

Detoxification Enhanced Lifestyle Intervention Targeting Endotoxemia (DELITE) in the Setting of Obesity and Pain: Results of a Pilot Group Intervention

Robert Alan Bonakdar, MD, FAAFP, FACN; Megan Sweeney, MPH; Sarah Dalhoumi, MD; Vanessa Adair, NP; Cathy Garvey, RD; Teresa Hodge, Leslie Herrala, CEP, MS; Ali Barbee, CEP, MS; Christina Case, CEP; Joe Kearney, MA, CPLC; Kendall Smith, ND; Jacob Hwang, ND

Abstract

Background: Obesity is a complex multifactorial disorder affecting a growing proportion of the population. While therapeutic lifestyle change (TLC) is foundational, results of interventional programs are often inconsistent. Factors related to systemic inflammation, toxin load and endotoxemia have been postulated to play a contributory role. This pilot study sought to evaluate the role of TLC with enhanced laboratory evaluation and interventions to address these emerging therapeutic targets.

Methods: Twelve participants with a body mass index (BMI) greater than 30 (or 27 with metabolic co-morbidities) were recruited from an outpatient clinic for participation with a primary outcome of pre/post changes in body composition. Participants completed a 12-week program involving weekly group and individualized dietary, exercise, and behavioral support, supplemented with a commercial, 30-day dietary detoxification intervention and ongoing nutritional counseling. All participants completed baseline and post-intervention evaluation including metabolic, toxin load, endotoxin, body composition and functional fitness profiles.

Results: After 12-weeks, participants as a group significantly improved body composition parameters including BMI, body fat, fat mass, and waist and hip circumference ($P < 0.01$). Significant improvement in several secondary outcomes including levels of lipopolysaccharide, zonulin and leptin were noted. Additionally, results demonstrate substantial improvements in pain, pain interference and functional fitness. Upon completion, all participants rated the program favorably with a high likelihood of continuing or recommending participation to others.

Conclusions: Obesity remains a challenging and often refractory clinical scenario with emerging evidence indicating the potential role of systemic inflammation, toxin load and endotoxemia. A group therapeutic lifestyle change program enhanced with a detoxification component is feasible and may provide a promising intervention for achieving weight loss while also addressing functional and pain related co-morbidities. Future randomized trials evaluating the components of such a program are needed to better delineate the role of specific interventions in the complex setting of obesity.

Robert Alan Bonakdar, MD, FAAFP, FACN; Megan Sweeney, MPH; Cathy Garvey, RD; Sarah Dalhoumi, MD; and Vanessa Adair, NP, Scripps Center for Integrative Medicine, La Jolla, California, USA. Teresa Hodge, Supervisor of Clinic Operations, Leslie Herrala, CEP, MS; Ali Barbee, CEP, MS; and Christina Case, CEP; Scripps Health Shiley Sports and Health Center, La Jolla, California, USA. Joe Kearney, MA, CPLC, Scripps Living Lite Lifestyle Management Program, San Diego, California, USA. Kendall Smith, ND; Alive Integrative Medicine Eugene, Oregon, USA. Jacob Hwang, ND, Susan Samuelli Integrative Health Institute, University of California-Irvine, Irvine, California, USA. Drs. Smith and Hwang contributed while at Bastyr University California, San Diego, California.

Corresponding author: Robert Alan Bonakdar, MD
E-mail address: bonakdar.robert@scrippshealth.org

Introduction

Obesity and overweight status are major public health concerns in the USA. As of 2018, more than 70% of adults met criteria for overweight status, with a body mass index (BMI) of 25 kg/m² or greater, while 42.4% were obese, with a BMI of 30 kg/m² or greater.^{1,2} This US rate of obesity is the highest for countries in the Organization for Economic Cooperation and Development (OECD) and is nearly double that of the mean rate for other OECD nations.³

Obesity

Obesity is strongly associated with negative health outcomes, including cardiovascular disease, diabetes, and mortality, placing it as the second leading cause of preventable death.⁴ Obesity also poses a significant financial burden, with direct and indirect costs being estimated at nearly \$200-billion per year.⁵

To address the obesity epidemic, major public health initiatives have been launched by the National Institutes of Health (NIH), including the Weight of the Nation campaign (Weight of the Nation, 2020).^{6,7}

While these initiatives have improved awareness and lowered obesity rates in some sectors, little progress has occurred in reducing population-wide obesity trends, with estimates noting that obesity will continue to rise to involve nearly half of the US population by 2030.²

Several theories have been offered for the difficulty of current approaches in achieving significant impacts on obesity trends, including one theory related to the failure of measurement of BMI to define the causes effectively and a second that considers that the traditional hypothesis of obesity being initiated through increased caloric intake, coupled with a reduced energy expenditure, as inadequate.

BMI. This current measurement of obesity doesn't appear to fully capture the metabolic and inflammatory underpinnings of obesity. For example, complications related to obesity appear in individuals with a normal BMI who exhibit a large waist circumference and/or abdominal obesity, termed normal weight obesity (NWO).⁸ The NWO phenomenon appears related to metabolic complications promoted by visceral fat accumulation, including insulin resistance and systemic inflammation.⁹

These factors have been associated with both gut-related inflammation and a tissue-level manifestation of inflammation, namely increased pain and pain sensitivity.^{10,11} When obesity treatment is based solely on BMI, without additional anthropometric and biological measurements of inflammatory underpinnings, it may underestimate risk and create a potential for undertreatment in certain scenarios, including obesity-related pain.¹²⁻¹⁴

Traditional hypothesis. Obesity has been traditionally hypothesized as being initiated through increased caloric intake, coupled with a reduced energy expenditure, that creates a positive energy balance.^{15,16} While this concept is foundational, research has noted that the increasing prevalence of obesity can't be fully explained by these factors alone. Recent analysis has shown that an adult today would have a BMI 2.3 points higher than an adult in 1988 with similar caloric intake and expenditure.¹⁷

While therapeutic lifestyle change (TLC) is foundational to treatment of obesity and overweight status, the results of interventional programs are often inconsistent. Factors related to systemic inflammation, toxin load, and endotoxemia may play a contributory role. While no etiologies easily explain this discrepancy, a number of hypotheses have been offered including nutrient, microbiome, activity-related, socioenvironmental, behavioral, and genetic contributors.¹⁸⁻²⁰ Two potentially modifiable contributory factors that haven't been traditionally targeted and that will be explored in the context of this trial include obesity-related toxin load and metabolic endotoxemia.²¹⁻²³

Toxin Load

Toxin exposure is recognized as an increasingly prevalent factor associated with chronic illness, including metabolic disease and obesity.^{21,24-26} Several metabolism-disrupting chemicals (MDCs) have been described that can promote diabetes and obesity.²⁵⁻²⁷ These include persistent organic pollutants (POPs) that consist mainly of pesticides, herbicides, and plastic-associated chemicals (PACs), such as bisphenol A and phthalates, as well as advanced-glycation end products (AGEs).

POPs are characterized as being highly lipophilic, long half-life compounds that can have tissue-disrupting effects.²⁹ As related to obesity, in-vitro studies have noted that these compounds promote adipogenesis in cell lines through activation of glucocorticoid receptors as well as modulate food intake.^{30,31} AGEs are naturally present in foods, especially in animal-food products but are typically a byproduct of high-temperature cooking, grilling, or frying, which can promote glycoxidation reactions. Studies have shown that diet, including food packaging and preparation, can account for a significant portion of exposure to MDCs.^{32,33} Importantly, a number of food-preparation strategies including cooking foods for a shorter period of time with lower, moist heat and addition of acidic ingredients such as lemon juice or vinegar can reduce exposure and toxin load.³⁴

Also important is the fact that environmental exposure in this scenario can refer both to traditionally recognized toxin exposures as noted above as well as to less commonly recognized lifestyle exposures that can affect metabolism. These exposures—including environmental stress, social isolation, and sedentary lifestyle as well as mood and sleep disruption—have also been shown to negatively affect metabolism and contribute to overall toxin burden.³⁵

Metabolic Endotoxemia

Experimental models of obesity have noted alterations in intestinal barrier integrity that promote increased intestinal permeability. These alterations have been associated with an enhanced translocation of microbiome-derived lipopolysaccharide (LPS) into the bloodstream, in a phenomenon known as metabolic endotoxemia (ME).^{36,37} The progression of ME appears to promote several factors associated with obesity and insulin resistance, which include low-grade systemic inflammation, changes in microbiome composition, and adipose dysfunction that is often measured through changes in adipokines, such as leptin and adiponectin. Notably, ME has also been demonstrated in humans in acute and chronic settings based on the introduction of obesogenic diets that are typically high in fat and low in fiber.³⁸⁻⁴²

Evaluating Toxin Load and Endotoxemia

Currently, no standardized measures exist for assessing toxin load with currently available measures

including organic-acids testing as well as direct toxin screens in serum, urine, or tissues; pre- and post-toxin measures after chelating or detoxification challenges; and measurement of toxin metabolites. One method that has received preliminary validation in animal and human models is measurement of porphyrin-metabolite levels.^{43,44} Various porphyrins, including urinary coproporphyrins, have been directly correlated with exposure to POPs.⁴⁵ Similarly, measurement of detoxification pathways, including phase I cytochrome P450 and phase II conjugation enzyme pathways, has also been introduced as a method for quantifying detoxification.⁴⁶

Several measures have been suggested for quantifying metabolic endotoxemia. Zonulin and LPS have been used in previous studies as measures of increased intestinal permeability and endotoxemia.⁴⁷ Importantly, elevated zonulin has also been associated with increased risk of obesity and metabolic disease placing it as a potential marker bridging intestinal permeability with cardiometabolic disease.^{48,49}

Addressing Toxin Load and Endotoxemia

A number of studies have identified associations between toxin load and endotoxemia in promoting obesity.⁵⁰⁻⁵² These preliminary investigations have noted exposure to persistent organic pollutants increasing levels of lipopolysaccharides (LPS) that possibly are modulated by changes in the microbiota.^{50,51}

The association between POPs and negative health outcomes has prompted research and recommendation to reduce exposure.⁵³ Several strategies, which are often termed detoxification, have been suggested to mitigate the effects of toxin load and endotoxemia in obesity and metabolic disease. These strategies fall into 2 broad categories, namely elimination and enhancement strategies.

Elimination strategies aimed to remove or reduce intake of MDC-associated foods have provided preliminary benefits in reducing body mass and fat percentage.⁵⁴ Common strategies examined in studies have included reduction or elimination of alcohol, processed meat, dairy, and grain.⁵⁵ Enhancement strategies often target pathways critical to detoxification, including intake of phytonutrients that may support phase 1 and -2 detoxification pathways. Dietary strategies that have been employed include increased intake of high-fiber phytonutrients, Omega-3 PUFAs, berberine, and pre- and probiotics.⁵⁶⁻⁶⁰ Lastly, long-term physical activity in isolation or as part of a lifestyle intervention has also been noted as a strategy for reducing endotoxemia-associated obesity.⁶¹⁻⁶³

The current pilot study sought to evaluate the role of therapeutic lifestyle change (TLC), using enhanced laboratory evaluation and interventions to address the emerging therapeutic targets.

Methods

Participants

The study was a single-arm pilot initiated in September of 2017 at a San Diego based outpatient clinic where the staff were affiliated. The participants were a convenience sample of patients of the clinic responding to an announcement regarding an upcoming lifestyle change program. The study staff completed an informational session which outlined the program as well as obtaining information from interested participants regarding their health status and ability to commit to a 12 week lifestyle program.

After considering 18 potential participants, 12 were offered participation in the program. Invitation was based on participants ability to meet inclusion criteria including BMI-defined obesity, BMI > 30, or a total BMI \geq 27 with metabolic comorbidities and ability to commit to a 12 week program including weekly meetings and no exclusion criteria present including history of bariatric surgery or major gastrointestinal or liver disease. The 12 participants including 10 females and 2 males between 47 and 73 years of age who all completed an informed consent for participation in the program.

Procedures

Intervention. Participants completed a 12-week program involving weekly group and individualized dietary, exercise, and behavioral support, with the addition of a commercial 28-day dietary detoxification intervention and ongoing nutritional support.

Outcome measures. All participants completed baseline and postintervention measurements of body composition; physical fitness and functional status; metabolic, lipid, and inflammatory and cardiovascular parameters; blood glucose and adipokine parameters; and parameters of the intestinal barrier. In addition, the participants completed hepatic detox and porphyrin panels at both points. Participants additionally completed methylation and hormone metabolism panels which will be reported separately.

Participants also completed survey during the trial including validated measures including the Brief Pain Inventory (BPI).⁶⁴ as well as study specific, feedback related to participation in the program.

Intervention

Laboratory and Symptom Review. After completion of baseline metabolic panels, participants reviewed the results with a physician and were provided individualized recommendations for areas of abnormality, which were predominately the use of supplements for vitamin D, vitamin B₁₂, and homocysteine. Participants who had additional concerns were able to consult a clinician on an as-needed basis to review status and nutritional recommendations. After 2 participants reported slight constipation, increased hydration and a whole-food fiber

Figure 1. Whole Food Fiber Supplement Facts Label

Supplement Facts		
Serving Size: 1 Level Tablespoon		
Servings per Container: 30		
Amount per Serving		
		%Daily Value
Calories	20	
Total Carbohydrate	5 g	2%*
Dietary Fiber	3 g	11%*
Proprietary Blend:	6 g	†
Oat fiber, beet fiber, rice bran, organic beet (root), apple pectin, organic carrot, organic sweet potato, and carrot fiber.		
*Percent Daily Values based on a 2,000 calorie diet.		
†Daily Value not established.		

supplement were incorporated as part of the intervention (Figure 1).

Diet. Participants met with a registered dietician at baseline and biweekly to review the 12-week program, which included a whole-food-based protein supplement, (SP Detox Balance, Standard Process (Palmyra, WI, USA)).

This product was chosen based on high protein content commonly utilized in weight management programs as well as whole-food based constituents potentially targeting toxin load and endotoxemia. The product was utilized 1 to 3 serving per day over the first 28 days of the program based on a titration schedule provided by the accompanying SP Detox Balance Program (Standard Process Standard Process, Palmyra, WI, USA). In addition, the guide recommended participants follow following a whole-food, organic, low-toxin diet, including avoidance of gluten and dairy as well as refined carbohydrates and processed meat and provided further guidance, including shopping lists, nutritional recommendations, and recipes. Dietician visits were utilized to individually adjust dietary intake based on incorporation of the whole-food based supplement and recommended dietary transitions.

Activity. Participants met at baseline and biweekly with a certified exercise physiologist to create a personalized daily activity regimen based on baseline-fitness status and comorbidities.

Behavior. Participants met at baseline and weekly with a trained behavioral specialist with expertise in weight management to discuss behavioral strategies related to the program.

Group Program. The program included a two-hour weekly meeting consisting of a lecture by program staff discussing topics relevant to the program, a behavioral group led by behavioral specialist, and a group-exercise session led by fitness staff.

Figure 2. SP Detox Balance Nutritional Facts Label

Supplement Facts		
Serving Size: 2 Scoops (37 grams)		
Servings per Container: 21		
Amount per Serving		
		%Daily Value
Calories	160	
Total Fat	5 g	6%*
Saturated Fat	0.5 g	3%*
Total Carbohydrate	11 g	4%*
Dietary Fiber	4 g	14%*
Total Sugars	1 g	†
Protein	17 g	34%*
Vitamin K1	4 mcg	3%
Choline	100 mg	18%
Calcium	70 mg	5%
Iron	4 mg	22%
Magnesium	70 mg	17%
Sodium	150 mg	7%
Potassium	230 mg	5%
Arginine	1300 mg	†
Glycine	600 mg	†
L-isoleucine	850 mg	†
L-leucine	1600 mg	†
DL-methionine	300 mg	†
L-valine	900 mg	†
Creatine	600 mg	†
Proprietary Blend	34.4 mg	†
Organic pea protein, flax meal, oat flour, organic pumpkin seed protein, organic buckwheat flour, organic beet (leaf) juice powder, organic buckwheat (aerial parts), apple pectin, juniper (berry) powder, organic spanish black radish (root), burdock (root) powder, organic beet (root), calcium citrate, organic barley (grass), dandelion (leaf), broccoli (aerial parts), inositol, organic alfalfa (aerial parts) juice powder, oregon grape (root) powder, globe artichoke (leaf), sunflower lecithin powder, milk thistle extract (80% silymarins), organic cordyceps mushroom powder, organic carrot, organic sweet potato, and red wine extract		
*Percent Daily Values based on a 2,000 calorie diet.		
†Daily Value not established.		

Other Ingredients: Creatine, L-leucine, xanthan gum, L-isoleucine, L-valine, DL-methionine, monk fruit extract, and choline bitartrate.
Caution: This product is processed in a facility that manufactures other products containing soy, milk, egg, wheat, peanut, tree nuts, fish and shellfish.

Outcome Measures

The primary endpoint of the trial was change in body composition. Secondary endpoints included changes in functional fitness and biomarkers of inflammation, toxin load, endotoxemia, and adipokines.

Body Composition. The testing included measurements of weight, BMI, body fat %, fat mass, waist circumference, hip circumference, and waist-to-hip ratio. The weight-loss goal for the current pilot was set at 5%.

Physical Fitness and Functional Status. The testing included measurements of metabolic parameters, including resting blood pressure and heart rate; blood pressure, heart rate, total distance, and speed after the six-minute walk, mean peak oxygen uptake (VO_2); and metabolic equivalents (METs). It also included measurements of strength and flexibility, including the right and left back scratch, the right and left sit-reach, the 30-second sit-stand, and the 30-second arm curl.

Metabolic, Lipid, and Inflammatory and Cardiovascular Parameters. The testing included measurements of metabolic parameters, including chloride, potassium, calcium, sodium, inorganic phosphorous, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, direct bilirubin, total bilirubin, blood urea nitrogen (BUN), uric acid, total creatine kinase, creatinine, estimated glomerular filtration rate (eGFR), cystatin-c, vitamin D, magnesium, vitamin B12, folate, thyroid stimulating hormone (TSH), T3, T4, free T3 and free T4.

The testing included measurements of lipid parameters, including total cholesterol, low density lipoproteins (LDL), small dense low density lipoproteins (sd-LDL), high density lipoproteins (HDL), HDL-2, HDL-3, HDL2%, lipoprotein-associated phospholipase A2 (Lp-PLA2) activity, lipoprotein a [Lp(a)], triglycerides, apolipoprotein A-I (Apo-A), apolipoprotein B (Apo B), and Apo B to Apo-A1.

The testing included measurements of inflammatory and cardiovascular parameters, including endothelin, interleukin-6, interleukin-17A, interleukin-10, tumor necrosis factor alpha (TNF- α), ferritin, high-sensitivity C-reactive protein (hs-CRP), homocysteine, cardiac troponin I, and N-terminal (NT)-pro hormone brain natriuretic peptide (BNP) (NT-proBNP).

Blood Glucose and Adipokine Parameters. The testing included measurements of blood glucose and adipone parameters, including insulin, hemoglobin A_{1c}, glucose, adiponectin, leptin, and leptin to adiponectin ratio.

Assessment of Intestinal Barrier. A serological intestinal-barrier assessment was completed to evaluate parameters commonly implicated in the breakdown of the intestinal barrier. The testing included measurements of zonulin, diamine oxidase, histamine, diamine oxidase to histamine, liposaccharides immunoglobulin A (IgA), liposaccharides IgG, and liposaccharides IgM.

Detoxification Panels. Participants completed a serological panel at baseline and after completing the first 28 day of the trial. The testing included: (1) a hepatic detox panel for phase 1 D-glucuronic acid, phase 2 mercapturic acids, and creatinine; (2) a porphyrin panel for uroporphyrins, heptacarboxylporphyrins, hexacarboxylporphyrins, pentacarboxylporphyrins, coproporphyrin 1, coproporphyrin 3, and coproporphyrin 1 to coproporphyrin 3; and (3) total porphyrins, including precoproporphyrin 1, precoproporphyrin 2, precoproporphyrin 3, total precoproporphyrins, precoproporphyrins to uroporphyrins, and creatinine.

Statistical Analysis

Statistical analyses were performed using Stata (StataCorp, College Station, Texas, USA). Two-tailed, chi-square tests were run to assess changes between baseline and postintervention. Results are shown as means \pm standard deviations (SDs). A significance level of $P < .05$ was established.

Results

All participants completed the trial and postintervention testing.

Body Composition and Functional Status

Participants collectively achieved statistically significant improvements in the primary endpoint of body composition (Table 1), including BMI, $P < .001$; weight, $P < .001$; body fat, $P < .007$; fat mass, $P < .001$; waist and hip circumferences, each $P < .001$; and waist-to-hip ratio, $P < .007$. Participants were also evaluated for potential changes in physical fitness and functional status (Table 2). While not all areas improved, the mean changes in several key areas were statistically significant, including resting blood pressure, $P = .017$; six-minute walk distance, $P = .001$, and six-minute walk speed, $P = .002$; mean peak oxygen uptake (VO_2), $P = .001$; metabolic equivalents (METs), $P = .003$; and upper body strength, $P = .001$.

Metabolic Function

Table 3 shows the results of the metabolic, inflammatory, and cardiovascular testing. No significant changes occurred in liver, kidney, lipid, or metabolic function other than elevation of calcium levels, which remained within the normal range. No significant changes occurred in thyroid function other than a reduction in T3, which was within the normal limits. Additionally, vitamin D, assessed via the 25-Hydroxy Vitamin D Test [25(OH)D], and vitamin B₁₂ increased significantly but both remained within the normal range. For cardiovascular and inflammatory markers, statistically significant improvements occurred in homocysteine, $P = .005$; and endothelin, $P = .003$.

Table 1. Body Composition

Parameter	Baseline Mean ± SD	Postintervention Mean ± SD	P Value
Weight, lb	220.3 ± 49.1	210.2 ± 45.6	<.001 ^a
Body mass index (BMI)	35.3 ± 6.7	33.6 ± 6.2	<.001 ^a
Body fat, %	43.0% ± 6.3%	40.9% ± 7.4%	.007 ^a
Fat mass, kg	94.9 ± 29.4	86.7 ± 27.8	<.001 ^a
Waist circumference, in	44.4 ± 5.9	41.8 ± 5.8	<.001 ^a
Hip circumference, in	48.7 ± 4.8	47.4 ± 5.2	<.001 ^a
Waist-to-hip ratio	0.91 ± 0.07	0.88 ± 0.09	.007 [*]

^aDenotes statistical significance at $P \leq .05$

Abbreviations: SD, standard deviation.

Table 2. Physical Fitness and Functional Status

Parameter	Baseline Mean ± SD	Postintervention Mean ± SD	P Value
Blood pressure—resting	134.2 ± 83.9	125.9 ± 80.6	.017 ^a
Heart rate, BPM —resting	69.7 ± 8.6	63.7 ± 10.8	.119
Blood pressure—6 min walk	175.7 ± 80.8	162.7 ± 86.5	.145
Heart rate, BPM—6 min. walk	112.7 ± 27.7	113.6 ± 26.6	.684
Total distance, meters—6 min. walk	468.3 ± 70.4	513.2 ± 58.8	.001 ^a
Speed, mph—6 min walk	2.9 ± 0.45	3.2 ± 0.39	.002 ^a
Mean peak VO ₂ , ml/kg/min	11.3 ± 1.2	12.1 ± 0.99	.001 ^a
METs	3.2 ± 0.32	3.4 ± 0.27	.003 ^a
Strength and flexibility			
Back scratch, right	-7.8 ± 7.3	-6.1 ± 7.9	.003 ^a
Back scratch, left	-8.4 ± 6.3	-6.0 ± 7.6	.065
Sit-reach, right	-2.5 ± 5.6	-0.77 ± 4.8	.083
Sit-reach, left	-1.6 ± 5.3	0.06 ± 4.6	.067
Sit-stand, 30 sec	13.4 ± 2.5	17.2 ± 3.3	<.001 ^a
Arm curl, 30 sec	22.0 ± 4.6	25.8 ± 4.2	<.001 ^a

^aDenotes statistical significance at $P \leq .05$

Abbreviations: SD, standard deviation; VO₂, oxygen uptake; METs, metabolic equivalents.

Table 3. Metabolic, Lipid, and Inflammatory Parameters

Parameter	Reference Range	Baseline Mean ± SD	Postintervention Mean ± SD	P Value
Metabolic Parameters				
Chloride	98-107 mmol/L	101.2 ± 1.9	101.5 ± 2.9	.792
Potassium	3.5-5.1 mmol/L	4.6 ± 0.62	4.7 ± 0.36	.639
Calcium	8.6-10.2 mg/dL	9.5 ± 0.54	9.9 ± 0.36	.023*
Sodium	136-145 mmol/L	142.1 ± 3.3	143.1 ± 2.8	.396
Phosphorous, inorganic	2.5-4.5 mg/dL	3.4 ± 0.38	3.6 ± 0.45	.212
Total protein	6.4-8.3 g/dL	7.2 ± 0.30	7.3 ± 0.34	.184
Albumin	3.5-5.2 g/dL	4.5 ± 0.21	4.6 ± 0.24	.319
ALT	5-33 U/L	24.5 ± 8.4	23.2 ± 8.1	.456
AST	5-32 U/L	25.9 ± 10.5	23.1 ± 5.3	.745
Alkaline phosphatase	35-104 U/L	78.3 ± 20.7	75.4 ± 23.6	.214
Bilirubin, direct	0.0-0.3 mg/dL	0.3 ± 0.14	0.23 ± 0.06	--
Bilirubin, total	<1.3 mg/dL	0.51 ± 0.25	0.55 ± 0.30	.681
BUN	6-23 mg/dL	15.5 ± 3.7	14.7 ± 2.8	.396
Uric acid	2.4-5.7 mg/dL	6.0 ± 1.2	5.9 ± 1.2	.666
Total creatine kinase	26-192 U/L	335.6 ± 528.2	95.4 ± 44.6	.307
Creatinine	0.50-0.90 mg/dL	0.81 ± 0.13	0.81 ± 0.12	.465
eGFR	>60 mL/min/BSA	80.9 ± 15.9	80.5 ± 15.2	.441
Cystatin-C	0.61-0.95 mg/L	0.99 ± 0.19	0.98 ± 0.16	.322
Vitamin D	30-100 ng/mL	33.8 ± 10.6	59.5 ± 11.8	<.001 ^a
Magnesium	1.6-2.6 mg/dL	2.2 ± 0.16	2.2 ± 0.22	.531
Vitamin B ₁₂	>231 pg/mL	541.7 ± 167.3	796.1 ± 303.4	.005 ^a
Folate	>4.4 ng/mL	16.4 ± 4.6	>20 ± 0	--
TSH	0.27-4.2 uIU/mL	2.1 ± 1.1	2.3 ± 1.0	.689
T3	0.80-2.00 ng/mL	1.1 ± 0.19	1.0 ± 0.20	.095
T4	4.5-11.7 ug/dL	7.6 ± 2.1	7.2 ± 1.3	.261
Free T3	2.0-4.4 pg/mL	3.1 ± 0.45	2.7 ± 0.32	.006 ^a
Free T4	0.9-1.7 ng/dL	1.1 ± 0.41	1.3 ± 0.36	.351
Parathyroid hormone	15-65 pg/mL	53.5 ± 23.9	49.1 ± 19.9	.024
Lipid Parameters				
Total cholesterol	<200 mg/dL	188.6 ± 48.8	201.5 ± 47.4	.145
LDL	>100 mg/dL	120.6 ± 36.1	123.6 ± 36.6	.477
sd-LDL	13.0-54.5 mg/dL	27.1 ± 7.5	30.0 ± 15.6	.544
HDL	>65 mg/dL	57.5 ± 20.8	59.1 ± 20.7	.670
HDL-2	>25.4 mg/dL	32.1 ± 14.6	34.5 ± 17.4	.191
HDL-3	>19.7 mg/dl	25.5 ± 6.8	24.6 ± 4.6	.305
HDL2%	>52%	54.5 ± 5.1	56.4 ± 7.1	.128
Lp-PLA2 activity	<225.0 nmol/min/mL	139.9 ± 29.8	131.9 ± 26.9	.268
Lp (a)	<30 mg/dL	35.6 ± 36.4	26.4 ± 28.0	.143
Triglycerides	<150 mg/dL	115.5 ± 37.4	128.2 ± 41.0	.588
Apo-A1	>124 mg/dL	158.0 ± 39.6	159.5 ± 31.6	.943
Apo B	60-117 mg/dL	94.5 ± 23.2	94.7 ± 24.6	.683
Apo B to Apo-A1	<0.60	0.62 ± 0.18	0.61 ± 0.17	.951

Table 3. (continued)

Parameter	Reference Range	Baseline Mean ± SD	Postintervention Mean ± SD	P Value
Inflammatory and Cardiovascular Markers				
Endothelin	0.0-3.7 pg/mL	1.8 ± 0.31	1.5 ± 0.23	.008 ^a
Interleukin-6	0.0-4.5 pg/mL	1.56 ± 1.2	1.5 ± 0.85	.922
Interleukin-17A	0.0-1.9 pg/mL	0.37 ± 0.19	0.31 ± 0.12	.208
Interleukin-10	0.27-2.80 pg/mL	0.56 ± 0.31	0.59 ± 0.31	.961
TNF-α	0.0-2.9 pg/mL	2.4 ± 0.74	2.2 ± 0.68	.589
Ferritin	22-287 ng/mL	138.7 ± 100.9	106.5 ± 73.0	.093
hs-CRP	0.0-0.9 mg/L	3.8 ± 3.1	2.6 ± 1.7	.276
Homocysteine	0-15 umol/L	10.5 ± 2.7	8.5 ± 1.6	.005 ^a
Cardiac troponin I	0.0-2.7 pg/mL	1.6 ± 1.2	1.2 ± 0.79	.057
NT-proBNP	<125 pg/mL	69.5 ± 50.1	63.5 ± 52.9	.321

^aDenotes statistical significance at $P \leq .05$

Abbreviations: SD, standard deviation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; TSH, thyroid stimulating hormone; LDL, low density lipoproteins; sd-LDL, small dense low density lipoproteins; HDL, high density lipoproteins; Lp-PLA2, lipoprotein-associated phospholipase A2; Lp (a), lipoprotein a; Apo-A1, apolipoprotein A-I; Apo B, apolipoprotein B; TNF-α, tumor necrosis factor alpha; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal (NT)-pro hormone brain natriuretic peptide (BNP).

Table 4. Blood Glucose and Adipone Parameters

Parameter	Reference Range	Baseline Mean ± SD	Postintervention Mean ± SD	P Value
Insulin	2.6-24.9 uU/mL	24.1 ± 16.2	13.7 ± 8.0	.057
Hemoglobin A _{1c}	4.0-5.6%	5.6 ± 0.78	5.7 ± 0.43	.735
Glucose	70-99 mg/dL	110.3 ± 25.7	106.3 ± 11.9	.193
Adiponectin	7.0-56.3 ug/mL	22.0 ± 15.9	19.4 ± 8.7	.260
Leptin	2.3-64.2 ng/mL	62.1 ± 27.4	35.0 ± 21.1	<.001 ^a
Leptin to adiponectin		0.39 ± 0.31	0.36 ± 0.17	.428

^aDenotes statistical significance at $P \leq .05$

Abbreviations: SD, standard deviation.

Glucose Metabolism and Adipokine

Glucose metabolism did not demonstrate any significant changes, although trends were noted for insulin reduction (Table 4). The reduction in adipokine leptin was statistically significant, $P < .001$, while no significant changes occurred in adiponectin.

Endotoxins

With regard to the intestinal-barrier assessment, a significant reduction occurred in zonulin, $P = .048$, and liposaccharides immunoglobulin M (IgM), $P = .009$, although the values remained within the normal range (Table 5).

Pain

Table 6 shows that the group overall noted statistically significant improvements in pain, $P = .014$, and pain interference $P = .008$. Of note, 4 participants who acknowledged pain at entry noted being pain free by the end of the intervention.

Detoxification Parameters

Table 7 shows that the majority of porphyrin markers showed no significant reductions, with some elevated markers—heptacarboxylporphyrin and total porphyrins—being reduced to within the normal range. One porphyrin, uroporphyrin, showed a significant reduction, $P = .01$,

Table 5. Assessment of the Intestinal Barrier

Parameter	Reference Range	Baseline Mean ± SD	Postintervention Mean ± SD	P Value
Zonulin	0.0 - 5.2 ng/mL	3.3 ± 1.1	2.0 ± 1.2	.048 ^a
Diamine oxidase	<33.9 - 134.5 ng/mL	62.0 ± 28.0	66.3 ± 20.6	.667
Histamine	0.0 - 2.0 ng/mL	1.0 ± 0.37	2.1 ± 1.9	.108
Diamine oxidase to histamine	1780 - 9980	72.5 ± 34.3	68.4 ± 66.3	.972
Liposaccharides IgA	0.0 - 47.3 ng/mL	23.3 ± 11.7	17.9 ± 9.4	.290
Liposaccharides IgG	5.0 - 117.9 ng/mL	74.7 ± 41.2	71.5 ± 22.9	.773
Liposaccharides IgM	1.1 - 36.1 mL	20.8 ± 13.5	10.2 ± 3.6	.009 ^a

^aDenotes statistical significance at $P \leq .05$

Abbreviations: SD, standard deviation; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M.

Table 6. Pain and Pain Interference

Parameter	Reference Range	Baseline Mean ± SD	Postintervention Mean ± SD	P Value
Brief Pain Inventory (BPI)	0 - 15	7.9 ± 7.4	3.2 ± 6.8	0.014 ^a
Pain Interference (PI)	0 - 35	9.3 ± 10.5	2.5 ± 6.2	0.008 ^a

^aDenotes statistical significance at $P \leq .05$

Abbreviations: SD, standard deviation.

Table 7. Detoxification Panels

Parameter	Reference Range	Baseline Mean ± SD	Postintervention Mean ± SD	P Value
Hepatic Detox Panel				
D-glucaric acid, phase 1	40 - 400	67.5 ± 45.0	138.5 ± 96.9	.01 ^a
Mercapturic acids, phase 2	40 - 95	68.3 ± 11.7	77.7 ± 37.0	.435
Creatinine	40 - 325	112.4 ± 53.2	97.7 ± 36.2	.778
Porphyrin Panel				
Uroporphyrins	<20.0	16.3 ± 5.9	14.6 ± 4.8	.05 ^a
Heptacarboxylporphyrins	<4.0	5.6 ± 11.5	2.3 ± 0.5	.760
Hexacarboxylporphyrins	<3.5	0.54 ± 0.27	0.58 ± 0.33	.778
Pentacarboxylporphyrins	<3.0	0.87 ± 0.41	1.0 ± 0.42	.124
Coproporphyrin 1	<24.0	23.7 ± 5.8	21.7 ± 6.0	.557
Coproporphyrin 3	<70.0	67.8 ± 10.6	62.9 ± 19.6	.536
Coproporphyrin 1 to coproporphyrin 3	<0.8	0.35 ± 0.06	0.35 ± 0.09	.611
Total Porphyrins	<110	116.3 ± 23.0	103.9 ± 27.0	.433
Precoproporphyrin 1	<2.0	1.0 ± 0.41	0.92 ± 0.29	.405
Precoproporphyrin 2	<1.2	0.83 ± 0.17	0.75 ± 0.27	.308
Precoproporphyrin 3	<1.2	0.02 ± 0.07	0.02 ± 0.08	.341
Total precoproporphyrins	<4.0	1.9 ± 0.55	1.7 ± 0.50	.271
Precoproporphyrins to uroporphyrins	<0.1	0.13 ± 0.05	0.12 ± 0.03	.942
Creatinine	30 - 225	105.0 ± 54.4	95.0 ± 36.9	.537

^aDenotes statistical significance at $P \leq .05$

Abbreviations: SD, standard deviation.

Table 8. Postintervention Survey

Parameter	Reference Range	Result Mean ± SD
Overall compliance	0 - 5	4.6 ± 0.67
Overall satisfaction	0 - 5	4.8 ± 0.45
Overall success	0 - 5	4.7 ± 0.64
Likelihood to recommend program	0 - 5	4.9 ± 0.30
Likelihood of continuing program	0 - 5	4.9 ± 0.30

Abbreviations: SD, standard deviation

with both baseline and postintervention values being in the normal range. Hepatic detoxification markers increased within the normal range for phase 1, D-glucuric acid, and phase 2, mercapturic acid, detoxification, with D-glucuric acid changes reaching statistical significance, $P = .05$.

Safety Compliance and Satisfaction

Mild adverse events of note included constipation for 2 participants, which was treated with additional hydration and as-needed fiber supplementation. Table 8 shows the results of the five-point Likert scale related to participation in the intervention.

Discussion

The current study’s intervention attempted to incorporate several emerging concepts within a therapeutic lifestyle-change program for obesity to evaluate their acceptability and potential benefit. The current 12-week intervention found that such a program was feasible, well tolerated, and able to reach significance for all primary endpoints of body composition, including body weight and fat mass. In addition, the intervention was able to modify several factors potentially associated with refractory obesity, related to endotoxemia, adipokines imbalance, and toxin load. While the current findings are encouraging, a number of important points should be reviewed.

In a multicomponent program not structured to isolate each component, it’s not possible to attribute all benefits to one factor in isolation. While detoxification may have been bolstered by use of the whole food supplement, it has also been shown to be supported by intense exercise and behavioral change.⁶⁵ While it would be attractive to attribute benefits to isolated factors, it’s important to remember that such programs are successful because of the synergy of the multiple components.

The current research team’s goal was to incorporate techniques such as a detoxification to evaluate their acceptability in standard programs to allow them to be considered in larger trials, where their singular contribution can be better evaluated. Based on these primary findings of feasibility and acceptability within

such a program, they should be considered in such a fashion.

In a pilot such as the current one, the results can often be viewed based solely on weight loss. While this was a primary endpoint of the current study, it’s important to keep in mind that the benefits of a therapeutic-lifestyle program may be linked to many factors that go beyond weight loss, such as hormonal, endotoxin, and functional change. Based on this reasoning, the current research team attempted to ascertain a number of additional factors beyond BMI to better understand potential contributory factors.

Thus, while the current research team acknowledges the importance of gauging weight changes in such a program, the incorporation of additional markers may be helpful to examine emerging factors such as leptin, zonulin, or toxin load, which could be associated. However, as these factors are emerging as indications of a successful intervention, their measurements haven’t been standardized.

The current study incorporated one available version of such indications, and results should be viewed cautiously. For example, zonulin can be tested in both serum and stool, with only conjecture being available about what testing may be optimal.⁶⁶ Similarly, toxin load can be measured in many ways, including and beyond those noted in the current trial. The current research team looks forward to additional studies to consider incorporating emerging makers to help determine their optimal use and measurement.

The weight-loss goal for the current pilot was set at 5%. Although clinical and research programs often attempt higher percentages, especially for extreme obesity, the research team chose this level based on previous findings in trials such as the IDEA trial where similar levels of weight loss translated into levels of improvement in pain and functionality of 25-30%.⁶⁷

Similarly, because weight-loss programs can suffer from high dropout rates, the current research team hoped that creating feasible weight-loss targets in the setting of a supportive group environment would improve compliance, incorporation of other healthy behaviors, and transition

into a long-term lifestyle change. While no long-term data is available for the current trial, all of the participants completed the entire program, with zero attrition.

On the five-point Likert scale, participants rated their likelihood of continuing the program at 4.9. It could be argued and hopefully noted in future larger-scale trials that the lifestyle changes incorporated with the pursuit of weight loss may of themselves have significant benefits in improving functionality and may be a parallel pursuit in conjunction with weight loss.

The current trial didn't have pain reduction as a primary endpoint. However, because obesity can often be comorbid with pain, the research team aimed to evaluate changes in pain because those have been noted in previous trials. Notably, all participants who entered the program with pain noted a reduction, with 4 participants noting being pain-free by the end of the trial. While no definitive conclusions can be based on this pilot data, it's reassuring that such a lifestyle-change program doesn't appear to worsen pain and may be significantly helpful in reducing pain using a multicomponent approach.

Toxin load and endotoxemia were targeted in the current trial based on the inclusion of a convenience sample of participants with obesity. Although improvements were noted in these areas, it would be interesting to plan future trials to prescreen participants for elevations in these areas in conjunction with obesity to further examine the benefits of such a program for targeting more overt cases of toxin load and endotoxemia.

The current trial incorporated both group and individual offerings. The current research team chose this format based on previous feedback on the benefits of a group format for its components, including group behavioral discussion and exercise. These components allowed for building a group motivational setting to strategize lifestyle change and provide support throughout the program.

Individual consultations took place throughout the program with clinical staff, including dietary, fitness, behavioral, and medical staff. This component was equally important to personalize the program in areas such as diet, supplementation, activity, and behavioral change, where personal history and findings could inform components of the program based on individual needs.

It's recommended that such consultations start prior to the program to assist with planning and targeting of strategies. For example, laboratory testing to identify and treat hypovitaminosis D has been shown to be potentially beneficial as a component of weight loss.^{68,69} Thus, both group and individual components should be considered based on the setting to help optimize compliance and results.

While the biochemical concept of detoxification has been established, mainstream use of the term is often linked to quick weight-loss regimens that may be both unhealthy and not evidence-based. One of the challenges

of recent trials has been to use a rational detoxification protocol while also promoting the foundational tenets of a therapeutic-lifestyle program.⁷⁰

In the case of the current trial, the attempt was to provide adequate nutritional, behavioral, and activity support while also providing detoxification support. Based on participants' feedback and satisfaction, this potential appears possible, and future TLC programs should further consider how detoxification can be feasibly introduced into the protocol based on what has been previously established concerning the underpinnings of refractory obesity.

Conclusions

Obesity remains a challenging clinical scenario, with emerging evidence indicating the contributory role of toxin load, hormonal imbalance, and endotoxemia. A group program for therapeutic lifestyle change, enhanced with a detoxification component, is both feasible and beneficial in promoting weight loss and may provide a promising intervention for approaching obesity that is comorbid with metabolic dysfunction and pain. Future randomized trials evaluating the components of such a program are needed to better delineate the role of specific interventions in the complex setting of obesity.

Acknowledgments

The research team wishes to acknowledge the contribution of Darlene Carrreon, MA, as well as Robin Beltran, PhD, who was instrumental in the original creation of the program. The team also wishes to acknowledge Standard Process for providing the educational materials, nutritional samples, and laboratory testing used in this pilot study.

Authors' Disclosure Statement

Robert Alan Bonakdar is a consultant to Standard Process, which had no role in the study's design; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

References

1. CDC. Overweight and Obesity. Adult Obesity Facts. doi:10.1377/hlthaff.28.5.w822
2. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of Obesity Among Adults and Youth: United States, 2015-2016. *NCHS Data Brief*. 2017.
3. Hamann A. Obesity Update 2017. *Diabetologie*. 2017. doi:10.1007/s11428-017-0241-7
4. Hurt RT, Kulisek C, Buchanan LA, McClave SA. The obesity epidemic: Challenges, health initiatives, and implications for gastroenterologists. *Gastroenterol Hepatol*. 2010.
5. Cawley J, Meyerhoefer C. The medical care costs of obesity: An instrumental variables approach. *J Health Econ*. 2012. doi:10.1016/j.jhealeco.2011.10.003
6. MacLean PS, Wing RR, Davidson T, et al. NIH working group report: Innovative research to improve maintenance of weight loss. *Obesity*. 2015. doi:10.1002/oby.20967
7. Weight of the Nation | National Institutes of Health (NIH) accessed at <https://www.nih.gov/health-information/nih-weight-nation> accessed September 29, 2020
8. Oliveros E, Somers VK, Sochor O, Goel K, Lopez-Jimenez F. The concept of normal weight obesity. *Prog Cardiovasc Dis*. 2014. doi:10.1016/j.pcad.2013.10.003
9. Bentham Science Publisher BSP. Metabolic obesity: The paradox between visceral and subcutaneous fat. *Curr Diabetes Rev*. 2012. doi:10.2174/1573399810602040367
10. Afari N, Mostoufi S, Noonan C, et al. C-reactive protein and pain sensitivity: Findings from female twins. *Ann Behav Med*. 2011. doi:10.1007/s12160-011-9297-6

11. Stone AA, Broderick JE. Obesity and pain are associated in the United States. *Obesity*. 2012. doi:10.1038/oby.2011.397
12. Bonakdar RA. Targeting systemic inflammation in patients with obesity-related pain: Obesity-related pain: time for a new approach that targets systemic inflammation. *J Fam Pract*. 2013.
13. Okifuji A, Hare BD. The association between chronic pain and obesity. *J Pain Res*. 2015. doi:10.2147/JPR.S55598
14. Di Renzo L, Cammarano A, De Lorenzo A. The misclassification of obesity affects the course of migraine. *J Headache Pain*. 2018. doi:10.1186/s10194-018-0895-6
15. Church T, Martin CK. The obesity epidemic: A consequence of reduced energy expenditure and the uncoupling of energy intake? *Obesity*. 2018. doi:10.1002/oby.22072
16. Hill JO, Wyatt HR, Peters JC. The Importance of Energy Balance. *Eur Endocrinol*. 2013;9(2):111-115. doi:10.17925/EE.2013.09.02.111.
17. Brown RE, Sharma AM, Ardern CI, Mirdamadi P, Mirdamadi P, Kuk JL. Secular differences in the association between caloric intake, macronutrient intake, and physical activity with obesity. *Obes Res Clin Pract*. 2016. doi:10.1016/j.orcp.2015.08.007
18. Williams EP, Mesidor M, Winters K, Dubbert PM, Wyatt SB. Overweight and obesity: Prevalence, consequences, and causes of a growing public health problem. *Curr Obes Rep*. 2015. doi:10.1007/s13679-015-0169-4
19. Berthoud HR, Klein S. Advances in obesity: Causes, consequences, and therapy. *Gastroenterology*. 2017. doi:10.1053/j.gastro.2017.03.045
20. Ravussin E, Ryan DH. Three new perspectives on the perfect storm: What's behind the obesity epidemic? *Obesity*. 2018. doi:10.1002/oby.22085
21. Yang C, Kong APS, Cai Z, Chung ACK. Persistent organic pollutants as risk factors for obesity and diabetes. *Curr Diab Rep*. 2017. doi:10.1007/s11892-017-0966-0
22. Davis CD. The gut microbiome and its role in obesity. *Nutr Today*. 2016. doi:10.1097/NT.0000000000000167
23. Davis RAH, Plaisance EP, Allison DB. Complementary Hypotheses on contributors to the obesity epidemic. *Obesity*. 2018. doi:10.1002/oby.22071
24. Neel BA, Sargis RM. The paradox of progress: Environmental disruption of metabolism and the diabetes epidemic. *Diabetes*. 2011. doi:10.2337/db11-0153
25. Papalou O, Kandaraki EA, Papadakis G, Diamanti-Kandarakis E. Endocrine disrupting chemicals: An occult mediator of metabolic disease. *Front Endocrinol (Lausanne)*. 2019. doi:10.3389/fendo.2019.00112
26. Grün F, Blumberg B. Environmental obesogens: Organotins and endocrine disruption via nuclear receptor signaling. *Endocrinology*. 2006. doi:10.1210/en.2005-1129
27. Heindel JJ. History of the obesogen field: Looking back to look forward. *Front Endocrinol (Lausanne)*. 2019. doi:10.3389/fendo.2019.00014
28. Heindel JJ, Vom Saal FS, Blumberg B, et al. Parma consensus statement on metabolic disruptors. *Environ Heal A Glob Access Sci Source*. 2015. doi:10.1186/s12940-015-0042-7
29. Lee YM, Kim KS, Jacobs DR, Lee DH. Persistent organic pollutants in adipose tissue should be considered in obesity research. *Obes Rev*. 2017. doi:10.1111/obr.12481
30. Hatch EE, Nelson JW, Stahlhut RW, Webster TF. Association of endocrine disruptors and obesity: Perspectives from epidemiological studies. In: *International Journal of Andrology*.;2010. doi:10.1111/j.1365-2605.2009.01035.x
31. Marraudino M, Bonaldo B, Farinetti A, Panzica GC, Ponti G, Gotti S. Metabolism disrupting chemicals and alteration of neuroendocrine circuits controlling food intake and energy metabolism. *Front Endocrinol (Lausanne)*. 2019. doi:10.3389/fendo.2018.00766
32. Fürst P. Dioxins, polychlorinated biphenyls and other organohalogen compounds in human milk. Levels, correlations, trends and exposure through breastfeeding. *Mol Nutr Food Res*. 2006. doi:10.1002/mnfr.200600008
33. Szybiak A, Rutkowska A, Wilczewska K, Wasik A, Namieśnik J, Rachoń D. Daily diet containing canned products significantly increases serum concentrations of endocrine disruptor bisphenol A in young women. *Polish Arch Intern Med*. 2017. doi:10.20452/pamw.4005
34. Uribarri J, Woodruff S, Goodman S, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. *J Am Diet Assoc*. 2010. doi:10.1016/j.jada.2010.03.018
35. Hirotsu C, Tufik S, Andersen ML. Interactions between sleep, stress, and metabolism: From physiological to pathological conditions. *Sleep Sci*. 2015. doi:10.1016/j.slsci.2015.09.002
36. Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes*. 2007. doi:10.2337/db06-1491
37. Neves AL, Coelho J, Couto L, Leite-Moreira A, Roncon-Albuquerque R. Metabolic endotoxemia: A molecular link between obesity and cardiovascular risk. *J Mol Endocrinol*. 2013. doi:10.1530/JME-13-0079
38. Boutagy NE, McMillan RP, Frisard MI, Hulver MW. Metabolic endotoxemia with obesity: Is it real and is it relevant? *Biochimie*. 2016. doi:10.1016/j.biochi.2015.06.020
39. Clemente-Postigo M, Queipo-Ortuño MI, Murri M, et al. Endotoxin increase after fat overload is related to postprandial hypertriglyceridemia in morbidly obese patients. *J Lipid Res*. 2012. doi:10.1194/jlr.P020909
40. Laugerette F, Alligier M, Bastard JP, et al. Overfeeding increases postprandial endotoxemia in men: Inflammatory outcome may depend on LPS transporters LBP and sCD14. *Mol Nutr Food Res*. 2014. doi:10.1002/mnfr.201400044
41. Clemente-Postigo M, Oliva-Olivera W, Coin-Araguez L, et al. Metabolic endotoxemia promotes adipose dysfunction and inflammation in human obesity. *Am J Physiol-Endocrinol Metab*. 2019. doi:10.1152/ajpendo.00277.2018
42. Cândido TLN, Bressan J, Alfenas R de CG. Dysbiosis and metabolic endotoxemia induced by high-fat diet. *Nutr Hosp*. 2018. doi:10.20960/nh.1792
43. Rudolph I, Chiang G, Galbán-Malagón C, et al. Persistent organic pollutants and porphyrins biomarkers in penguin faeces from Kopaatic Island and Antarctic Peninsula. *Sci Total Environ*. 2016. doi:10.1016/j.scitotenv.2016.07.091
44. Sunyer J, Alvarez-Pedrerol M, To-Figueras J, Fitó-Ribas N, Grimalt JO, Herrero C. Urinary porphyrin excretion in children is associated with exposure to organochlorine compounds. *Environ Health Perspect*. 2008. doi:10.1289/ehp.11354
45. Sunyer J, Herrero C, Ozalla D, et al. Serum organochlorines and urinary porphyrin pattern in a population highly exposed to hexachlorobenzene. *Environ Heal A Glob Access Sci Source*. 2002. doi:10.1186/1476-069X-1-1
46. Hodges RE, Minich DM. Modulation of metabolic detoxification pathways using foods and food-derived components: A scientific review with clinical application. *J Nutr Metab*. 2015. doi:10.1155/2015/760689
47. Fasano A. All disease begins in the (leaky) gut: role of zonulin-mediated gut permeability in the pathogenesis of some chronic inflammatory diseases. *F1000Res*. 2020;9:F1000 Faculty Rev-69. Published 2020 Jan 31. doi:10.12688/f1000research.20510.1.
48. Ohlsson B, Orho-Melander M, Nilsson PM. Higher levels of serum zonulin may rather be associated with increased risk of obesity and hyperlipidemia, than with gastrointestinal symptoms or disease manifestations. *Int J Mol Sci*. 2017. doi:10.3390/ijms18030582
49. Sun L, Yu Z, Ye X., et al. A marker of endotoxemia is associated with obesity and related metabolic disorders in apparently healthy Chinese. *Diabetes Care*. 2010.
50. Zhang L, Nichols RG, Correll J, et al. Persistent organic pollutants modify gut microbiota - host metabolic homeostasis in mice through aryl hydrocarbon receptor activation. *Environ Health Perspect*. 2015. doi:10.1289/ehp.1409055
51. Potera C. POPs and gut microbiota: Dietary exposure alters ratio of bacterial species. *Environ Health Perspect*. 2015. doi:10.1289/ehp.123-A187
52. Jin Y, Wu S, Zeng Z, Fu Z. Effects of environmental pollutants on gut microbiota. *Environ Pollut*. 2017. doi:10.1016/j.envpol.2016.11.045
53. Lee DH. Evidence of the possible harm of endocrine-disrupting chemicals in humans: Ongoing debates and key issues. *Endocrinol Metab*. 2018. doi:10.3803/EnM.2018.33.1.44
54. Kim JA, Kim JY, Kang SW. Effects of the dietary detoxification program on Serum γ -glutamyltransferase, Anthropometric data and metabolic biomarkers in adults. *J Lifestyle Med*. 2016. doi:10.15280/jlm.2016.6.2.49
55. Lee DH, Lee INK, Jin SH, Steffes M, Jacobs DR. Association between serum concentrations of persistent organic pollutants and insulin resistance among nondiabetic adults: Results from the National Health and Nutrition Examination Survey 1999-2002. *Diabetes Care*. 2007. doi:10.2337/dc06-2190
56. Cani PD, Neyrinck AM, Fava F, et al. Selective increases of bifidobacteria in gut microflora improve high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxemia. *Diabetologia*. 2007. doi:10.1007/s00125-007-0791-0
57. Cani PD, Bibiloni R, Knauf C, Neyrinck AM, Delzenne NM. Changes in gut microbiota control metabolic diet-induced obesity and diabetes in mice. *Diabetes*. 2008. doi:10.2337/db07-1403.Additional
58. Ferguson JE, Mulvey CK, Patel PN, et al. Omega-3 PUFA supplementation and the response to evoked endotoxemia in healthy volunteers. *Mol Nutr Food Res*. 2014. doi:10.1002/mnfr.201300368
59. Xu JH, Liu XZ, Pan W, Zou DJ. Berberine protects against diet-induced obesity through regulating metabolic endotoxemia and gut hormone levels. *Mol Med Rep*. 2017. doi:10.3892/mmr.2017.6321
60. Sung J, Ho CT, Wang Y. Preventive mechanism of bioactive dietary foods on obesity-related inflammation and diseases. *Food Funct*. 2018. doi:10.1039/c8fo01561a
61. Lira FS, Rosa JC, Pimentel GD, et al. Long-term interdisciplinary therapy reduces endotoxin level and insulin resistance in obese adolescents. *Nutr J*. 2012. doi:10.1186/1475-2891-11-74
62. Phillips MD, Flynn MG, McFarlin BK, Stewart LK, Timmerman KL. Resistance training at eight-repetition maximum reduces the inflammatory milieu in elderly women. *Med Sci Sports Exerc*. 2010. doi:10.1249/MSS.0b013e3181b11ab7
63. Mori C, Todaka E. For a healthier future: A virtuous cycle for reducing exposure to persistent organic pollutants. *J Epidemiol Community Health*. 2017. doi:10.1136/jech-2016-208088

64. Cleeland CS. 1991 BPI User Guide accessed at https://www.mdanderson.org/documents/Departments-and-Divisions/Symptom-Research/BPI_UserGuide.pdf on October 2, 2020.
65. Leeds AR. Formula food-reducing diets: A new evidence-based addition to the weight management tool box. *Nutr Bull*. 2014. doi:10.1111/nbu.12098
66. Ajamian M, Steer D, Rosella G, Gibson PR. Serum zonulin as a marker of intestinal mucosal barrier function: May not be what it seems. *PLoS One*. 2019. doi:10.1371/journal.pone.0210728
67. Messier SP, Mihalko SL, Legault C, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: The IDEA randomized clinical trial. *JAMA - J Am Med Assoc*. 2013. doi:10.1001/jama.2013.277669
68. Salehpour A, Hosseinpanah F, Shidfar F, et al. A 12-week double-blind randomized clinical trial of vitamin D3 supplementation on body fat mass in healthy overweight and obese women. *Nutr J*. 2012. doi:10.1186/1475-2891-11-78
69. Migliaccio S, Di Nisio A, Mele C, Scappaticcio L, Savastano S, Colao A. Obesity and hypovitaminosis D: causality or casualty? *Int J Obes Suppl*. 2019. doi:10.1038/s41367-019-0010-8
70. Jung S-J, Kim W-L, Park B-H, Lee S-O, Chae S-W. Effect of toxic trace element detoxification, body fat reduction following four-week intake of the Wellnessup diet: a three-arm, randomized clinical trial. *Nutr Metab (Lond)*. 2020. doi:10.1186/s12986-020-00465-9