVIEW, 1987). Significant main and interaction effects were further assessed using ANOVA. In all instances, the post-hoc Scheffe test was used for identifying significant pair-wise differences between means.

Results

Animal Characteristics and Food Intake

The effect of the diet and exercise manipulations on mean body mass is presented in Figure 1. There was a significant increase in the average body mass of all groups over the study period. However, by week 4, the rate of weight gain in TE rats began to decline, such that the mean body mass of this group increased by only 126 g throughout the remainder of the experimental period, while the mean body mass of T, CE and C animals increased 176, 181, and 222 g respectively. By week 13, the mean body mass of T, CE and C were each significantly greater than TE (Figure 1). A higher average weekly food intake (kcals) was noted in groups T (632.9 ± 16.13), CE (649 + 16.51) and C (680.5 ± 16.15) than in TE (572.6 ± 18.84), however this difference was only significant between TE and C, and TE and CE. SDH activity (umol g^{-1}. min^{-1}) in the soleus muscle was highest in the two exercising groups (TE = 5.7 ± 3.3; CE = 3.4 ± 2.0; T = 2.7 ± 1.3; C = 3.0 ± 1.3), and the difference between TE and T was significant. A second marker of exercise training, heart mass (g) expressed relative to body mass (g/100), was also greatest in the TE and CE groups (TE = .23 ± .01; CE = .21 ± .01; T = .20 ± .003; C = .19 ± 0.1). No differences were found in the weight of the soleus muscle between groups.

Serum Glucose, Insulin, Triglycerides and Cholesterol

Fasting blood glucose was not significantly different between treatment groups at any point during the study. Within groups, the control (C) group had consistent increases in fasting serum glucose over time, with significantly higher glycemia at week 13 compared to study onset. (Fig. 2).

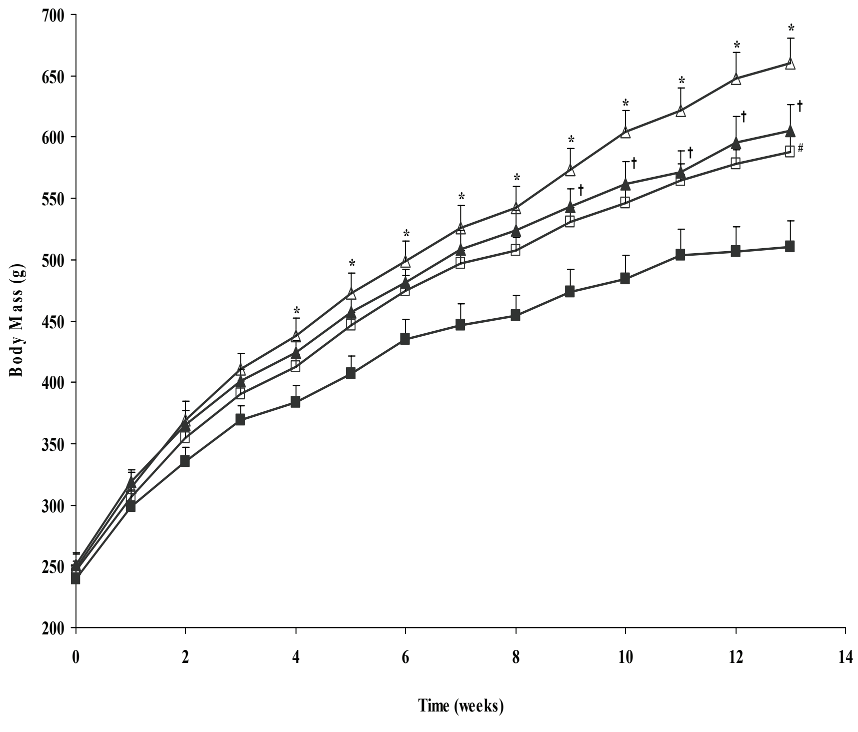

Figure 1: The effect of diet and exercise on mean body mass (g) of female fa/fa rats. Comparison of control diet (C) rats (Δ; n=10) with control diet + exercise (CE) (▲; n=10), tepary bean diet (T) (□; n=10) and tepary bean diet + exercise (TE) (■; n=10) rats. Values are expressed as mean ± sem. * p <0.05 C vs. TE; † P<0.05 CE vs. TE; # P<0.05 T vs. TE.

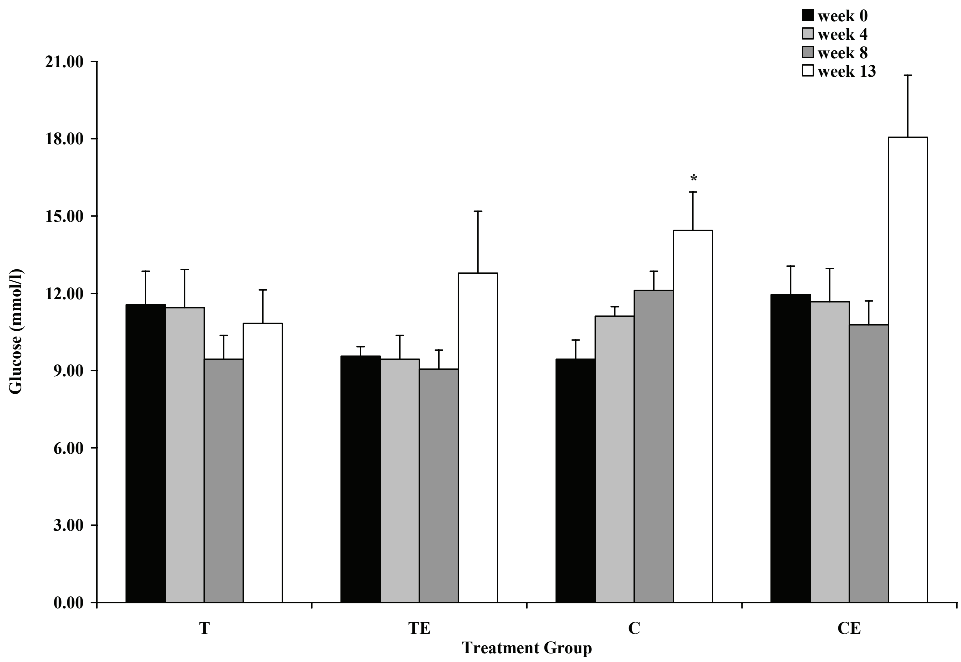

Figure 2: The effect of diet and exercise on mean fasting serum glucose concentration (mmol/L) over time. Values are expressed as mean + SEM * p<0.05 study onset vs. week 13.

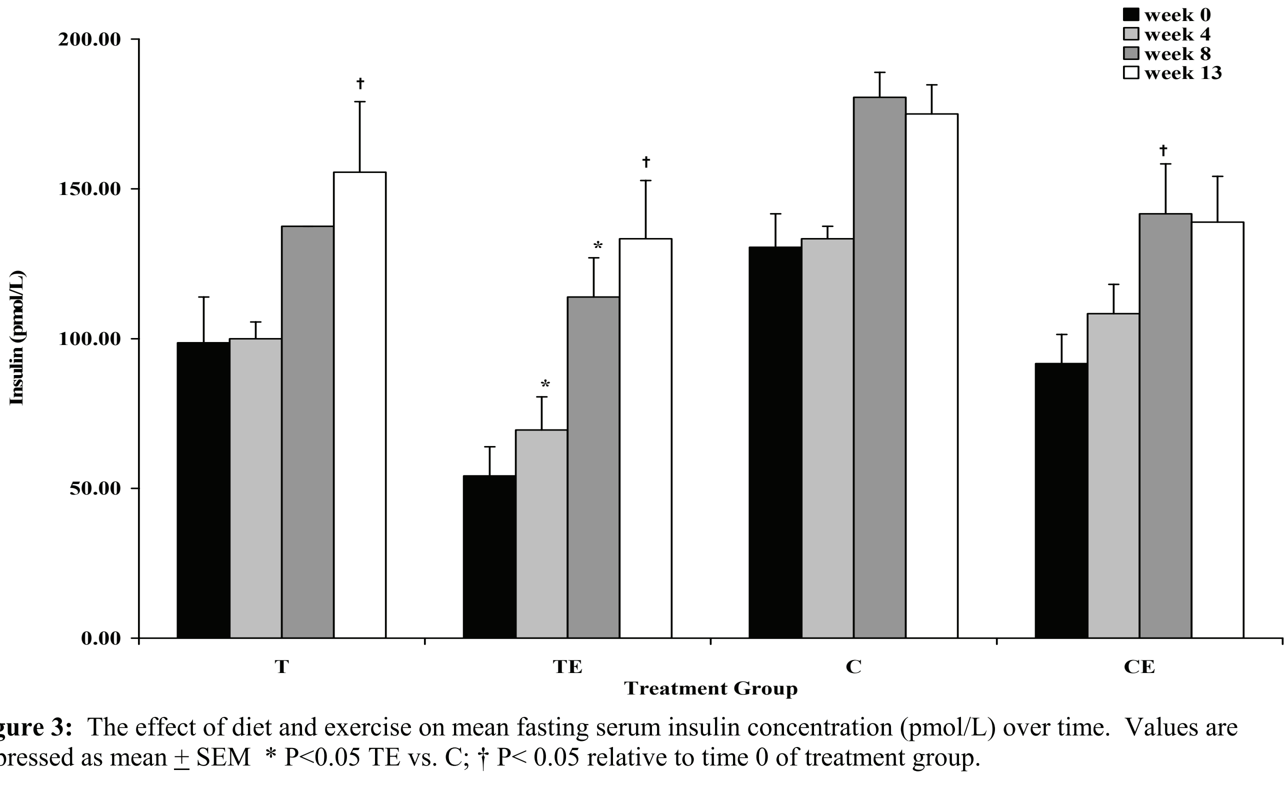

Figure 3: The effect of diet and exercise on mean fasting serum insulin concentration (pmol/L) over time. Values are expressed as mean + SEM * P<0.05 TE vs. C; † P< 0.05 relative to time 0 of treatment group.

Serum insulin concentrations were not significantly different between the two diet (T vs. C) or exercise groups (TE vs. CE) throughout the study. The interaction effect of exercise and the consumption of the tepary bean diet did however result in a significantly lower insulin concentration in TE than in C at weeks 4 and 8, even when the data were co-varied for the initial difference in baseline values. Serum insulin rose with time in all treatment groups, however C and CE groups reached peak insulin production by week 8, while T and TE groups showed a rise in insulin concentration up to 13 wks. (Fig. 3). Treatment diet induced significant changes in serum triglycerides, with the tepary bean diet (T) resulting in significantly lower triglyceride levels compared to the control diet (C) at both 6 and 13 weeks (Fig. 4). A parallel, nonsignificant, trend was also noted when exercise was combined with these dietary changes. With the control diet, exercise significantly decreased triglyceride levels below non-exercised group levels, as indicated by the higher (2x) midpoint triglyceride level (6wks) in C versus CE ($p < 0.05$). Throughout the study period, serum cholesterol increased in all four treatment groups (Fig. 5), however concentrations were significantly lower in those groups fed the tepary bean diet compared to those fed the control diet. Compared to the T group, cholesterol in C was twice as high at 6 wk and 2.3-fold higher at 13 wk. As was observed for triglyceride concentration, exercise exerted a significant impact on reducing cholesterol concentrations in rats fed the control diet, with the concentration in CE rats found to be 40% lower than in C rats at both 6 and 13 wk.

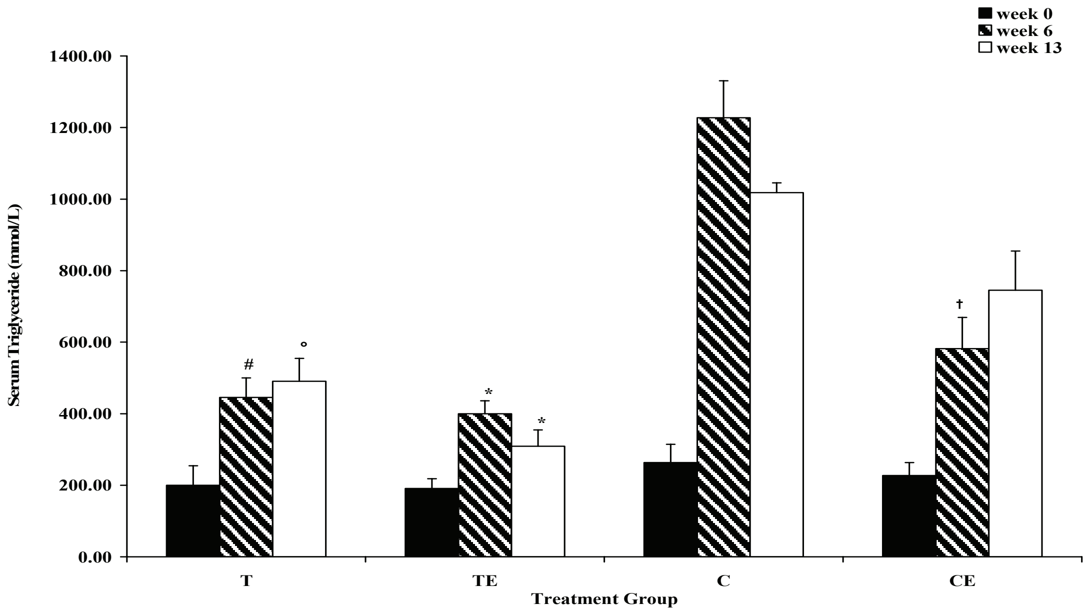

Figure 4: The effect of diet and exercise on mean fasting serum triglyceride concentration (mmol/L) over time. Values are expressed as mean ± SEM * P< 0.05 TE vs. C; # P<0.05 T vs. C; ° P<0.07 T vs. C; † P<0.05 CE vs. C.

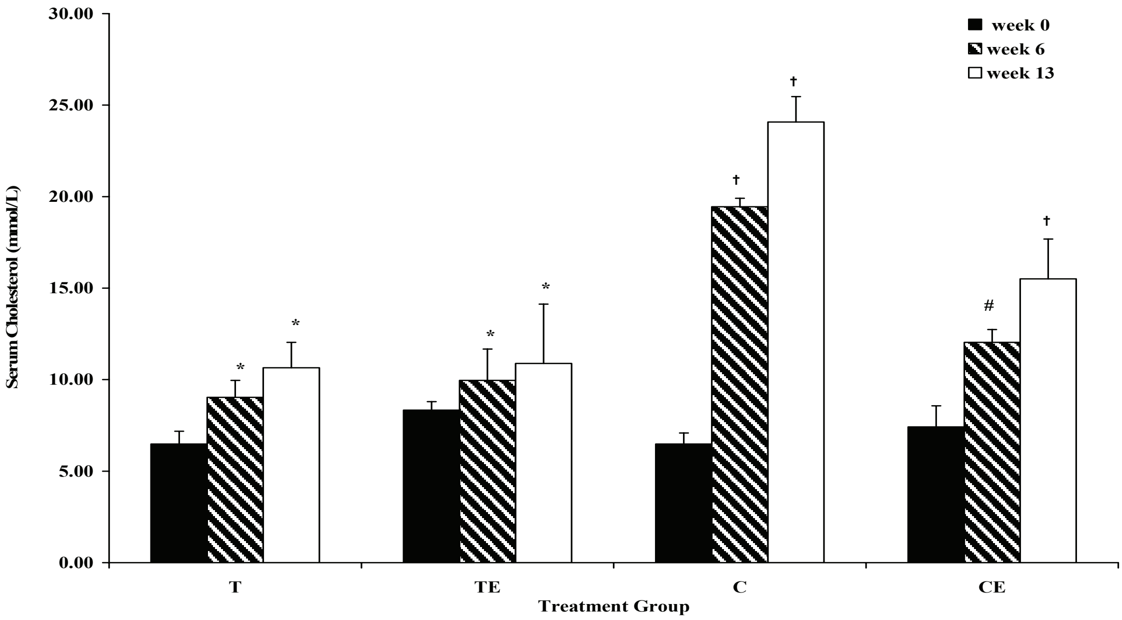

Figure 5: The effect of diet and exercise on mean fasting serum cholesterol (mmol/L) over time. Values are expressed as mean ± SEM * P<0.05 TE and T vs. C; # P<0.05 CE vs. C; † P<0.05 relative to time of treatment group.

Discussion

This study has examined the impact of a tepary bean (legume) diet, exercise, and the combination of diet and exercise, on the development of hyperinsulinemia, hyperglycemia, and hyperlipidemia in fa/fa rats, an animal model known to develop metabolic characteristics typical of Type 2 diabetes. While it is well known that consumption of a diet high in fiber, [1-3, 6-9] in particular legume fiber [4,5,12,37] improves diabetes control, our study is unique in that it assessed the effect of legumes on overall capacity to delay the biochemical manifestation of Type 2 diabetes in a susceptible animal model, despite consumption of a high fat diet. Consumption of a diet that is high in leguminous seeds is associated with an improvement in a variety of aspects of diabetes control in both insulin and non-insulin dependent diabetics.[4,9-12,37,38] Most previous investigations [4,5,10,11] have concentrated on the positive effect of legumes on the glycemic index, with little attention being given, until more recently[12] to the overall profile of the animal. Our study is one of the first to evaluate the interplay between exercise and a legume diet, either as a combined treatment or as a single comparison with no change of diet (C) or the addition of an activity component to a regular diet (CE). Although much of the literature indicates that diet and exercise together results in the greatest effect on health, this premise has yet to be evaluated in the context of a legume diet or a legume diet plus exercise.

In this study we present evidence of three main findings: 1. A tepary bean diet combined with exercise, despite 37% of calories from fat, results in significantly less weight gain and mean body mass compared with fa/fa rats who were fed either a tepary bean diet alone, or control diet with or without exercise. 2. Exercise and the consumption of a tepary bean diet results in significantly lower insulin concentration compared to control fed animals at weeks 4 and 8 of the intervention program. 3. A tepary bean diet, with or without exercise, results in significantly lower serum triglycerides and cholesterol relative to animals fed the control diet.

In this study we present evidence that a tepary bean diet combined with exercise, in fa/fa rats, results in significantly lower body mass and a decreased rate of weight gain compared to rats fed either a tepary bean diet alone or a control diet with or without exercise. Obese individuals are more likely to develop diabetes and therefore it is important to determine the effect of a legume diet on this condition. A legume diet has been shown by our group and others to be effective for decreasing obesity-related factors. We have shown previously that rats fed a tepary bean diet have 19% less fat mass compared to control fed animals and that rats who are exercised and fed tepary beans have 30% less fat than control fed animals who were also exercised.[19] Recently, the additive effect of soy protein and exercise on enzymes involved in fatty acid accumulation and accumulation of body fat has been reported in Sprague-Dawley rats.[39] While there are numerous reports of the health benefits of soy protein[39,40] similar evidence for non-soy legumes such as the tepary bean is new. Also unique to our work is the evidence we present which shows that tepary beans are effective for curbing body mass and fat accumulation in an animal model that is genetically prone to obesity.

Our findings of overall lower serum glucose in tepary bean fed animals supports a role for both a legume diet, and a legume diet in conjunction with exercise, as having a positive impact on metabolic state. The positive effect of a leguminous diet on this aspect of diabetes control is likely due to the small increase in blood sugar that occurs during the breakdown of these products into simple sugars.[30] This may be due to either the high proportion of amylase in these food sources, which results in a more extensive breakdown period, or an enhanced ability of the liver to metabolize glucose due to the fermentation of the soluble fiber to short chain fatty acids. Fatty Zucker rats have been shown to demonstrate an age-dependent increase in glycemia.[41] It is therefore of interest to note that there was no significant increase in plasma glucose concentration over the thirteen week period in either of the groups which consumed the tepary bean diet (T, TE). In contrast, control animals had glucose levels that increased significantly with time, suggesting that consumption of the legume diet helped to decrease the magnitude of change in glucose concentration that would naturally occur in the fa/fa rat. Animals who consumed the tepary beans weighed less at all time points of the study relative to control fed animals. There is a strong relationship between insulin resistance and obesity and it is possible that the improved glucose and insulin profiles that we found were a direct function of the lower body weight of these animals.

Previous studies have suggested that there may be a critical stage in the lifespan of fa/fa rats when the expression of obesity may be more amenable to modification by the manipulation of environmental factors such as diet and exercise. The lack of an effect of exercise training on fasting plasma glucose and insulin levels, as was observed in the present study, is congruent with the findings of others.[42] Reports have found no difference in basal insulin or glucose levels between trained and untrained fa/fa rats following a moderate treadmill running program (5-6 d wk^{-1}; 6-8 wk; 2 h d^{-1}; 20 m min^{-1}; 8% grade). In the present study, the pattern of decreased serum plasma glucose concentration over the first eight weeks of the study when the rats were younger suggests a potential benefit of the exercise training program over this initial period. However, when the rats had reached 15-16 weeks of age, the animals in both exercise groups (TE and CE) demonstrated a large increase in fasting serum glucose levels, thereby suggesting that any benefits of exercise training on glucose metabolism or insulin sensitivity were lost with time.

We report here that a tepary bean diet, with or without exercise has a large effect on the magnitude of hyperlipidemia in fa/fa rats. The effect of fiber based diets on lipid profiles in fatty Zucker rats has yielded conflicting findings, with reports that when fa/fa rats consume a diet mixture of various fibers and crude potato starch, plasma triglycerides and cholesterol levels decrease,[43] balanced with studies which have failed to show any change in plasma triglyceride or plasma cholesterol levels over a fourteen week period in fa/fa rats that consumed a diet high in soybean fiber.[44]

We found that a tepary bean diet combined with exercise, yields enhanced suppression of serum triglycerides and cholesterol compared to exercise alone. Exercise has been shown previously to effectively decrease blood lipids in fa/fa rats, [27, 45] however the combined effect of a legume diet and exercise has not been reported previously. It has been suggested that exercise likely enhances levels of lipoprotein lipase activity, thereby facilitating the removal of triglycerides from the circulation and increasing HDL cholesterol.[34,46] Further studies are needed to determine if legumes may exert similar physiological changes.

In summary, consumption of a tepary bean diet altered the natural pattern of plasma glucose and cholesterol concentrations typically seen over time in the fa/fa rat, despite a diet that contained 37% fat. The observed differences in cholesterol and triglyceride concentrations between groups, suggests that the tepary bean diet had a significant effect on the final level of hyperlipidemia at 20 weeks of age (week 13 on the study). Our results indicate that a tepary bean diet, with exercise, can decrease typical changes in weight gain, glycemic regulation and lipid profile in fa/fa rats. The adoption of such a program in individuals showing signs of type 2 diabetes would also likely serve to protect against these physiological changes.

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