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An Anti-Inflammatory Diet Coupled with Detoxification and Microbiome Nutritional Support Improves Weight and Markers of Insulin Sensitivity.

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Abstract

Overweight and obesity have many contributing factors, including not only the energy imbalance between diet and physical activity common in Western countries, but also an obesogenic environment, which may include socioeconomic status, stress, altered circadian rhythms, etc. Growing recognition of the role of endocrine-disrupting chemicals (EDCs), so called "obesogens," as part of this obesogenic environment makes clear that these ubiquitous chemicals act through multiple mechanisms, including the modulation of nuclear receptors, such as PPARγ, as well as induction of pro-inflammatory mediators and adverse modification of the gut microbiome.

The purpose of this study was to evaluate the use of an anti-inflammatory, hypoallergenic diet with nutritional supplementation designed to support hepatic detoxification and microbiome diversity. In this open-label 6-week pre-post intervention study with no control arm, participants with a BMI >30 kg/m² (n = 15; 9 women, 6 men; median 51 yo, median BMI 38.3 kg/m²) adopted the "Metabolic Cleanse Diet." Additionally, on weeks 1-2 they were instructed to replace two meals per day with NutriClear® Plus, a base of organic pea protein with supplemental nutrients to support detoxification, followed on weeks 3-6 with two meals per day of MetabolicBiome Plus™, also organic pea protein based, with prebiotics and other nutrients to support microbiome diversity. After 6 weeks, all participants lost weight, an average loss of 15.9 lb (7.2 kg), ranging from -5 to -39.8 lb (-2.3 to -18.0 kg). Improvements in anthropometric markers as well as scores in an online symptom assessment questionnaire were observed in all participants. No consistent change in lipids or high-sensitivity C-reactive protein (hs-CRP) was observed, though triglycerides and fasting insulin improved in 9 of10 participants with laboratory data available, and fasting glucose in 8 of10. The short-term improvement in measures of weight control and insulin resistance suggest a longer term controlled trial is indicated.

Introduction

Nearly 40% of US adults have obesity and an additional 31.8% are overweight.[1] This epidemic has broad consequences, promoting obesity-related cancers, cardiovascular disease and diabetes, as well as susceptibility to infection.[2,3,4] While calorically dense and nutrient depleted diets combined with sedentary lifestyles are primary drivers of overweight and obesity, a substantial body of evidence also indicates the importance of a number of other underappreciated risk factors.[5]

Exposure to EDCs has emerged as a potentially significant contributing factor to obesity, with persistent pollutants such as bisphenol A associated with an increased risk for both overweight and obesity.[6] More than just a storage depot for EDCs, adipose tissue metabolism is modulated by these chemicals. For example, several bisphenols have been shown to be activators of the constitutive androstane receptor (CAR), which in turn modulates multiple pathways related to energy metabolism, including bile acid biosynthesis, basal metabolic rate, lipogenesis, and gluconeogenesis. Other EDCs which influence CAR activation include fungicides, pesticides, perfluoro-alkylated substances, phthalates, etc.[7] EDCs also alter peroxisome proliferator-modulated pathways, insulin secretion and sensitivity; modification of gene expression, particularly with prenatal exposure, may induce epigenetic changes which predispose to weight gain later in life.[8] Prenatal exposure to EDCs, even at low concentrations, has been associated with an adverse impact on a number of cardiometabolic risk factors in preschoolers, including body mass index, percentage of fat mass, weight circumference, and risk of overweight.[9]

There may also be some overlap between EDCs and a growing recognition of obesity as an inflammatory state. An increase in visceral adiposity induces low grade local and systemic inflammation, marked by activation of M1 macrophages, increased release of pro-inflammatory cytokines, and an acceleration in disease progression, including cardiovascular disease.[10] Specific EDCs, such as organochlorine (OC) pesticides, have been associated with a hyperinflammatory milieu. In a remarkable analysis of nearly 750 non-diabetics among the general US population, not only were CRP levels associated with OC pesticide exposure, but CRP levels were not associated with HOMA-IR (homeostasis model assessment of insulin resistance) among participants with low levels of OC pesticides or polychlorinated biphenyls (PCBs). Yet CRP was strongly associated with HOMA-IR among participants with high concentrations of these compounds, suggesting a greater role of EDCs in promoting insulin resistance than previously suspected.[11]

Additionally, awareness of the influence of the gut microbiome on obesity and obesity-related conditions, such as the metabolic syndrome, type 2 diabetes, and non-alcoholic fatty liver disease, has also continued to grow, highlighting the importance of a rich and diverse microbial population.[12] Altered gut flora as a predisposing risk factor for weight gain now appears quite plausible. In a recent meta-analysis of 23 observational studies with over 1.2 million combined participants, antibiotic use during infancy as well as the second trimester of pregnancy was associated with an increase in risk for childhood overweight and obesity.[13] While causality has not been clearly established in humans, a reduction in microbial diversity as well as specific bacterial strains in animals support a clear link between gut dysbiosis and subsequent risk for obesity and its complications.[14]

Given the influence of EDCs, low-grade inflammation, and an altered gut microbiome on obesity, we designed a pilot pre-post intervention trial to evaluate the effects of a 6-week program on body mass index (BMI) and other anthropometric outcomes, as well as serum markers of inflammation, glucose handling, and lipids. We enrolled participants with a BMI > 30 kg/m^2, selected by their general practitioners, and provided instructions to adopt an anti-inflammatory diet combined with supplemental polyphenol and prebiotic rich nutrients, supportive of hepatic detoxification and microbial diversity.

Methods

Study Population & Data Collection

Participants were recruited from physicians in general practice clinics, using a convenience sampling technique which enrolled individuals expressing an interest in weight loss. Participants (n=17) ranged in age from 33 to 71, with a median age of 51. Sixty percent of participants were female and 40% male, with an initial mean BMI of 38.3 kg/m^2. Pregnancy was the only specific criteria for exclusion, though physicians individually selected participants with no apparent contraindications to weight loss. Designed as a pre-post intervention trial, it was unblinded with no comparator group.

Initial data for each participant was collected once before beginning the program, and a second time after completion of the 6-week program. Anthropometric measurements included body weight, height, BMI, waist and hip circumferences, and laboratory panels included a standard lipid panel, hs-CRP, fructosamine, glucose, and insulin. All laboratory analyses were performed by Labcorp© through Professional Co-op.

Additionally, a nutritional and symptom assessment questionnaire was completed by the participants at the initiation as well as the completion of the program. A total symptom score was recorded which reflected a broad array of symptoms, ranging from pain and fatigue to cravings and digestive function, for which participants assigned a score ranging from 0 (no symptoms) to 3 (severe or daily symptoms).

Intervention

All participants received written instructions for the 6-week program, which included guidelines to follow the "Metabolic Cleanse Diet," a whole-foods based diet emphasizing vegetables, fruits, and specific meats such as organic chicken and turkey, while eliminating common allergens, such as dairy, soy, and gluten, as well as refined foods, hydrogenated oils, and added sugars.

In addition, for the first two weeks of the program participants were instructed to replace two meals per day with NutriClear® Plus (each meal comprised of one packet of powder to be consumed as a shake, and one supplement packet), as well as snacks and a third meal of their choosing from the "Metabolic Cleanse Diet" options. For weeks 3-6, this pattern was repeated with two meals per day of MetabolicBiome Plus™, comprised of one shake powder packet and one supplement packet per meal. All participants received nutritional shakes and supplements at no cost by Biotics Research Corporation.

Participants were not instructed to restrict calories and could add additional meals and/or snacks from the "Metabolic Cleanse Diet" as desired. Written instructions also encouraged participants to consume organic foods when possible, increase physical activity, and sleep 7-9 hours per night during the 6-week program.

Results

Pre and post intervention results were available for the 15 participants that completed the program; 2 of the 17 participants withdrew from the program, with no post-intervention results available, and were excluded from the analysis. Lab values for five participants were not included in the analysis because either the pre or post values were non-fasting. No adverse effects were reported.

Outcome Measures

ANTHROPOMETRIC OUTCOMES

Figure 1 summarizes the changes in symptom scores. All participants reported an improvement, with an average reduction in symptom scores of 53% (ranging from -17% to -83%).

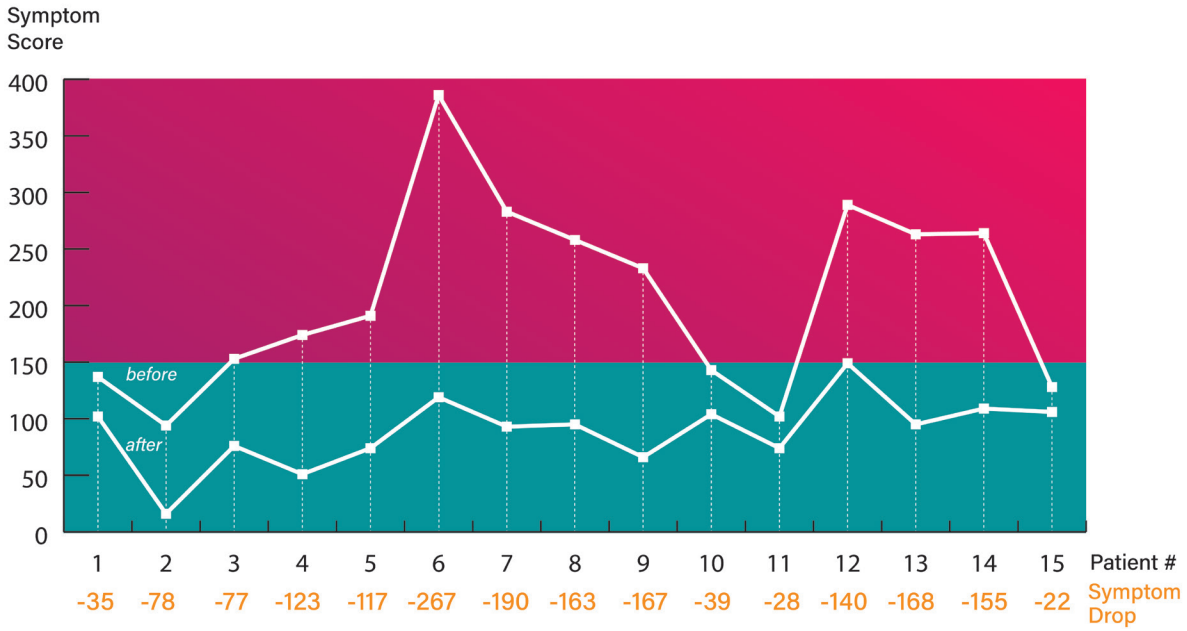

Figure 1: Pre and post symptom score totals for the nutritional and symptom questionnaire . Scores are shown for participants who completed the questionnaire at the initiation and conclusion of the trial, with the absolute drop in scores indicated in orange.

Figure 2 summarizes the changes in body weight which occurred over the 6-week program. The initial mean weight of the group was 255.9 lb (116.1 kg) with a post-intervention mean of 239.9 lb (108.8 kg). All participants lost weight, with an average loss of 15.9 lb (7.2 kg), ranging from -5.0 to -39.8 lb (-2.3 to -18.0 kg). As a percentage of initial body weight, participants lost an average of 6.1%, ranging from -2.3% to -14.6%.

The average reduction in BMI was 2.5 kg/m², with decreases between -0.8 to -5.4 kg/m², corresponding to an average percent reduction in BMI of -2.2 to -14.6%. All participants had a reduction in waist circumference and all but one had a reduction in hip circumference. The average decrease in waist and hip circumference was 2.62 and 2.95 inches, respectively.

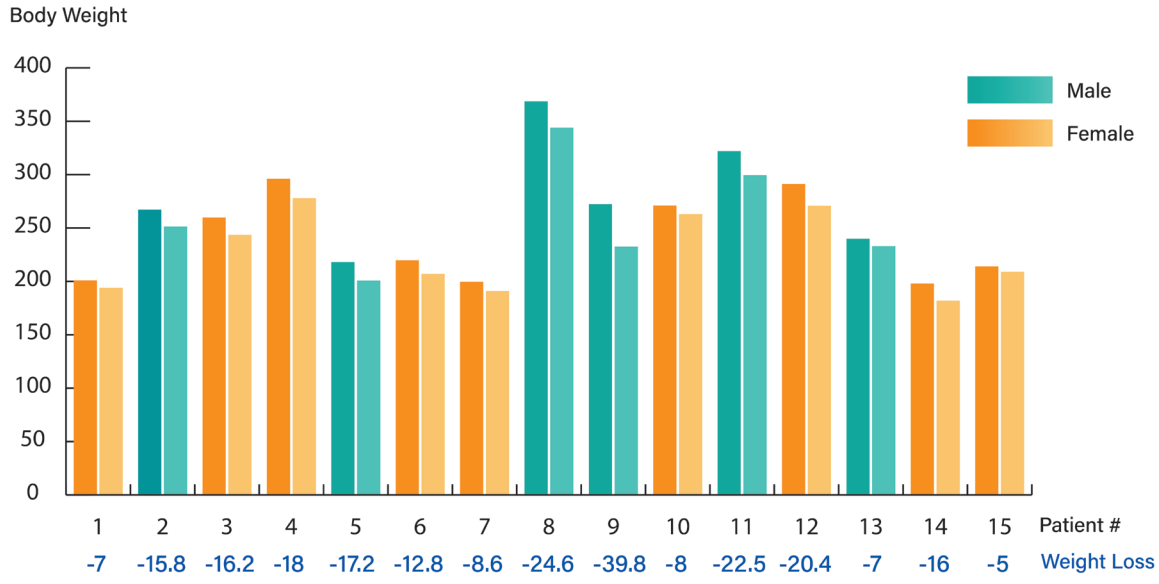

Figure 2: Pre and post intervention body weight over the 6-week program. Values in pounds, with total pounds lost indicated in blue.

LABORATORY OUTCOMES

Five participants were excluded from analysis because either the pre-test or post-test laboratory sample was non-fasting. Pre-post intervention triglycerides decreased in 9 of the 10 participants, with an average reduction of 21.5 mg/dL among all participants **(Figure 3)**. No consistent effect was observed for other lipids, though there was an average increase in HDL cholesterol of 1.5 mg/dL, and an average decrease of 4.8 mg/dL in total cholesterol, 3.9 mg/dL VLDL, 2.4 mg/dL LDL, and 0.2 in the ratio of LDL to HDL. No consistent effect was observed for hs-CRP. Serum glucose and insulin levels decreased in 80% and 90% of the ten participants with fasting lab data available; from a preintervention mean of 94.3 mg/dL to a postintervention mean of 90.9 mg/dL, and 20.8 to 16.1 mIU/L, respectively. Serum fructosamine levels increased slightly in 8 of 10 participants, from a mean of 222.2 to 228.3 umol/L.

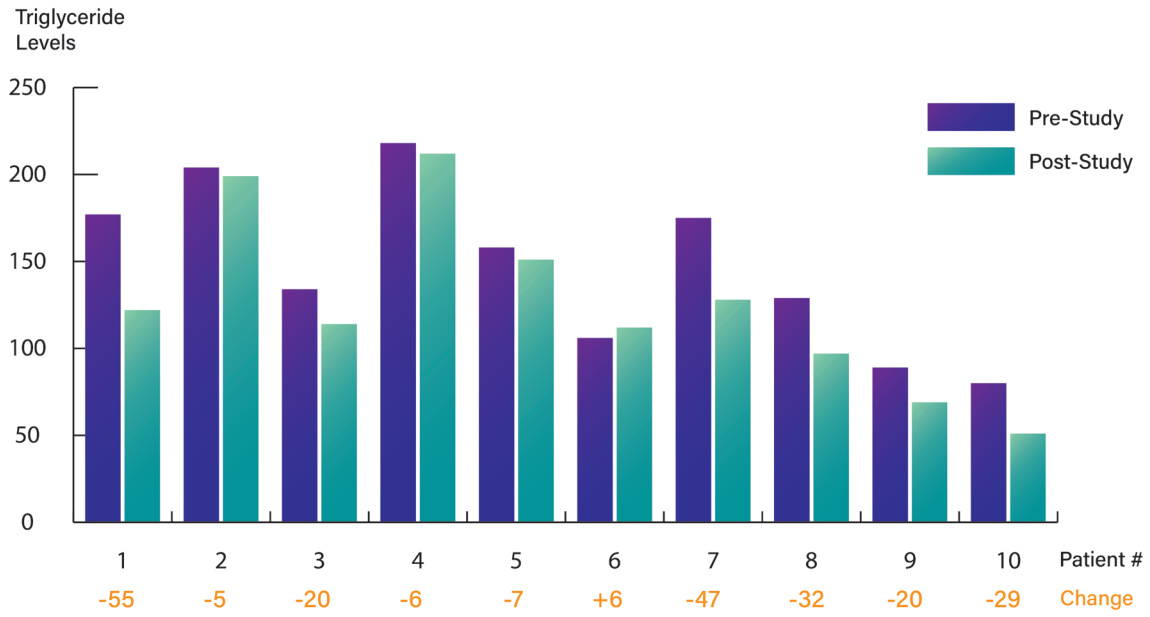

Figure 3: Pre and post intervention triglyceride levels in mg/dL. Values in orange indicate the absolute change during the program. Five participants' lab data was excluded from the analysis due to non-fasting pre or post intervention samples.

Discussion

All the participants in this 6-week pilot program experienced weight loss, with a clinically meaningful 2.5 kg/m² average drop in BMI, and general improvement in anthropometric measures of overweight/obesity, as well as subjective improvements in symptom scores per the nutritional and symptom questionnaire. Improvements in glucose, insulin, and serum triglycerides suggest a possible increase in insulin sensitivity, notable in this normoglycemic obese patient population.

The use of an anti-inflammatory, calorie-restricted, whole foods diet has been previously used to improve both cardiometabolic risk factors as well as to induce weight loss.[15] Weight loss itself has an anti-inflammatory effect, with the vast majority of studies indicating weight loss by any means is likely to reduce the production of pro-inflammatory cytokines.[16] In this study, participants were also supplemented with a combination of nutrients and phytochemicals shown to improve hepatic detoxification and/or improve glycemic control, as well as satiety, including medium chain triglycerides, omega-3 fatty acids, organic greens, beet fiber, and milk thistle.[17,18,19,20] Both alpha lipoic acid and N-acetylcysteine induce glutathione production, particularly important for conjugation with a variety of EDCs as well as the non-alcoholic fatty liver disease which often accompanies obesity.[21] Indeed, a previously published dietary detoxification program was found to decrease serum γ-glutamyltransferase (GGT) levels, a potential biomarker for EDC exposure in the absence of alcohol exposure.[22,23]

The use of plant protein as a replacement for animal protein has also been shown to improve glycemic control. A previously published systematic review and meta-analysis concluded that among diabetics, modest improvements in HbA1c, fasting glucose, and fasting insulin occurred when plant proteins replaced animal proteins at ≥35% of total protein over a median duration of 8 weeks.[24] In a small study of healthy young male participants, pea protein specifically was found to improve pre and post meal blood glucose levels.[25]

Gut microbiota modulation is also likely to play an important role in weight management. Animal studies suggest that microbiota changes due to prebiotic supplementation improve intestinal permeability and tight junction integrity via an upregulation of glucagon-like peptide-2 (GLP-2).[26] Among adolescents with obesity, GLP-2 has been found to be blunted postprandially, and inversely correlated with insulin resistance.[27] Use of the prebiotic inulin has been associated with significantly higher GLP-2 levels as well as lower zonulin levels compared to a control group in healthy volunteers, suggesting enhanced intestinal integrity.[28] In our study, prebiotics were also included in the supplemental component of the 6-week program; chicory root inulin, beet and apple fiber, and other vegetable extracts provided 6-9 g fiber per serving. Interestingly, inulin supplementation has also been associated with an improved mood in subjects with obesity in a randomized controlled trial.[29] A specific profile, including greater insulin resistance, higher baseline *Coprococcus* levels, and higher IL-8 levels were predictive of a larger response.

Limitations

This was a preliminary pilot study, created and implemented in order to provide a basis for a more in-depth randomized controlled trial. Thus, as with general preliminary research, certain limitations were ascertained. This study was not randomized and did not have a control group, preventing any conclusions about causality regarding the observed improvements, or which, if any of the components of the 6-week program had an influence on the outcomes. The short-term nature of this study also does not fully assess the lasting influence of the program, an important factor given the frequent regaining of lost weight. Finally, the actual dietary intake and compliance of participants was not fully assessed, posing difficulty in analyzing details of the program's effectiveness. Yet, this fundamental exploratory study imparts a solid foundation for future endeavors.

In this study, fructosamine levels increased in the majority of participants, though the absolute increase was insubstantial. Given that these were normoglycemic individuals, this may not have relevance, particularly in the context of improved fasting glucose and insulin levels. In all participants with a baseline insulin level > 10 mIU/L, post-intervention insulin levels decreased, as much as -17.7 mIU/L in one participant, suggesting improved glycemic control among subjects at greatest risk. The use of more specific markers, such as HOMA-IR, may help elucidate changes in insulin sensitivity in future trials.

In summary, a 6-week program of dietary changes complemented by nutritional supplementation was associated with improved weight and other anthropomorphic measures of obesity, as well as subjective symptom improvement. A subsequent randomized and well-controlled trial of adequate power would be necessary to confirm the validity of results presented here.

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