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Searching for Evidence of an Anti-Inflammatory Diet in Children: A Systematic Review of Randomized Controlled Trials for Pediatric Obesity Interventions With a Focus on Leptin, Ghrelin, and Adiponectin

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Abstract

Problem: To address the complex phenomenon of pediatric obesity, one must understand the physiological mechanisms regulating energy intake and inflammation. The peptide hormones leptin, ghrelin, and adiponectin are involved in both, but their functions are dysregulated in obesity. The purpose of this systematic review is (1) to characterize studies of nutrition interventions for weight management in children who measure these peptides as outcomes, (2) to assess risk of bias in the studies, and (3) to determine the relationships between these peptides and body mass index (BMI). **Eligibility Criteria:** Peer-reviewed articles written in English, published in 2001–2016, and describing randomized controlled trials of pediatric interventions involving a nutrition component with the outcome measures leptin, ghrelin, and/or adiponectin were included. Articles were excluded if the intervention involved pharmaceuticals, supplements, infant formula, breastfeeding, or surgery. **Sample:** The 25 international studies represented 2,153 obese children. **Results:** Ten diets were identified. Successful interventions included both structured exercise and hypocaloric dietary components, with or without counseling, resistance training, or medical components. Direct measures of adiposity were used in 69% of studies. Comparison group designs were disparate. Leptin levels decreased as BMI decreased. Evidence regarding the relationships of ghrelin and adiponectin with BMI was inconclusive. **Conclusions:** Despite known effects of maturation on hormones, studies did not consistently differentiate findings by maturational stage. Common anti-inflammatory and disease risk modification diets were missing or underrepresented. Studies that include children with comorbidities are needed. BMI and leptin levels have a positive relationship, but evidence on ghrelin and adiponectin was inconclusive.

Keywords

pediatric obesity, dietary interventions, leptin, ghrelin, adiponectin, inflammation

Pediatric obesity is a complex health problem with great costs for both the individual and the society. According to the World Health Organization (WHO, 2012), 65% of the world's population lives in a country where overweight and obesity cause more deaths than underweight, and over 170 million children under age 18 are overweight. Pediatric obesity is most common in middle- to high-income countries, but it is increasing in low-income countries as well.

The consequences of obesity, such as chronic disease and increased mortality, are well-documented (Calder, Albers, & Antoine, 2009; Expert Panel on Integrated Guidelines, 2011). Obesity is related to chronic inflammation in the body, which is a key pathophysiological process in the development of diseases such as heart disease and diabetes (Mraz & Haluzik, 2014; Vieira, Sadie-Van Gijsen, & Ferris, 2016). Both inflammation and excess weight can exacerbate existing chronic conditions such as cardiovascular disease and juvenile arthritis (Coulson, Ng, Goff, & Foster, 2013). During childhood and adolescence, the critical developmental period of identity formation, obesity can also affect quality of life and complicate peer relationships (Tsiros et al., 2009).

To address the complex phenomenon of pediatric obesity adequately, one must acquire an understanding of the physiological mechanisms that regulate energy intake and inflammation in children. Three physiological components studied most often with regard to obesity are leptin, ghrelin, and adiponectin,

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which belong to a larger group of appetite-regulating hormones also referred to as gut peptides or obesity-related hormones (Scarpellini, 2012).

Leptin, produced in the adipose tissue, signals the brain to decrease food intake when fat stores are adequate (Iikuni, Lam, Lu, Matarese, & La Cava, 2008). Yet this normal function of leptin seems to be ineffective in obesity, resulting in elevated leptin levels, called leptin resistance, which contribute to the persistent low-grade inflammation implicated in chronic disease.

Ghrelin opposes the actions of leptin. Produced in the stomach, ghrelin signals the brain to increase food intake and adiposity (Bataar, Patel, & Taub, 2011). But as is the case with leptin, ghrelin's mechanism of action is likewise impaired in obese people, in whom ghrelin levels decrease in response to prolonged elevation in leptin (Klok, Jakobsdottir, & Drent, 2007). Ghrelin plays an attenuating role in inflammatory disease states (e.g., in cardiovascular disease and arthritis), and research has shown it to be related to the alleviation of pain caused by inflammation (Baatar, Patel, & Taub, 2011). It remains unclear how nutritional status and the severity or progression of chronic diseases and accompanying inflammation are related to serum or plasma ghrelin levels, particularly in the pediatric population.

Adiponectin, produced by the adipose tissue, is another gastrointestinal signaling hormone. It is both cardioprotective and anti-inflammatory (Ouchi et al., 2001). Hotta et al. (2001) found that a decline in circulating levels of adiponectin coincides with the onset of diabetes in rhesus monkeys. Researchers have also found low levels of adiponectin in adults and children with obesity, diabetes, and cardiovascular disease (Pyrzak, Ruminska, Popko, & Demkow, 2010).

Many types of interventions reduce inflammation in children, including medications, exercise, and diet. Dietary interventions are a logical starting point because obesity hormones regulate food intake and metabolism. Reducing obesity through dietary interventions affects the levels of obesity hormone levels, which subsequently reduces inflammation. Although scientists have explored the physiological properties of leptin, ghrelin, and adiponectin, there is more to learn about these hormones in the context of weight management dietary interventions in children. So far, reviews have been limited in scope, typically focusing on individual peptide hormones, and have not looked at all three combined for a more comprehensive view of their roles in the context of weight loss interventions for children.

The present review is a contribution toward a broader search for evidence of an anti-inflammatory diet in children. Aguilar, Gonzalez-Jimenez, Antelo, and Perona (2012) concluded in their study on inflammatory markers and insulin resistance in adolescents that nurses should have an adequate understanding of the inflammatory process in order to provide adequate care. Further, the National Institute of Nursing Research at the National Institutes of Health considers the integration of biological research into nursing science to be a priority for advancing the field (Rudy & Grady, 2005). The research questions for the present review are as follows: What are the characteristics of randomized controlled trials that have implemented a nutrition-based intervention for weight management and also measure the selected obesity hormones in the pediatric population? And, what is the relationship between each of the three hormones and body mass index (BMI) in the context of pediatric weight management interventions? Accordingly, the purpose of this systematic review is (1) to characterize studies of nutrition interventions for weight management in children that measure leptin, ghrelin, and/or adiponectin as outcomes; (2) to assess risk of bias in the studies to aid in the analysis of findings; and (3) to determine the relationships between each of these three gut peptides and BMI.

Method

We systematically searched six online databases (PubMed, CINHAL, Web of Science, JSTOR, PsychINFO, and the Cochrane Library) for articles published from 2000 through February 2016, using combinations of the search terms *leptin, ghrelin, adiponectin, obesity, BMI, gastrointestinal peptides* or *hormones, obesity hormones, appetite peptides* or *hormones*, *nutrition intervention, dietary intervention, diet, weight management, and weight loss*. We chose these search dates because the WHO released a report in 2000 declaring obesity to be a global epidemic (WHO, 2000). Peer reviewers critiqued the systematic review protocol prior to our conduct of the search. The authors mutually agreed on decisions about inclusion/exclusion criteria and data extraction, or we consulted with a third-party expert. Figure 1 provides an outline of the search strategy. To identify missing information, we contacted study authors when applicable.

Articles we included in this review were peer-reviewed presentations in English of randomized controlled trials of weight management or weight loss interventions that included measurement of BMI plus at least one of the three target peptides (leptin, ghrelin, or adiponectin) as outcomes in children or adolescents 2–18 years old. Because of the emerging nature of this topic, we applied a broad age range to fully capture the literature. The interventions had a nutrition or dietary component with or without additional components such as exercise, psychological counseling, and/or medical treatment. We excluded studies if the intervention involved supplements, pharmaceutical products, infant formulas, breastfeeding, or weight loss surgery.

The measurement of obesity in children is complex. Obesity is characterized by excess adiposity, which is approximated in a variety of ways: skinfold thickness, bioelectrical impedance, densitometry, dual-energy x-ray absorptiometry, or BMI (Centers for Disease Control [CDC], 2015; Whitlock, Williams, Gold, Smith, & Shipman, 2005). BMI is a less direct measure of adiposity than the others. However, the more direct measures are inconsistently included in existing pediatric obesity research. The CDC (2015) considers BMI to be an acceptable alternative to direct measures of body fat. Although the CDC

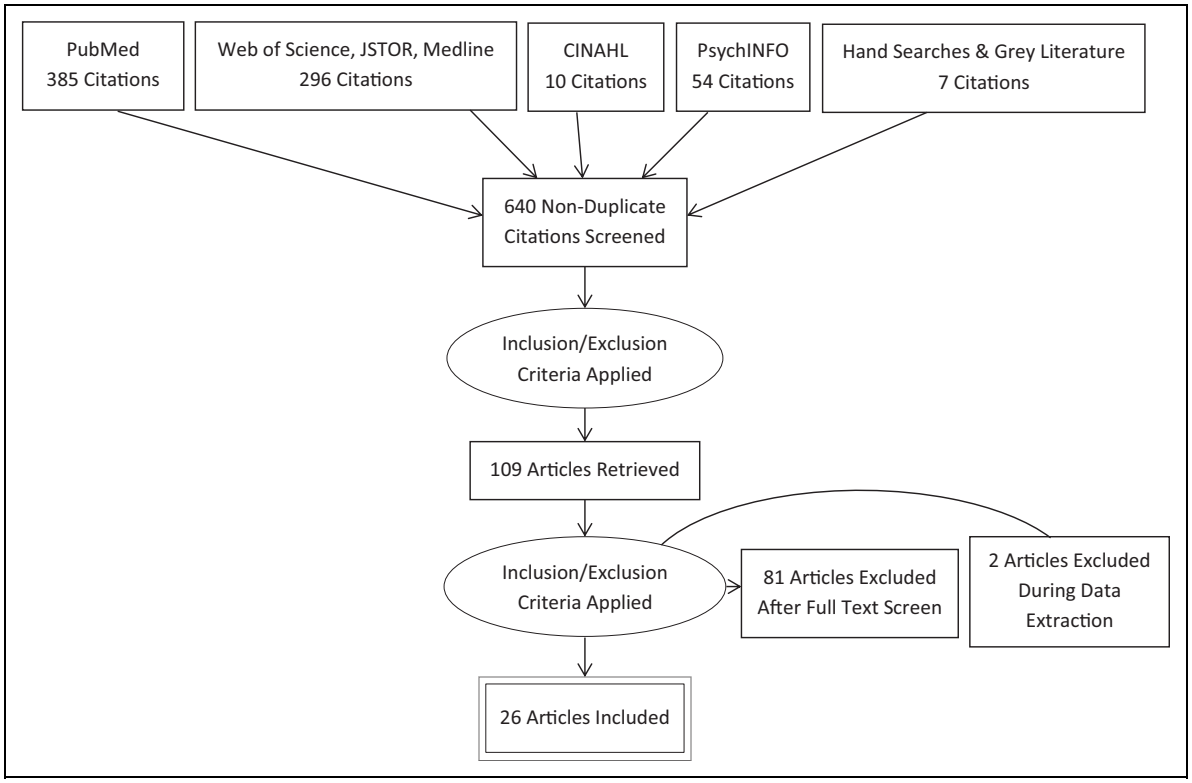

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the literature search process.

recommends that researchers use BMI percentiles to compare children based on age and sex, these measures are also inconsistently used in this population. As a result, we used BMI as the outcome measure of choice for the purpose of this study because it is the outcome that researchers most consistently measure and the one most likely to be used in the clinical setting. We will also discuss the findings related to other measures of adiposity used in the studies.

In our analysis, we grouped the interventions by target, design, setting, duration, type of dietary intervention, type of peptide hormone measured, and pubertal status. Dietary intervention categories were based on authors' definitions of their interventions. We noted in our analysis whether or not the study recruited samples and/or differentiated findings based on pubertal status. The most common method of characterizing pubertal status is the Tanner method, which defines physical maturation in five stages (Tanner, Whitehouse, & Takaishi, 1966). As a result, we used the Tanner method terminology in this analysis. We defined successful studies as those with a statistically significant ($p < .05$) decrease in BMI between pre- and postintervention measures or significant between-group differences, depending on the purpose of the study. We evaluated studies to determine whether the hypothesis was to achieve no difference between groups or a statistically significant difference between groups. We evaluated the studies' risk of bias based on reported attrition, sample size, recruitment strategy, blinding, and the limitations stated by the authors of each study.

Results

Table 1 summarizes the general characteristics of the included studies, while Table 2 delves into the details of each study. Table 3 presents the studies' findings, including the interventions' effects on BMI. We numbered the articles in the tables and, for brevity's sake, used these numbers to cite individual studies throughout the remainder of this review. The 26 articles we found in our search represented 25 studies because 2 articles reported on the same study. The articles were published from 2003 to 2015, with a majority (16/26, 61.5%) published recently, from 2012 to 2015. A majority of the total sample of participants was from Middle Eastern and Mediterranean countries, followed by the United States, Mexico, and South America. Other studies were conducted in Europe, East Asia, and Australia.

Although prior research has shown that the appetite hormones vary with maturational stage, investigators in a majority of the studies did not measure, report, or differentiate their findings in terms of participants' developmental stages. The seven studies in which researchers did not measure or report pubertal stages account for the largest proportion of the total sample (32%), followed by 30% of participants in studies with mixed samples (multiple Tanner stages), 22% in studies including only prepubertal subjects, and 16% in studies looking only at postpubertal subjects.

The studies examined a total of 10 diets. The hypocaloric diets were low carbohydrate, low fat, and balanced. The normocaloric diets were high-protein breakfast, low carbohydrate,

Table 1. General Characteristics of the Combined Sample Across All Reviewed Articles.

Characteristic	Description
Participants, *N*	Randomized = 2,153, final sample = 1,705 (20.8% attrition rate)
Sample size	
Range	21–221 per study
Mean and median	Mean = 84, median = 73
Intervention delivery settings	Community, school, university, clinic, obesity center, hospital
Ages of participants, range (years)	3–19
Age-groups of samples (WHO, 2012), % of studies	
Adolescents (10–19 years)	60
Children (2–9 years)	12
Mixed (2–19 years)	28
Duration of intervention, % of studies	
<6 months	60
6 to <12 months	24
≥ 12 months	16

Note. $N = 26$, representing 25 studies. WHO = World Health Organization.

ketogenic, dietary approaches to stop hypertension (DASH) diet, whole grains, lifestyle education/balanced, and the Institute of Medicine's Dietary Reference Index for sedentary individuals by age-balanced diet. All of the studies involving hypocaloric diets achieved significant reductions in BMI ($p < .05$), while only 8 of the 14 studies with normocaloric diets achieved significant reductions in BMI. We performed a χ^2 test of independence to examine the relationship between the category of diet (normocaloric vs. hypocaloric) and change in BMI and found it to be significant, $\chi^2(1, N = 25) = 6.203$, $p < .05$. Interventions with hypocaloric diets were more likely to result in a reduction in BMI than interventions with normocaloric diets. Notably, some studies achieved significant improvement in the obesity hormone levels in response to the normocaloric diets without a corresponding reduction in BMI, which we detail below in the discussion of individual hormone results.

Experimental Comparison Groups

Among the 25 studies described in the 26 articles we reviewed, designs of the intervention groups versus the comparison groups varied. To strengthen the analysis, we categorized studies by comparison group. In seven studies, researchers compared one type of nutrition intervention versus another, with or without a nondiet intervention control group (Galhardo et al., 2012; Hajihashemi, Azadbakht, Hashemipour, Kelishadi, & Esmailzadeh 2014; Ibarra-Reynoso et al., 2015; Jensen et al., 2014; Partsalaki, Karvela, & Spiliotis, 2012; Saneei, Hashemipour, Kelishadi, & Esmaillzadeh 2014; Wang, Yang, Lu, & Mu 2015). These studies were less likely than the others to result in significant intervention versus control group differences in BMI (2/7 studies found group differences), indicating that the control group's dietary modification was similar to the intervention group's dietary modification (Jensen et al., 2014; Wang et al., 2015). For example, the low-carbohydrate, low-fat, and ketogenic diets were equally effective in yielding significant pre-/postintervention reductions in BMI and leptin, and results did not vary by dietary content (Ibarra-Reynoso et al., 2015; Jensen et al., 2014; Partsalaki et al., 2012). The normocaloric diets (whole grain, DASH, and high-protein breakfast) did not result in a significant change in BMI from baseline, though the whole-grain diet resulted in a significant reduction in leptin after intervention (Hajihashemi et al., 2014; Saneei et al., 2014; Wang et al., 2015).

In three studies, investigators compared a mixed intervention with a nonintervention control group, such as a wait-list control or measured-twice-without-intervention control (Nunes et al., 2015; Park, Hong, Lee, & Kang 2007; Rosenbaum et al., 2007). These studies achieved a significant intervention effect on BMI, indicating that use of a nonintervention control group may have generated the greatest contrast in findings between groups. Adiponectin increased in the intervention groups and decreased in the control groups, although the changes were statistically significant in only one of the three studies (Nunes et al., 2015). Notably, the interventions included an exercise component, and findings are consistent with previous studies in which adiponectin increased in response to an exercise intervention.

In six studies, researchers compared a mixed intervention with usual care (defined as medical treatment only, in-clinic referrals to a dietitian, or usual dietary advice typically provided in the clinic; Abd El-Kader, Al-Jiffri, & Ashmawy 2013; Balagopal, George, Yarandi, Funanage, & Bayne, 2005; Balagopal et al., 2010; Bocca, Corpeleijn, Stolk, Wolffenbuttel, & Sauer, 2014; Chae et al., 2010; McFarlin et al., 2013; Nemet, Oren, Pantanowitz, & Eliakim 2013). In two thirds of these studies, the mixed intervention was significantly more effective than usual care in reducing BMI (Abd El-Kader et al., 2013; Balagopal et al., 2005; Balagopal et al., 2010; Chae et al., 2010; McFarlin et al., 2013). However, only two of the six studies found significant reductions in leptin in the mixed intervention groups (Abd El-Kader et al., 2013; Balagopal et al., 2005; Balagopal et al., 2010). The adiponectin levels increased

Table 2. Characteristics of Research Studies (Published January 2000–2016) Testing Dietary Interventions in Children With BMI and Leptin, Ghrelin, and/or Adiponectin as Outcomes.

Article	Purpose	Setting	Sample Description	Intervention
1. Abd El-Kader, Al-Jiffri, and Ashmawy (2013)	Determine effects of weight loss on markers of systemic inflammation	Saudi Arabia; pediatric unit of a hospital	$N = 80$ obese adolescents (42 boys; aged 12–18 years) with asthma; pubertal status not measured/undifferentiated	Mixed: low-calorie diet (15% protein, 30–35% fat, 50–55% carbohydrate, 250 kcal deficit) + exercise + medical therapy vs. medical therapy alone; duration = 8 weeks
2. Ackel-D'Elia et al. (2014)	Compare outcomes of body composition, leptin, and insulin resistance between varying levels of PA + nutrition and counseling vs. a nutrition + counseling intervention alone	Sao Paolo, Brazil; recruited from the community	$N = 132$ obese adolescents; 72 included in final analysis (50 girls, 22 boys; aged 15–19 years); postpubertal (Tanner Stage 5)	Mixed: PA (aerobic and resistance training, aerobic only, or leisure activity) + psychological therapy + clinical therapy (endocrinologist) + individualized reduced calorie diet based on Institute of Medicine levels for sedentary adolescents plus weekly education sessions; duration = 6 months
3. Balagopal, George, Yarandi, Funanage, and Bayne (2005). 4. Balagopal et al. (2010)	Obesity-related alterations and effect of an intervention on satiety factors	Jacksonville, FL; research center of children's hospital	$N = 21$ adolescents aged 14–18 years (15 obese and 6 lean); postpubertal (Tanner Stage 4 or 5)	Mixed: PA plus calorie-reduction intervention with in-clinic monitoring vs. education only without inpatient monitoring. Lean controls for baseline comparison only; duration = 3 months
5. Barbeau et al. (2003)	Compare effects of three treatments (LSE, LSE and moderate PA, or LSE and high-intensity PA) on leptin in obese adolescents	Georgia, recruited from community	$N = 75$ obese adolescents aged 12–16 years (54 female; 23 Caucasian, 51 Black, 1 Hispanic), only 55 who completed intervention were included in the final analysis; pubertal status not measured/undifferentiated	Mixed: LSE (nonspecific nutrition and behavior modification) as control, LSE and moderate PA, or LSE and high-intensity PA; duration = 8 months
6. Bocca, Corpeleijn, Stolk, Wolffenbuttel, and Sauer (2014)	Determine effects of an intervention to reduce BMI on inflammatory parameters and adipokines	Holland; outpatient pediatric obesity center	$N = 75$ overweight or obese children aged 3–5 years (13 lost to follow-up); prepubertal	Mixed: multidisciplinary intervention with 6 personalized sessions with a dietitian on LSE, normocaloric diet, feedback on food diaries, PA sessions, and parent counseling vs. usual care; duration = 16 weeks
7. Chae et al. (2010)	Investigate the effect of a structured exercise program on body weight, body composition, and inflammatory markers	Seoul, Korea; pediatric obesity clinic	$N = 38$ obese children aged 9–15 years (21 boys); pubertal status not measured/undifferentiated	Mixed: normocaloric diet with exercise and lifestyle counseling vs. usual care with conventional counseling in outpatient clinic; duration = 12 weeks
8. Damaso et al. (2014)	Determine whether AT + RT is more effective than AT at reducing inflammatory markers and cardiovascular risk	Sao Paolo, Brazil; recruited from community	$N = 139$ obese adolescents aged 15–19 years (82 girls), 116 completed 1 year; postpubertal (Tanner Stage 5)	Mixed: AT + RT vs. AT alone. Both also had clinical, nutritional, and psychological therapies; low-calorie diet set at DRI for sedentary individuals; duration = 1 year
9. De Piano et al. (2012)	To compare the effects of AT with those of AT + RT on adipokines	Sao Paolo, Brazil; original sample recruited from community	$N = 58$ obese adolescents with or without NAFLD (27 boys) aged 15–19 years; AT group = 15 patients without NAFLD, 14 with NAFLD; AT + RT group = 15 patients without NAFLD, 14 with NAFLD; postpubertal (Tanner Stage 5)	Mixed: nutrition, physical activity, and psychological interventions; low-calorie DRI based on sedentary individuals and food pyramid; duration = 1 year

(continued)

Table 2. (continued)

Article	Purpose	Setting	Sample Description	Intervention
10. Elloumi et al. (2009)	Investigate the effects of a weight loss program on plasma levels of adiponectin and leptin	Tunisia; two schools in central region	$N = 21$ obese adolescent boys aged 12–14 years; prepubertal, pubertal, and postpubertal (Tanner Stages 1–4)	Mixed: energy restriction, personalized exercise, or energy restriction + exercise; duration = 2 months
11. Galhardo et al. (2012)	To determine the clinical effectiveness of a device to retrain eating behavior (Mandometer)	United Kingdom; Bristol Children's Hospital	$N = 27$ obese children aged 9–18 years; prepubertal ($n = 11$), pubertal ($n = 12$), and postpubertal ($n = 5$)[a]	Use of a device to slow down eating speed versus LSE alone; duration = 12 months
12. Hajihashemi, Azadbakht, Hashemipour, Kelishadi, and Esmailzadeh (2014)	Determine the effect of whole grains on serum levels of inflammatory biomarkers	Iran; recruited via private clinic or referred by pediatrician	$N = 44$ overweight or obese girls aged 8–15 years; pubertal status not measured/ undifferentiated	Replace half of grain servings per day with whole grains; duration = 6-week intervention, crossover design with 4-week washout period between the groups
13. Hasson et al. (2012)	Examine ethnic differences in metabolic responses to intervention	Los Angeles, CA	$N = 168$ screened and consented, $n = 100$ obese adolescents (48 African American, 52 Latino) aged 14–18 years completed intervention; mixed Tanner Stages 1–5	Mixed: control, nutrition only, or nutrition + strength training; nutrition focused on decreased sugar and increased fiber; duration = 16 weeks
14. Ibarra-Reynoso et al. (2015)	Determine the effects of carbohydrate vs. fat restriction on appetite regulation and leptin	Leon City, Mexico; recruited from grammar schools	$N = 120$ obese children aged 6–12 years; mixed Tanner stages	Low-carb versus low-fat diet; duration = 2 months
15. Jensen et al. (2014)	Determine the effect of dietary interventions on satiety hormones	Queensland, Australia; recruited from community	$N = 74$ obese participants age 10–17 years of age; prepubertal, pubertal, and postpubertal; 87% commenced puberty with Tanner score >2.	Reduced carb, low-fat or wait-listed control; duration: 12 weeks
16. Kelishadi, Hashemipour, Mohammadifard, Alikhassy, and Adeli (2008)	Compare short- and long-term change in ghrelin concentration after increasing energy expenditure vs. after decreasing intake; determine factors associated with relationship between change in ghrelin and metabolic syndrome	Iran; pediatric obesity clinic	$N = 100$ obese children aged 7–9 years; $n = 92$ completed 6-month intervention and 87 returned for 1-year follow-up; prepubertal (Tanner Stage 1)	Balanced diet plus monthly nutrition counseling intervention vs. exercise therapy; duration = 6 months
17. McFarlin et al. (2013)	Biologically validate an established school-based intervention designed to reduce standardized BMI	Houston, TX; urban charter school	$N = 221$ Mexican-American children, overweight, at risk for overweight, or obese, aged 12–14 years; pubertal status measured but not reported	Mixed: exercise + nutrition counseling for 6 months vs. self-help control group; nutrition focused on lifestyle modifications; duration = 6-month intervention, follow-up at 12 months
18. Nemet, Oren, Pantanowitz, and Eliakim (2013)	Examine the effects of a multidisciplinary intervention on BMI, PA patterns and fitness, inflammatory cytokines, and adiponectin	Israel; pediatric obesity clinic	$N = 42$ obese subjects aged 6–13 years; pre- and early pubertal (Tanner Stages 1 & 2)	Mixed: exercise + dietitian meetings with lifestyle modifications and nutrition education as well as a hypocaloric diet of 1,200–2,000 kcal (30% decrease from reported intake); duration = 3 months
19. Nunes et al. (2015)	Evaluate effect of interdisciplinary therapy on anti-inflammatory responses	Uberlandia, Brazil; conducted through university	$N = 57$ obese participants aged 14–17 years; postpubertal (Tanner Stage 5)	Mixed: exercise + weekly nutrition education sessions and hypocaloric diet; duration = 6-month intervention

(continued)

Table 2. (continued)

Article	Purpose	Setting	Sample Description	Intervention
20. Park, Hong, Lee, and Kang (2007)	Investigate effects of a 12-week lifestyle + exercise intervention on adiponectin and metabolic syndrome markers	Korea; recruited from middle school	$N = 44$ obese Korean adolescents aged 13–15 years; control group mean Tanner Stage 3.7 $\pm$ 0.6, intervention group mean Tanner Stage 3.8 $\pm$ 0.7	Mixed: lifestyle + exercise intervention group vs. no-intervention control; duration = 12 weeks
21. Partsalaki, Karvela, and Spiliotis (2012)	Compare efficacy and metabolic impact of ketogenic and hypocaloric diets	Greece; recruited from a pediatric endocrinology clinic	$N = 58$ obese children and adolescents aged 8–18 years; prepubertal, pubertal, and postpubertal (Tanner Stages 1–5)	Ketogenic diet vs. hypocaloric diet; duration = 6 months
22. Pedrosa et al. (2011)	Evaluate effect of a lifestyle intervention program (nutrition and exercise counseling) on metabolic syndrome components, adipokines, and ghrelin	Portugal; recruited from a pediatric endocrinology clinic	$N = 61$ overweight children aged 7–9 years; pre- & early pubertal (Tanner Stages 1 and 2) at baseline in obese children, prepubertal only (Tanner Stage 1) in normal weight controls	Mixed: exercise + nutrition, individual or group interventions; normocaloric, lifestyle interventions; duration = 1 year
23. Rosenbaum et al. (2007)	Examine effects of an intervention consisting of health, nutrition, and exercise classes plus an aerobic exercise program on diabetes risk	New York, NY; recruited from a public school	$N = 73$ predominantly Hispanic adolescents aged 13–14 years; pubertal status not measured/undifferentiated	Mixed: health, nutrition, exercise classes focused on LSE; duration = 3–4 months
24. Saneei, Hashemipour, Kelishadi, and Esmaillzadeh (2014)	Examine the effects of the DASH diet on markers of systemic inflammation	Iran; recruited from clinic or referred by pediatrician	$N = 60$ girls with metabolic syndrome aged 11–18 years; postpubertal (menstrual cycle for at least 6 months)	DASH diet vs. usual dietary advice was the Healthy Eating Plate; duration = 6 weeks for each arm, plus 4-week washout between and 2-week washout prior to study start
25. Shalitin et al. (2009)	Determine short- and long-term effects of intervention programs on body weight and cardiometabolic risk	Israel; recruited from a pediatric obesity center	$N = 162$ obese children aged 6–11 years; prepubertal (Tanner Stage 1)	Mixed: exercise, diet (balanced hypocaloric diet with dietitian meetings), and diet + exercise groups; duration = 12-week intervention plus 9-month follow-up period
26. Wang, Yang, Lu, and Mu (2015)	Determine impact of a high-protein breakfast on weight loss and appetite hormones	Beijing, China	$N = 156$ obese Chinese adolescents aged 13–16 years; pubertal status measured but not reported; no difference between groups at baseline	High-protein breakfast (boiled egg, $n = 81$) vs. high-carb breakfast (steamed bread, $n = 75$); duration = 3 months

Note. AT = aerobic training; BMI = body mass index; DASH = dietary approaches to stop hypertension; DRI = dietary reference index; LSE = lifestyle education; NAFLD = nonalcoholic fatty liver disease; PA = physical activity; RT = resistance training.

[a]The original article lists one extra participant when the sample is categorized by pubertal status.

Table 3. Summary of the Findings of Research Studies on Dietary Interventions in Children Pertaining to Effects on Leptin, Ghrelin, Adiponectin, and Body Mass Index (BMI).

	Findings				
Article	Leptin (ng/ml)	Ghrelin (pg/ml)	Adiponectin (μg/ml)	BMI (kg/m^2)	Conclusions
1. Abd El-Kader, Al-Jiffri, and Ashmawy (2013)	Training group ($n = 40$): pre = 31.43 ± 5.47, post = 26.98 ± 4.50, Δ = −4.45 (−14.1%; $p < .05$). Control group ($n = 40$): pre = 30.53 ± 5.22, post = 31.02 ± 4.84, Δ = +0.49 (+1.6%; $p > .05$)	N/A	Training group: pre = 10.61 ± 3.45, post = 14.72 ± 3.21, Δ = +4.11 (+38.7%; $p < .05$). Control group: pre = 11.20 ± 3.17, post = 10.76 ± 2.85, Δ = −0.44 (−3.9%; $p > .05$)	Training group: pre = 32.31 ± 2.46, post = 27.15 ± 2.38, Δ = −5.16 (−15.9%; $p < .05$). Control group: pre = 31.73 ± 2.12, post = 32.14 ± 2.16, Δ = +0.41 (+1.2%; $p > .05$)	Changes in training group differed significantly from changes in control group ($p < .05$); weight loss decreased markers of inflammation and increased adiponectin
2. Ackel-D'Elia et al. (2014)	Aerobic/resistance ($n = 24$): pre = 38.15 ± 16.08, post = 24.81 ± 14.69, Δ = −13.34 ± 10.76 ($p < .05$). Aerobic only ($n = 24$): pre = 25.28 ± 19.47, post = 16.66 ± 18.01, Δ = −8.62 ± 15.38 ($p < .05$). Leisure ($n = 24$): pre = 46.09 ± 19.07, post = 48.55 ± 22.29, Δ = +2.46 ± 11.00 (not significant)	N/A	N/A	Aerobic/resistance: pre = 35.10 ± 4.67, post = 31.82 ± 3.90, Δ = −3.28 ± 1.56 ($p < .05$). Aerobic only: pre = 35.06 ± 3.90, post = 33.22 ± 3.70, Δ = −1.85 ± 1.60 ($p < .05$). Leisure: pre = 34.57 ± 3.84, post = 34.33 ± 4.2, Δ = −0.24 ± 0.98 (not significant)	The largest decrease in leptin levels was seen in the group with the largest decrease in BMI. Changes in leptin and BMI levels were not significantly different from baseline in nutrition + leisure group, although the change in BMI z-score was significantly decreased in this group
3. Balagopal, George, Yarandi, Funanage, and Bayne (2005).	Intervention ($n = 8$): pre = 22.1 ± 2.9, post = 15.6 ± 2.0, Δ = −6.5 ($p = .001$).	Intervention: pre = 306 ± 19, post = 274 ± 31, Δ = −32 ($p = .20$).	Intervention: pre = 4.44 ± 0.47 to post = 5.95 ± 0.49 mg/L, Δ = +1.51 ($p = .0002$).	Intervention: pre = 38.1 ± 2.09, post = 37.5 ± 3.1, Δ = −0.6 ($p = .13$).	BMI and leptin levels were higher and ghrelin levels were lower in obese group at baseline than in lean controls ($p < .001$).
4. Balagopal et al. (2010).	Control ($n = 7$): no significant change from baseline per authors, actual values not reported	Control: no significant change, values not reported	Control: pre = 4.61 ± 0.67 to post = 4.11 ± 0.69 mg/L, Δ = −0.5 ($p = .07$)	Control: pre = 41.2 ± 4.2, post values not reported; no significant change from baseline per authors	Intervention led to no change in ghrelin and reduced leptin from baseline. Significant reduction in BMI in intervention group compared to obese control group ($p < .05$)
5. Barbeau et al. (2003)	LSE ($n = 16$): Δ = +6.7 ± 20.0. LSE + moderate-intensity PA ($n = 20$): Δ = +6.6 ± 16.6. LSE + high-intensity PA ($n = 19$): Δ = +1.1 ± 24.2.	N/A	N/A	BMI measured but values not reported	Leptin levels at baseline were correlated with body fat mass. No difference in leptin or body fat among the groups after an 8-month intervention. Small sample sizes may be contributing to lack of significance. Separated Blacks from Whites in analysis of data. Percentage of body fat was not significantly different among the groups, but percentage of body fat decreased significantly in all PA groups combined when compared to LSE ($p \leq .001$)
6. Bocca, Corpeleijn, Stolk, Wolffenbuttel, and Sauer (2014)	Intervention group ($n = 40$): Δ = −1.4 ± 6.8 ($p = .25$). Usual care group ($n = 35$): Δ = −1.3 ± 9.6 ($p = .46$)	N/A	Intervention group: Δ = −0.9 ± 3.9 ($p = .22$). Usual care: Δ = −1.3 ± 4.0 ($p = .08$)	Intervention group: Δ = −1.2 ± 1.0 Usual care: Δ = −0.6 ± 1.1(p values not reported)	Significant correlation between change in leptin and change in BMI z-score ($r = .535$, $p < .001$). No difference between groups for leptin ($p = .46$) or adiponectin ($p = .64$)

(continued)

Table 3. (continued)

Article	Findings				Conclusions
	Leptin (ng/ml)	Ghrelin (pg/ml)	Adiponectin (μg/ml)	BMI (kg/m^2)	
7. Chae et al. (2010)	N/A	N/A	Intervention group ($n = 19$): no change, actual values not reported. Usual care ($n = 19$): significant decrease ($p < .05$), actual values not reported	Intervention group: pre = 26.6 ± 0.8, post = 25.0 ± 0.7, Δ = −1.7 ± 1.1. Usual care: pre = 26.2 ± 1.0, post = 26.7 ± 1.1, Δ = +0.5 ± 0.3	The intervention had no effect on serum adiponectin level but improved body weight and composition. Significant difference in BMI between intervention and usual care groups ($p < .05$)
8. Damaso et al. (2014)	AT ($n = 55$): pre = 23.60 ± 19.58, post = 17.93 ± 18.73, Δ = −6.57 ± 17.48. AT + RT ($n = 61$): pre = 48.32 ± 27.1, post = 26.68 ± 20.15, Δ = −21.64 ± 22.94	N/A	AT: pre = 6.25 ± 2.4, post = 5.78 ± 2.23, Δ = −0.55 ± 2.27. AT + RT: pre = 5.59 ± 3.15 post = 7.03 ± 4.48, Δ = 1.43 ± 2.45	AT: pre = 35.7 ± 4.3, post = 32.6 ± 4.5, Δ = −3.2 ± 3.0. AT + RT: pre = 36.7 ± 4.9, post = 31.9 ± 4.6, Δ = −4.7 ± 2.6	Both interventions improved clinical parameters, but AT + RT was more effective. Changes in leptin and adiponectin were significantly different between AT and AT + RT groups. Body fat positively correlated with leptin levels ($r = .50$, $p < .001$), and adiponectin levels inversely correlated with subcutaneous fat ($r = -.26$, $p = .04$)
9. De Piano et al. (2012)	AT without NAFLD ($n = 15$): pre = 5.9, post = 3.83, Δ = −7.13 ± 12.68. AT with NAFLD ($n = 14$: pre = 10.29, post = 4.91, Δ = −12.17 ± 17.22. AT + RT without NAFLD ($n = 15$): pre = 36.50, post = 31.21, Δ = −9.19 ± 13.61. AT + RT with NAFLD ($n = 14$): pre = 33.36, post = 22.68, Δ = −11.95 ± 13.08	N/A	AT without NAFLD: pre = 5.21, post = 3.83, Δ = –0.13 ± 1.73. AT with NAFLD: pre = 4.65, post = 4.86, Δ = –0.13 ± 2.78. AT + RT without NAFLD: pre = 8.52, post = 10.70, Δ = +2.57 ± 2.50. AT + RT with NAFLD: pre = 9.22, post = 12.71, Δ = +2.69 ± 2.54	AT without NAFLD: pre = 33.53 ± 3.58, post = 29.95 ± 2.65, Δ = −3.38 ± 2.91. AT with NAFLD: pre = 37.99 ± 3.64, post = 34.49 ± 5.13, Δ = –3.72 ± 2.77. AT + RT without NAFLD: pre = 36.46 ± 4.49, post = 31.74 ± 3.60, Δ = −4.72 ± 2.97. AT + RT with NAFLD: pre = 38.43 ± 5.26, post = 32.98 ± 6.05, Δ = –5.44 ± 2.95	Combined training was more effective in promoting a high level of change in adiponectin in group without NAFLD; significant differences in leptin and adiponectin at baseline between groups ($p \leq .05$); no difference in food intake at baseline
10. Elloumi et al. (2009)	R ($n = 7$): Δ = −17.6% ($p < .05$). E ($n = 7$): Δ = −16.8% ($p < .05$). RE ($n = 7$): Δ = −38.8% ($p < .01$)	N/A	R: Δ = +39.1% ($p < .05$). E: Δ = +34.8% ($p < .05$). RE: Δ = +73.7% ($p < .01$)	R: pre = 30.7 ± 2.3, post = 28.0 ± 3.1 ($p < .01$), Δ = −2.7. E: pre = 30.3 ± 3.2, post = 29.6 ± 3.5, Δ = −0.7. RE: pre = 31.6 ± 3.3, post = 27.2 ± 3.4 ($p < .001$), Δ = −4.4	Moderate exercise training + energy restriction improves the ability to oxidize lipids, which is associated with a normalization of adiponectin and leptin levels, resulting in improved insulin sensitivity
11. Galhardo et al. (2012)	N/A	Standard ($n = 13$): pre = 62.41 ± 22.13, post = 82.23 ± 41.87, Δ = +19.82 ($p = .15$). Treatment ($n = 14$): pre = 68.45 ± 17.78, post = 48.14 ± 18.47, Δ = −20.31 ($p = .002$)	N/A	Standard: pre = 3.10 ± 0.54 post = 2.95 ± 0.60, Δ = −0.14 ($p = .17$). Treatment: pre = 3.44 ± 0.48, post = 3.03 ± 0.60, Δ = −0.41 ($p = .001$)	Significant reduction in BMI and ghrelin levels in treatment group at 12 months

(continued)

Table 3. (continued)

Article	Findings				Conclusions
	Leptin (ng/ml)	Ghrelin (pg/ml)	Adiponectin (μg/ml)	BMI (kg/m^2)	
12. Hajihashemi, Azadbakht, Hashemipour, Kelishadi, and Esmailzadeh (2014)	Whole grain ($n = 22$): pre = 11.85 ± 10.1, post = 10.7 ± 5.52 ($p = .02$), Δ = −0.011 or −9.7%. Control ($n = 22$): pre = 9.37 ± 7.11, post = 13.05 ± 8.58, Δ = +3.68 (+39.2%; $p = .02$).[a]	N/A	N/A	BMI measured but only baseline values reported	Significant difference in leptin from baseline to sixth week in both groups and between groups. No significant difference in change in BMI between intervention and control groups. No significant effect of the intervention on BMI
13. Hasson et al. (2012)	Control ($n = 59$): AA Δ = +7.6 ± 34.6, Latino Δ = −6.6 ± 15.7, not significant. Nutrition ($n = 50$): AA Δ = +0.3 ± 16.1, Latino Δ = −1.7 ± 20.2, not significant. Nutrition + strength ($n = 59$): AA Δ = +1.3 ± 17.4, Latino Δ = −4.4 ± 9.6, not significant	N/A	Control: AA Δ = +0.4 ± 5.2, Latino Δ = −0.6 ± 6.5, not significant. Nutrition: AA Δ = −1.9 ± 4.3, Latino 0.8 ± 7.8, not significant. Nutrition + strength: AA Δ = −4.3 ± 8.6, Latino Δ = +0.5 ± 7.8, not significant	Control: no significant change. Nutrition: no significant change. Nutrition + strength: no significant change	No intervention effects on leptin, adiponectin, or BMI
14. Ibarra-Reynoso et al. (2015)	Low carb ($n = 60$): pre = 25.75 ± 12.06, post = 17.03 ± 9.81, Δ = −8.72 ($p < .0000001$). Low fat ($n = 60$): pre = 27.94 ± 10.02, post = 19.96 ± 10.62, Δ = −7.98 ($p < .00001$)	N/A	Low carb: pre = 14.83 ± 7.78, post = 17.79 ± 10.24, Δ = +2.96 ($p = .09$) Low fat: pre = 15.10 ± 6.90, post = 16.77 ± 9.35, Δ = +1.67 ($p = .22$)	Low carb: pre = 27.62 ± 3.28, post = 26.41 ± 3.22, Δ = −1.21 ($p < .0000001$). Low fat: pre = 28.75 ± 4.11, post = 27.54 ± 4.10, Δ = −1.21 ($p < .00002$)	The two diets were equally effective at reducing BMI. Both groups achieved significantly reduced leptin levels from baseline to 2 months. No significant effect of the intervention on adiponectin. Leptin was positively associated with BMI
15. Jensen et al. (2014)	Control ($n = 11$): pre = 61.3 ± 39.4, post = 67.3 ± 39.9, Δ = +6.0. Low carb ($n = 32$): pre = 51.4 ± 26.0, post = 44.5 ± 32.1, Δ = −6.9 ($p = .03$). Low fat ($n = 31$): pre = 58.3 ± 40.7, post = 43.5 ± 30.4, Δ = −14.8 ($p = .03$)	Control: pre = 60.4 ± 22.2, post = 71.8 ± 44.9, Δ = +11.4. Low carb: pre = 88.8 ± 46.2, post = 92.4 ± 48.4, Δ = +3.6. Low fat: pre = 89.0 ± 58.7, post = 94.7 ± 62.2, Δ = +5.7	Control: pre = 8.1 ± 2.5, post = 7.8 ± 1.8, Δ = −0.3. Low carb: pre = 8.9 ± 3.9, post = 10.2 ± 4.5, Δ = +1.3. Low fat: pre = 9.6 ± 3.9, post = 10.1 ± 4.0, Δ = +0.5 ($p = .05$)	Control: pre = 34.3 ± 6.7, post = 34.9 ± 6.8, Δ = +0.6. Low carb: pre = 32.1 ± 4.8, post = 30.9 ± 4.9, Δ = −1.2. Low fat: pre = 32.6 ± 5.9, post = 31.6 ± 6.0, Δ = −1.0 ($p < .0001$)	No significant changes in ghrelin with weight loss. Significant reduction in BMI and leptin and significant increase in adiponectin in intervention groups
16. Kelishadi, Hashemipour, Mohammadifard, Alikhassy, and Adeli (2008)	Diet group at 6 months ($n = 47$): Δ = −7.2 ± 0.7 ($p < .05$). Diet group at 12 months ($n = 45$): Δ = +1.4 ± 0.5. Exercise group at 6 months ($n = 45$): Δ = −6.9 ± 0.3 ($p < .05$). Exercise group at 12 months ($n = 42$): Δ = +1.1 ± 0.2	Diet group, 6 months: Δ = +417.1 ± 95.4 ($p < .05$). Diet group, 12 months: Δ = +278.4 ± 89.1 ($p < .05$). Exercise group, 6 months: Δ = +387.5 ± 87.2 ($p < .05$). Exercise group, 12 months: Δ = +241.2 ± 66.8	N/A	Diet group, 6 months: Δ = −1.1 ± 0.3 ($p < .05$). Diet group, 12 months: Δ = +0.7 ± 0.1. Exercise group, 6 months: Δ = −1.04 ± 0.2 ($p < .05$). Exercise group, 12 months: Δ = +0.5 ± 0.01	Ghrelin decreased in both dietary and exercise intervention groups in response to weight and/or calorie reduction. Ghrelin is unlikely to regulate long-term energy balance in obese prepubertal children
17. McFarlin et al. (2013)	Control: increased by 100% from baseline to 12 months ($p < .05$). Intervention: increased by 78% from baseline to 12 months ($p < .05$)	N/A	Control: decreased by 50% from baseline to 12 months. Intervention: decreased by 32% from baseline to 12 months	Reported as BMI z-score	Improved leptin and adiponectin levels were related to decrease in BMI z-scores. Intervention group had a significant decrease in BMI from baseline to 6 months (−0.211) and to 12 months (−0.105, $p < .05$). No significant difference at any time point in pubertal status between groups

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Table 3. (continued)

Article	Findings				Conclusions
	Leptin (ng/ml)	Ghrelin (pg/ml)	Adiponectin (μg/ml)	BMI (kg/m^2)	
18. Nemet, Oren, Pantanowitz, and Eliakim (2013)	Intervention ($n = 21$): pre = 13.566 ± 9.053, post = 14.335 ± 10.671, Δ = +0.769. Control ($n = 20$): pre = 16.335 ± 9.619, post = 19.001 ± 9.575, Δ = +3.334	N/A	Intervention: Δ = +2.308 ± 1.640. Control: Δ = –0.801 ± 0.465	Intervention: Δ = –0.96 ± 1.29. Control: Δ = +0.19 ± 0.8	No significant change in leptin within or between groups. Significant between-group difference in BMI percentile pre to post ($p < .01$). Adiponectin increased with a ≥7% increase in PA ($p < .005$) and was inversely correlated with body fatness and positively correlated with PA
19. Nunes et al. (2015)	N/A	N/A	Intervention ($n = 17$): Pre = 40.9 ± 29.34, post = 49.05 ± 41.22, Δ = +8.15. Control ($n = 8$): pre = 31.56 ± 18.88, post = 18.01 ± 11.66, Δ = −13.55 ($p < .05$)	Intervention: pre = 34.99 ± 3.70, post = 33.36 ± 3.75, Δ = −1.63 ($p < .05$). Control: pre = 34.85 ± 4.32, post = 35.68 ± 4.07, Δ = +0.83	Intervention was effective in improving the anti-inflammatory responses and the antioxidant defenses in obese adolescents. Adiponectin levels decreased in control group but not in intervention group
20. Park, Hong, Lee, and Kang (2007)	Control ($n = 22$): pre = 14.183, post = 12.884, Δ = –1.382. Intervention ($n = 22$): pre = 15.583, post = 12.583, Δ = –3.081 ($p = .032$)	N/A	Control: pre = 10.38 ± 3.3, post = 9.9 ± 3.5, Δ = –0.4 ± 1.0. Intervention: pre = 10.4 ± 3.4, post = 10.8 ± 4.6, Δ = +0.3 ± 2.8	Control: pre = 29.2 ± 2.4, post = 29.1 ± 2.2, Δ = –0.1 ± 0.6 ($p < .001$). Intervention: pre = 29.3 ± 2.9, post = 27.5 ± 3.0, Δ = –1.9 ± 0.9 ($p < .001$)	Significant reduction in leptin in intervention group ($p = .032$), but no significant change in adiponectin ($p = .258$)
21. Partsalaki, Karvela, and Spiliotis (2012)	N/A	N/A	Ketogenic: initial ($n = 29$) 2.5 ± 1.7, completed ($n = 21$) 1.9 ± 1.1, Δ = −0.6 ($p = .025$) Hypocaloric: initial ($n = 29$) 2.3 ± 2.0 ($p = .384$), completed ($n = 17$) 2.1 ± 2.3, Δ = −0.2 ($p = .906$)	Ketogenic: initial 30.8 ± 8.1, completed 30.0 ± 4.3, Δ = –3.7 ($p = .001$). Hypocaloric: initial 28.0 ± 4.2, completed 28.1 ± 3.1, Δ = –3.3 ($p = .001$)	The ketogenic diet was associated with more pronounced improvements in weight loss and metabolic parameters than the hypocaloric diet and may be a feasible and safe alternative for weight loss. No significant differences in results between pubertal status groups
22. Pedrosa et al. (2011)	IT ($n = 58$): pre = 10.9 (range: min 1.4; max 40.2), post = 8.0 (3.3; 25.0), 1 year 8.9 (1.6; 35.5), $t \times T$ effect ($p = .341$). GT ($n = 25$): pre = 10.4 (2.5; 19.3), post = 9.2 (3.6; 22.6), 1 year 8.6 (3.8; 18.0)	IT: pre = 1,060.6 (387.6; 3,329.0), post = 984.4 (211.8; 2,686.3), 1 year 889.6 (369.4; 3,627.9), t ($p = .030$), $t \times T$ ($p = .039$), T ($p = .702$). GT: pre = 1,162.7 (511.5; 1,606.9), post = 963.6 (611.5; 2,317.9), 1 year 1,373.6 (623.1; 2,355.0)	IT: pre = 26.0 (3.1; 61.5), post = 19.8 (4.4; 57.6), 1 year 19.1 (3.0; 65.5), t ($p = .505$), $t \times T$ ($p = .114$), T ($p = .602$). GT: pre = 24.6 (6.4; 41.1), post = 20.0 (6.7; 53.1), 1 year 27.9 (3.3; 49.4)	Reported as BMI z-score. IT: pre = 1.98 (1.31; 2.61), post = 1.84 (1.18; 2.44), 1 year 1.76 (1.18; 2.46), t ($p \leq .001$), $t \times T$ ($p = .582$), T ($p = .042$). GT: pre = 1.87 (1.54; 2.37), post = 1.82 (0.94; 2.36), 1 year 1.57 (1.01; 2.27)	Ghrelin levels differed significantly at baseline between Tanner 1 and 2 groups ($p = .007$). Leptin levels differed significantly between normal weight and overweight participants at baseline ($p < .001$). Could not confirm the effect of weight loss on adiponectin or ghrelin since their levels increased in the GT group and decreased in the IT group over time. GT seems to be more successful, though both GT and IT led to weight loss and improved parameters. Leptin and ghrelin were associated with the metabolic syndrome, but adiponectin levels were not

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Table 3. (continued)

Article	Findings				Conclusions
	Leptin (ng/ml)	Ghrelin (pg/ml)	Adiponectin (μg/ml)	BMI (kg/m^2)	
23. Rosenbaum et al. (2007)	N/A	N/A	Control ($n = 24$): pre = 9.98 ± 1.71, post = 9.65 ± 1.70, Δ = −0.33. Intervention ($n = 49$): pre = 9.54 ± 1.07, post = 9.93 ± 1.12, Δ = +0.39	Control: pre = 24.3 ± 1.8, post = 24.8 ± 1.9, Δ = +0.5. Intervention: pre = 24.7 ± 1.4, post = 24.0 ± 1.5, Δ = −0.7 ($p < .05$)	No significant change in adiponectin levels from baseline to postintervention in either group. No significant difference between groups in adiponectin levels
24. Saneei, Hashemipour, Kelishadi, and Esmaillzadeh (2014)	N/A	N/A	DASH ($n = 30$): pre = 4.89 ± 1.10, Week 6 3.99 ± 1.15, Δ = −0.9. UDA ($n = 30$): pre = 4.20 ± 1.12, Week 6 3.53 ± 1.11, Δ = −0.67 (time $p = .11$, group $p = .21$)	DASH: Δ = –0.28 ± 0.08. UDA: Δ = –0.14 ± 0.08 ($p = .17$)	No significant change in BMI or adiponectin with either diet
25. Shalitin et al. (2009)	Exercise ($n = 52$): Δ = −2.53 ± 18.21. Diet ($n = 55$): Δ = −12.37 ± 17.31 (baseline to 12 weeks, $p < .05$). Exercise + diet ($n = 55$): Δ = −10.7 ± 14.07 (baseline to 12 weeks, $p < .05$). Significant difference in pre–post outcomes between groups ($p = .025$)	Exercise: Δ = +83.99 ± 171 (baseline to 12 weeks, $p < .05$). Diet: Δ = +19.52 ± 126.8. Exercise + diet: Δ = +58.83 ± 127.2 (baseline to 12 weeks, $p < .05$). No significant between-group difference in pre–post outcomes	Exercise: Δ = −708 ± 2,054; diet: Δ = 769 ± 2,588; exercise + diet: Δ = 793 ± 2,012. Significant change in adiponectin from baseline to 12 weeks ($p < .05$) in exercise + diet group only, and significant difference between groups ($p = .003$)	Exercise: baseline 25.5 ± 0.52, 12 weeks = 24.5 ± 0.54, Δ = −1.0 ($p < .05$), 52 weeks = 25.9 ± 0.58, Δ = +0.4. Diet: baseline 26.5 ± 0.51, 12 weeks = 24.6 ± 0.54, Δ = −1.9 ($p < .05$), 52 weeks = 26.9 ± 0.56, Δ = +0.4. Diet + exercise: baseline 25.9 ± 0.51, 12 weeks = 23.9 ± 0.52, Δ = −2.0 ($p < .05$), 52 weeks = 26.0 ± 0.55, Δ = +0.1 ($p < .001$). Significant between-group difference in pre–post outcomes ($p \leq .001$)	Diet alone or with exercise are most effective short-term interventions for weight loss and improved cardiometabolic profiles
26. Wang, Yang, Lu, and Mu (2015)	N/A	Actual values not reported	N/A	No change per authors, but the actual values were not reported	Significant weight loss reported for egg breakfast (3.9% vs. 0.2%, $p < .001$). Strong correlations among weight loss, appetite, subsequent food intake, and changes in levels of appetite hormones

Note. Peptide hormone levels and BMI values are presented as mean ± standard deviation. Δ = change; AA = African American; AT = aerobic training; E = exercise; GT = group therapy; IT = individual therapy; LSE = lifestyle education; NAFLD = nonalcoholic fatty liver disease; PA = physical activity; R = calorie restriction; RT = resistance training.

[a]Leptin data were presented in the original article in ng/L. When we converted them into ng/ml, they differed from leptin levels reported in the other studies by a factor of 100. We have thus assumed a reporting error in the reviewed article and have corrected the converted levels accordingly.

significantly in three of these six studies (Abd El-Kader et al., 2013; Balagopal et al., 2005; Balagopal et al., 2010; Nemet et al., 2013) but did not change significantly in the others.

Finally, seven of the studies were two- or three-group designs comparing mixed interventions with varying components (Ackel-D'Elia et al., 2014; Barbeau et al., 2003; Damaso et al., 2014; De Piano et al., 2012; Elloumi et al., 2009; Hasson et al., 2012; Shalitin et al., 2009). For example, researchers might compare an exercise-only intervention group with both an exercise/nutrition intervention group and an exercise/resistance training/nutrition group. This group of studies was more successful than the other groups at pre-/postintervention BMI and within-group leptin decreases (five of the seven studies; Ackel-D'Elia et al., 2014; Damaso et al., 2014; De Piano et al., 2012; Elloumi et al., 2009; Shalitin et al., 2009) and was moderately effective at achieving between-group differences in changes in BMI (Ackel-D'Elia et al., 2014; Barbeau et al., 2003; Shalitin et al., 2009), adiponectin (Damaso et al., 2014; De Piano et al., 2012; Shalitin et al., 2009), and leptin (Ackel-D'Elia et al., 2014; Damaso et al., 2014; De Piano et al., 2012; Shalitin et al., 2009). The successful studies were those with mixed interventions containing hypocaloric diets of any macronutrient composition and a structured exercise component—with or without resistance training, counseling, or medical treatment. Two studies were unique: one compared an exercise-only intervention with a nutrition-only intervention (Kelishadi, Hashemipour, Mohammadifard, Alikhassy, & Adeli, 2008) and one compared a group-based mixed intervention with an individual mixed intervention (Pedrosa et al., 2011).

Specific Outcomes

Leptin. Leptin was measured in 18 of the 25 studies listed in the tables. Researchers found a significant pre-/postintervention decrease in leptin in 11 of the studies listed in the tables (Abd El-Kader et al., 2013; Ackel-D'Elia et al., 2014; Balagopal et al., 2005; Balagopal et al., 2010; Damaso et al., 2014; De Piano et al., 2012; Elloumi et al., 2009; Hajihashemi et al., 2014; Ibarra-Reynoso et al., 2015; Kelishadi et al., 2008; Park et al., 2007; Shalitin et al., 2009). In one study (Hajihashemi et al., 2014), leptin in the not-whole-grain control group increased significantly from baseline. Researchers found a significant difference in the change in leptin between the intervention and the control groups in eight studies (Abd El-Kader et al., 2013; Ackel-D'Elia et al., 2014; Balagopal et al., 2005; Balagopal et al., 2010; Damaso et al., 2014; De Piano et al., 2012; Hajihashemi et al., 2014; Jensen et al., 2014; Shalitin et al., 2009). A significant decrease in leptin most often paralleled a significant decrease in BMI, except in four studies in which BMI decreased but leptin did not change significantly (De Piano et al., 2012; McFarlin et al., 2013; Nemet et al., 2013; Pedrosa et al., 2011) and in three studies in which BMI did not change significantly but leptin decreased (Elloumi et al., 2009; Hajihashemi et al., 2014; Shalitin et al., 2009). One study, conducted in the United States, differentiated between ethnicities: leptin responded in different directions in African American groups (leptin increased over time) and Latino American groups (leptin decreased over time), though the changes were not statistically significant (Hasson et al., 2012).

Ghrelin. Researchers measured ghrelin in only 6 of the 25 studies, and the findings were contradictory across studies. Of the three studies that measured ghrelin at two or more time points, researchers in one found significantly increased ghrelin at 6 months but decreased ghrelin at 12 months in both the diet and the exercise groups (Kelishadi et al., 2008); researchers in another found significantly increased ghrelin at two time points (12 weeks and 12 months) in both the exercise-only and the mixed-intervention groups plus significantly increased ghrelin at 12 months only in the hypocaloric diet group (Shalitin et al., 2009); and in the third, researchers found significantly decreased ghrelin at both time points (6 months and 12 months) in only the individual-based mixed-intervention group (Pedrosa et al., 2011). Of the three studies that measured ghrelin at only one time point, researchers in two found nonsignificant decreases in both the groups (Balagopal et al., 2005; Balagopal et al., 2010; Jensen et al., 2014; Wang et al., 2015) and researchers in the third found nonsignificant increases in all groups (Kelishadi et al., 2008). In a unique study, a Mandometer group achieved significantly lower ghrelin levels, while a lifestyle-education-only group had a nonsignificant increase (Galhardo et al., 2012).

Adiponectin. Of the 25 studies reviewed, 19 measured adiponectin (Abd El-Kader et al., 2013; Balagopal et al., 2005; Balagopal et al., 2010; Bocca et al., 2014; Chae et al., 2010; Damaso et al., 2014; De Piano et al., 2012; Elloumi et al., 2009; Hasson et al., 2012; Ibarra-Reynoso et al., 2015; Jensen et al., 2014; McFarlin et al., 2013; Nemet et al., 2013; Nunes et al., 2015; Park et al., 2007; Partsalaki et al., 2012; Pedrosa et al., 2011; Rosenbaum et al., 2007; Saneei et al., 2014; Shalitin et al., 2009), but only one measured high-molecular-weight adiponectin (Partsalaki et al., 2012). All the others measured total adiponectin, which is unusual because high-molecular-weight adiponectin is considered to be a more accurate measure in pediatrics. In 10 study groups, researchers found significant changes in pre-/postintervention adiponectin levels, but the direction of the change differed across studies. Levels significantly increased in six study groups (Abd El-Kader et al., 2013; Balagopal et al., 2005; Balagopal et al., 2010; Chae et al., 2010; Elloumi et al., 2009; Partsalaki et al., 2012; Shalitin et al., 2009). Levels significantly decreased in four study groups: a usual dietary advice control group (Chae et al., 2010), two mixed-intervention control groups (Damaso et al., 2014; Nunes et al., 2015), and an exercise-only group at 52 weeks (Shalitin et al., 2009).

Investigators found significant between-group changes in seven of the studies, with six of seven intervention groups achieving significantly increased adiponectin levels in comparison to control groups over the duration of the study (Abd El-

Kader et al., 2013; Balagopal et al., 2005; Balagopal et al., 2010; De Piano et al., 2012; Jensen et al., 2014; Nemet et al., 2013; Nunes et al., 2015; Shalitin et al., 2009). Two of the studies appear to have been conducted at the same research site and had the same design but different samples (Damaso et al., 2014; De Piano et al., 2012). In the one that included participants with or without nonalcoholic fatty liver disease (NAFLD), the mixed-intervention group that participated in resistance training showed significantly decreased adiponectin in comparison to the control group of mixed interventions without resistance training (De Piano et al., 2012). These findings are the opposite of the other study's, which were that adiponectin increased significantly in the mixed-intervention group that included resistance training (Damaso et al., 2014).

Risk of Bias

Table 4 presents the studies' risks of bias, including the study authors' stated limitations. Common limitations included compliance in adolescents, varying levels of gut peptides throughout the day and among individuals, length of intervention, differences between groups at baseline, or near-normal levels of inflammation at baseline despite presence of the metabolic syndrome. The 20.8% overall attrition rate was reasonable for the type of studies in this review. Of the total, nine studies had no attrition, partly because some samples were subsets of larger studies. The attrition rate was unrelated to duration of the interventions, most likely because follow-up periods also varied in length.

Only four studies had final samples of 100 participants or more, which increases the potential margin of error. Of the total, 4 studies were clearly identified as multisite, and participants in 13 of the studies were recruited from a single site. The remaining studies had population-based recruitment strategies that precluded a defined number of sites. Neither blinding of the people who delivered the intervention nor blinding of the data collectors was common in this sample of studies. Thus, although the studies' designs were rigorous, their findings are difficult to generalize, owing to the risk of bias.

Discussion

The results of this systematic review suggest that hypocaloric diets are more effective than less structured lifestyle/behavioral interventions for short-term BMI reductions in overweight or obese children and/or adolescents. In the reviewed studies, the usual dietary advice and lifestyle-education interventions designed without structure and monitoring failed to achieve any significant BMI changes. Thus, it seems logical to recommend that health-care providers should prescribe specific hypocaloric diets followed by regular monitoring and follow-up as opposed to providing general self-help dietary guidelines. However, this recommendation should be considered in the context of the maturation and growth that occurs in children. Adequate caloric intake is required for growth, and therefore, it is essential to consider how much caloric restriction, if any, is safe and appropriate for children.

The appetite hormones that were the focus of this systematic review can vary with maturational stage, a factor that can confound study results (Baatar et al., 2011; Hotta et al., 2001; Klok et al., 2007; Pyrzak et al., 2010). In 7 of the 25 studies, researchers did not measure or report findings based on the pubertal status of their samples. As a result, we cannot know how developmental stages might have influenced the results of those studies. There was no difference in BMI reduction between studies that did (Ackel-D'Elia et al., 2014; Balagopal et al., 2005; Balagopal et al., 2010; Bocca et al., 2014; Damaso et al., 2014; Galhardo et al., 2012; Hasson et al., 2012; Ibarra-Reynoso et al., 2015; Jensen et al., 2014; Kelishadi et al., 2008; Nemet et al., 2013; Nunes et al., 2015; Park et al., 2007; Partsalaki et al., 2012; Pedrosa et al., 2011; Saneei et al., 2014; Shalitin et al., 2009) and did not (Abd El-Kader et al., 2013; Barbeau et al., 2003; Chae et al., 2010; Hajihashemi et al., 2014; McFarlin et al., 2013; Rosenbaum et al., 2007; Wang et al., 2015) differentiate findings according to pubertal status, $\chi^2(1, N = 25) = 0, p > .05$. To confirm the findings of this review, researchers in future studies should measure pubertal status, separate samples by maturational stage, and report findings for pubertal groups.

The current literature provides insufficient evidence regarding other types of diets used in pediatric populations, so we cannot draw any conclusions about their effectiveness. Of particular interest were the few studies that achieved significant improvement in obesity hormone levels without a change in BMI. This finding could indicate a trend worthy of exploring due to the challenges that obese children experience related to normalizing BMI percentile as they grow. Leptin, ghrelin, and adiponectin levels contribute to chronic disease, but it is unknown how these hormones might have influenced the results in the 18 studies that included obese but otherwise healthy children. Only two of the studies looked at the relationship between weight loss interventions and peptide hormones in children with a diagnosed comorbidity (asthma and NAFLD; Abd El-Kader et al., 2013; De Piano et al., 2012). An additional study included all obese girls without excluding comorbidity (Partsalaki et al., 2012). Further exploration of the role of comorbidity in hormonal changes after obesity interventions is warranted for two reasons. First, there is a lack of literature available on this topic, and second, there is a potential for the identification of novel biomarkers in obese children with comorbidities. Additionally, future literature reviews and high-quality studies that compare the gut peptides with inflammatory markers might yield insights.

One study involved the use of a device to retrain eating behavior called the Mandometer, a unique approach to lifestyle/behavioral interventions (Hajihashemi et al., 2014). The Mandometer, a scale placed under the plate while a participant is eating, communicates wirelessly to a smartphone and provides instant feedback on the rate of eating, cuing the eater to slow the rate as needed. Since this study was the only one of its kind included in our review, we cannot draw definitive

Table 4. Risk of Bias in Reviewed Studies.

Reference	Related Author-Stated Limitations	Attrition (%)	Sample
1. Abd El-Kader, Al-Jiffri, and Ashmawy (2013)	No stated limitations	$N = 80$ equally randomized between groups, no attrition mentioned (0%)	Single site, recruited from clinic
2. Ackel-D'Elia et al. (2014)	Physical energy expenditure not measured explicitly at baseline or in activity groups	$N = 132$ selected; $n = 72$ included in final data analysis (45%)	Recruited by a university-based obesity program
3. Balagopal, George, Yarandi, Funanage, and Bayne (2005) 4. Balagopal et al. (2010)	No discussion of limitations related to adiponectin in 2005 article. In 2010 article, authors acknowledge the following: small sample size, correlative nature of the study analysis, postpubertal sample means that generalizability of the findings to all children is not possible, satiety hormones measured while fasting only and not correlated with self-report of appetite and satiety, ethnicity may have been a factor but was not explored due to small sample size	$N = 21$ (15 obese, 6 lean controls); no attrition mentioned (21 enrolled, 21 in data analysis [0%])	Single site
5. Barbeau et al. (2003)	Sexual maturation or Tanner stages were not measured throughout the study period	$N = 75$ individuals with baseline leptin data; only $n = 55$ included in the analysis with data at 8 months (27%)	Recruited from community
6. Bocca, Corpeleijn, Stolk, Wolffenbuttel, and Sauer (2014)	Limited power to detect differences between baseline and end of treatment; no control group of nonoverweight children to compare findings	$N = 75$ enrolled, 15 lost to follow-up (20%)	Sample referred to the obesity clinic from other providers in the community
7. Chae et al. (2010)	Failure to maintain weight reduction from short-term intervention over long-term follow-up period; limited generalizability due to small sample size and short duration of study	$N = 38$ enrolled, $n = 38$ in final data analysis; no attrition mentioned (0%)	Single site
8. Damaso et al. (2014)	No stated limitations	$N = 139$ enrolled; $n = 116$ completed intervention. Subjects who completed 75% or more of the intervention were included in final analysis (17%)	University medical center–based obesity program
9. De Piano et al. (2012)	Small sample size	$N = 58$; no attrition mentioned (0%)	University medical center–based obesity program
10. Elloumi et al. (2009)	No stated limitations	$N = 21$ randomized & analyzed, no attrition mentioned (0%)	Two schools, multisite
11. Galhardo et al. (2012)	No stated limitations	$N = 27$ randomized & analyzed, no attrition mentioned (0%)	Hospital, single-site
12. Hajihashemi, Azadbakht, Hashemipour, Kelishadi, and Esmailzadeh (2014)	Dietary data based on self-reported records; budget restraints led to an inability to measure a biological marker for whole-grain intake to verify self-report documents; higher energy intake in whole-grain group may contribute to lack of expected outcomes; limitations of crossover designs may have contributed to results (learning effect, lack of adequate washout)	$N = 44$ total; $n = 9$ failed to complete study period; analyzed with intention-to-treat approach (20%)	Recruitment strategies unknown. Sample came from a particular city in Iran
13. Hasson et al. (2012)	No stated limitations	$N = 168$ randomized, $n = 100$ completed; clear description of attrition (40.4%)	Unknown; limited description of site and recruitment
14. Ibarra-Reynoso et al. (2015)	No stated limitations	$N = 120$ subjects; $n = 98$ completed the study period and were included in the data analysis (18%)	Multiple schools in the city of Leon, Mexico
15. Jensen et al. (2014)	Modest weight loss; large biological variant in gut peptides; gut hormones only measured in fasting state; compliance in adolescents is difficult; short duration of study does not provide information about long-term effect	$N = 87$ randomized into trial, $n = 74$ included in data analysis: 1 case excluded as outlier from final analysis, others did not complete the entire intervention (15%)	Single site
16. Kelishadi, Hashemipour, Mohammadifard, Alikhassy, and Adeli (2008)	Risk of recall bias for recording food intake; mean ghrelin had a high degree of variation	$N = 100$ recruited, $n = 92$ completed 6 months (8%), $n = 87$ returned for 1-year follow up (13%)	Single site
17. McFarlin et al. (2013)	Lack of sustained weight loss at 12 months may have contributed to results	$N = 221$ for baseline randomization; only reported the sample who completed all three blood collection time points (0%)	Charter school, single site
18. Nemet, Oren, Pantanowitz, and Eliakim (2013)	No stated limitations	$N = 42$ randomized, $n = 41$ completed (2%)	Single site

(continued)

Table 4. (continued)

Reference	Related Author-Stated Limitations	Attrition (%)	Sample
19. Nunes et al. (2015)	No stated limitations	$N = 57$ randomized (47 intervention, 10 control), $n = 25$ completed (17 intervention, 8 control; 53%)	Presumably single site, but not completely clear from manuscript
20. Park, Hong, Lee, and Kang (2007)	Intervention was too short or too mild to produce a change in adiponectin; total adiponectin was measured instead of HMW adiponectin	$N = 44$ randomized, $n = 40$ completed study (9%)	Single site
21. Partsalaki, Karvela, and Spiliotis (2012)	Long-term safety and weight-loss benefits unknown	$N = 58$ randomized, $n = 38$ completed study; clear description of attrition (34%)	Single site
22. Pedrosa et al. (2011)	Small final sample size; most had normal values for metabolic parameters at baseline; both groups subjected to some type of intervention; almost half of subjects entered puberty at Year 1, which affects hormone levels	$N = 83$ randomized, $n = 22$ children dropped out of the study and their data were not included in the analysis (27%)	Population-based recruitment; large sample assessed in schools
23. Rosenbaum et al. (2007)	Lack of statistical difference may be related to the students in different groups knowing each other from being in class together; no clear separation of treatment vs. control group because they are in same grade/class; time spent in PA, intensity of PA, and dietary content were not quantified; smaller gym class may have led to increased activity in that group	$N = 73$ randomized, $n = 55$ subjects completed the study (25%)	Single site
24. Saneei, Hashemipour, Kelishadi, and Esmaillzadeh (2014)	Single measurement of proinflammatory status, though levels rise and fall each day, so multiple measures at varying time points would give a more complete picture; dietary compliance could not be 100% confirmed; near- normal levels of inflammatory markers at baseline despite presence of metabolic syndrome	$N = 60$ randomized, $n = 49$ completed trial; data analyzed by intention-to-treat method, $n = 60$ in final data analysis (18%)	Single site
25. Shalitin et al. (2009)	Absence of nonintervention control group; high rate of dropouts, especially in follow-up period; lack of refreshing sessions to strengthen compliance in follow-up period; possibility that exercise intervention was not rigorous enough; the effect of the intervention on behavior modification was not quantified; measured total adiponectin instead of HMW adiponectin	Detailed description of attrition and the sample size included in analysis. Total randomized $N = 174$, $n = 162$ commenced intervention (7%), ANOVA $n = 120$ (26% from randomization), follow-up period $n = 77$ (52% from randomization)	Three cohorts at two different sites; subjects recruited from multiple regions of the country
26. Wang, Yang, Lu, and Mu (2015)	Chinese obese adolescents only; difference in fat content in breakfasts; compliance unknown due to self-report	$N = 156$ enrolled, no attrition mentioned (0%)	Recruitment strategy unknown; from Beijing, army hospital institutional review board approved protocol

Note. ANOVA = analysis of variance; HMW adiponectin = high-molecular-weight adiponectin; PA = physical activity.

conclusions about the Mandometer's use; however, this study does provide a glimpse of the possibilities that may be afforded by future technology for obesity management.

Studies have shown that, most often, with a significant decrease in BMI, there is an associated decrease in leptin and increase in adiponectin. Reinehr, Kratzsch, Kiess, and Andler (2005) noted that the normalization of leptin with time after a weight loss intervention indicates that the fluctuating levels are a result of weight loss as opposed to a cause of obesity. Our results support this conclusion. However, the role of abnormal obesity hormone levels in the development of disease cannot be ignored. Ghrelin levels appear to be unrelated to BMI. The studies in this review reported findings from fasting ghrelin only, and a greater understanding might be gained from exploring the nuanced findings of postprandial ghrelin levels compared to fasting ghrelin over time.

In one study, adiponectin levels dropped initially in response to the intervention and then rebounded over time. More studies are needed to confirm this pattern and to determine whether it may have clinical implications. Authors have suggested that, because of its role in the inflammatory process, high-molecular-weight adiponectin is the most accurate measure of adiponectin for this population (Shalitin et al., 2009), but findings remain inconclusive; only one of the reviewed studies measured high-molecular-weight adiponectin in a pediatric sample (Partsalaki et al., 2012).

The reviewed studies did have limitations. First, the comparison groups were disparate. A persistent challenge in such studies is the decision about what is most appropriate as a control condition because comparing one type of intervention with another diminishes the effects of the experimental intervention. In this review, we organized the analysis by comparison groups, which gave a better indication of emerging trends in each category of comparison group. Another limitation is that three of the articles were from the same group in Sao Paolo (Ackel-D'Elia et al., 2014; Damaso et al., 2014; De Piano et al., 2012), and two others were published separately using data from the same sample (Balagopal et al., 2005; Balagopal et al., 2010). We considered these overlaps during the analysis process, but it is possible that one group was overrepresented. Also, some of the studies examined BMI, whereas others examined BMI *z*-scores. We considered this disparity during the analysis, but a meta-analysis converting all values to BMI *z*-scores would provide greater clarity. In addition, we could only clearly identify four of the studies as multisite, so future studies that compare larger, multisite samples are needed. Finally, because sample size influences statistical significance, findings related to change in outcome variables should be interpreted with caution, particularly in smaller studies that were likely to have insufficient power.

Gaps and Recommendations for Future Research

A notable gap in the literature on obesity interventions in children is the measurement of adiposity. A majority of the studies used at least one other direct measure of adiposity in addition to BMI ($n = 18$). Investigators reported body fat mass and/or body fat percentage ($n = 16$; Ackel-D'Elia et al., 2014; Balagopal et al., 2005; Balagopal et al., 2010; Barbeau et al., 2003; Chae et al., 2010; Damaso et al., 2014; De Piano et al., 2012; Elloumi et al., 2009; Galhardo et al., 2012; Hasson et al., 2012; Ibarra-Reynoso et al., 2015; Jensen et al., 2014; Kelishadi et al., 2008; Park et al., 2007; Partsalaki et al., 2012; Rosenbaum et al., 2007; Shalitin et al., 2009) and visceral or trunk fat mass ($n = 6$; Balagopal et al., 2005; Barbeau et al., 2003; Bocca et al., 2014; Damaso et al., 2014; De Piano et al., 2012; Hasson et al., 2012). Waist circumference was reported as a measure of visceral adiposity in 12 studies (Bocca et al., 2014; Elloumi et al., 2009; Hajihashemi et al., 2014; Ibarra-Reynoso et al., 2015; Jensen et al., 2014; Kelishadi et al., 2008; Nemet et al., 2013; Park et al., 2007; Partsalaki et al., 2012; Pedrosa et al., 2011; Saneei et al., 2014; Shalitin et al., 2009). Investigators measured adiposity using bioimpedance or ultrasound ($n = 9$; Bocca et al., 2014; Chae et al., 2010; Damaso et al., 2014; De Piano et al., 2012; Jensen et al., 2014; Park et al., 2007; Partsalaki et al., 2012; Rosenbaum et al., 2007; Shalitin et al., 2009), skinfolds ($n = 3$; Elloumi et al., 2009; Ibarra-Reynoso et al., 2015; Kelishadi et al., 2008), x-ray absorptiometry ($n = 3$; Balagopal et al., 2005; Balagopal et al., 2010; Barbeau et al., 2003; Hasson et al., 2012), plethysmography air displacement method ($n = 3$; Ackel-D'Elia et al., 2014; Damaso et al., 2014; De Piano et al., 2012), and magnetic resonance imaging ($n = 2$; Barbeau et al., 2003; Hasson et al., 2012).

Despite the known effects of maturation on hormone levels, only 69% of studies differentiated their samples based on maturational stage. This confounding variable makes it difficult to isolate the effect of the intervention on the hormones.

Another surprising gap in the literature relates to the diets tested as interventions. For example, we found no studies that investigated vegetarian, vegan, gluten-free (allergen-free), or Mediterranean diets, all of which might have some link to modification of the risk for inflammation or chronic disease. Finally, since comorbidity is increasingly common with obesity, studies should also investigate the effects of diets in children with obesity plus related chronic conditions as did two of the studies included in this review (Abd El-Kader et al., 2013; De Piano et al., 2012).

The correlation between physiological changes and subjective self-report measures is beyond the scope of this review; however, future research could examine such relationships to determine the relevance of physiological changes to subjective experience, particularly in research on eating disorders. Gender differences in peptide hormone levels and the response to obesity interventions could be other important topics for future examination.

Implications

The findings of this systematic review have implications for both clinical practice and research. Gut peptides have the potential to become biomarkers for future diagnosis and disease management in obese children with one or more chronic

conditions. Consistent with previous research (Ho et al., 2012; Ling, Robbins, & Wen, 2016; Waters et al., 2011), the evidence in our review suggests that passive distribution of educational information to obese children and their families is an ineffective intervention for weight loss and improvements in gut peptide levels. Instead, caregivers should prescribe a specific hypocaloric diet and build monitoring and follow-up into any clinical program. Based on this evidence, we further recommend continued integration of mixed, multidisciplinary interventions in both clinical care and research because they are more successful than those relying on individual components.

Conclusion

To summarize, a variety of diets can affect BMI and leptin, ghrelin, and adiponectin levels in children. Use of specific diet prescriptions with monitoring is more effective than lifestyle education alone. Our findings in this review for leptin are consistent with previous research in that leptin levels decrease after obesity interventions, and those decreases correspond with decreases in BMI (Ho et al., 2012); however, we found that the evidence regarding the relationships between ghrelin and adiponectin and BMI in the context of weight management interventions is inconclusive, and these questions warrant additional research.

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Author Contribution

K. A. Lewis contributed to conception and design, acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. S. A. Brown contributed to conception and design, acquisition, analysis, and interpretation; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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