Dietary Epigenetic Factors Influencing Central Obesity

Research Article

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Abstract

Background: Central obesity, a major public health concern in the Asia-Pacific region, is a result of genetic predisposition as well as epigenetic influences. Nutritional factors influence obesity, through the calorie intake and modulating gene expression.

Objectives: To conduct a systematic review of the efficacy of dietary interventions through clinical trials, in the management of obesity.

Methods: PubMed and Google Scholar databases were searched for 20 years ending December 30, 2014, to find meta-analyses, systematic reviews, and randomized, placebo-controlled studies for central obesity-related clinical trials. The search terms were "central obesity" and "dietary interventions" or "calorie recommendation". All clinical trials on the effects of dietary interventions with the key outcome measures as change in BMI, waist-hip circumference and body fat were included.

Results: Several dietary regimens with varying macronutrients composition are used to combat obesity, such as low-calorie diets, very low-calorie diets (VLCD), low-fat diets, high-fiber diets, low-carbohydrate diets, low glycemic index (GI) diets and plant-based diets. However, very low-calorie-ketogenic and high protein diets have demonstrable significant adverse health effects.

Conclusion: The studies reviewed show promise of benefits with changes in epigenetic dietary factors. To draw definite conclusions, there is a need for more long-term studies, with larger sample sizes; and clinical interventions trials, to minimize the risk of false positives and confounding factors influencing the results.

Keywords: Central Obesity; Dietary Interventions; Low-Fat; Low-Carbohydrate.

Introduction

Obesity is a major public health and economic problem of global significance [1], and is of grave concern in the Asia-Pacific region, where there is a genetic predisposition to metabolic abnormalities leading to central adiposity [2]. Coincident with the high rates of central obesity in these areas, the prevalence of chronic diseases such as type 2 diabetes, cancer, fatty liver disease, hypertension and cardiovascular diseases (CVD) is also escalating [3].

In humans, studies have failed to find any mutant gene to be a unique 'obesity gene' [4], with multiple factors involving the actions of numerous polymorphic gene products causing obesity.

Loss-of-function mutations in B2 Andregenic receptor gene (ADRB2) which regulates lipolysis and energy expenditure [5], neuropeptide Y (NPY) gene [6] which regulates anabolic processes, genes which regulate catabolic processes like melanocortin4 receptor (MC4R) [7], hormone pro-opiomelanocortin (POMC) [8] and proprotein convertase 1 (PC1) [4], as well as genes involved in taste preference (Taste 2 receptors [T2Rs]) [9] lead to increased food intake, central obesity, and hyperinsulinemia.

Gene-environment (GXE) interactions also play a significant role in the epidemic of obesity via the modifications in DNA methylation patterns [10]. Thus, apart from genetic mutations at the DNA sequence level, epigenetic factors also play a defin-

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ing role in weight gain which is clearly evident from modern day sedentary lifestyle. Epigenetic influences include the intrauterine atmosphere [11], such as maternal genes, maternal BMI, maternal smoking, maternal alcohol and drug use, exercise during pregnancy, paternal genes as well as diet and lifestyle during early and later development [10] which cause variations in birth weight and lead to the onset of central adiposity.

This review presents some of the nutritional factors related to obesity that could modulate gene expression by affecting obesity-prone epigenetic mechanisms. Understanding these interventions could prevent unhealthy diets and personalize treatments to combat obesity.

Dietary Interventions

Reducing calorie intake

An average calorie intake of 2000 kcal per day meets the American Heart Association 2006 Diet and Lifestyle Recommendations [12], which includes a ratio of 55-60 percent of calories from carbohydrates with less than 10 percent of carbohydrates coming from simple monosaccharide sugars, 20-30 percent of calories from fats with less than 7 percent coming from saturated fats and none from trans fats and about 15-20 percent of calories from proteins. This ratio may vary based on individual needs to maintain or lose weight, as well as daily energy expenditure. Controlling portion size is important in maintaining a healthy calorie intake, with large portions leading to increased energy intakes over the day which could be a potential contributor to obesity [13].

Several dietary regimens with varying macronutrients and total calorie composition are used in an effort to combat obesity, such as Low-calorie diets (LCD), Low-fat diets, Low-carbohydrate diets and Very low-calorie diets (VLCD) [14]. A randomized, controlled intervention trial [15] which compared the effects of a low-calorie (LC) diet and a very low-calorie-ketogenic (VLCK) diet among 53 obese subjects over a one year period, concluded that a VLCK diet was significantly more effective (p< 0.0001) in inducing weight loss, compared with a standard LC diet. Very Low Calorie Diets, which have an energy content of 200–800 kcal/day, have been proven to be highly efficient in inducing weight loss. However, these diets are recommended for short periods of two-four months, as there are significant adverse events such as electrolyte imbalance, low blood pressure, asthenia, headaches and increased risk of gallstones [14].

A stratified randomized study at the Philadelphia Veterans Affairs Medical Center [16], on 132 obese subjects who were randomly assigned to either a low-carbohydrate or a low-fat diet for a 6 month period, observed greater weight loss on a carbohydrate-restricted diet than on a fat-restricted diet. The researcher suggested that this could reflect a greater reduction in overall calorie intake, rather than a direct effect of macronutrient composition. The findings of this study are further limited as it is unclear whether these benefits extend beyond six months and the high dropout rate affected the results. Furthermore, the small overall weight loss indicated that both diet groups maintained a low dietary adherence.

Reducing dietary fats: Reduction of fat intake has for several

decades been the conventional approach for weight control. A recent systematic review based on 28 intervention trials, by Bray and Popkin (1998) [17], concluded that dietary fat plays an important role in human obesity, with a reduction of 10 percent in the fat proportion associated with a reduction in weight of 16 g/day. However, an editorial by Willet (1998) [18] pointed out the limitations in the findings of Bray and Poplin (1998) [17], such as the hypothesized association between reduction of fat and weight loss was not significant (P = 0.05). As Bray and Popkin (1998)[17] acknowledged, most of the studies analyzed had a short duration of only a few weeks, and long-term trials beyond 6 months did not show a continued decline in body weight. Willet (1998) [18] further noted that a 1 year long study by Knopp et al., (1997) [19] had been omitted from their analysis; this showed no differences in weight change among subjects randomly assigned to 1 of 4 levels of fat intake, which is at odds with the conclusions of the meta-analysis.

Hence, it is important to determine the long-term effects of dietary fat on adiposity. Findings based on inconclusive data have led to reducing fat in the diet and increasing carbohydrates, which promotes the storage of dietary fat as body fat and leads to increased obesity [20].

Under ad libitum conditions, the high energy density of fatty foods results in a weak satiating effect for the energy eaten, which coupled with its high palatability, promotes passive overconsumption leading to weight gain [21]. With this in mind, a dietary intervention by a Finnish Diabetes Prevention Study [22] was planned to encourage replacing fat with dietary polysaccharide fiber, which may increase satiation directly. This study, involving 522 middle-aged, overweight adults, recorded that a high fiber diet was associated with weight loss more than a high fat diet. However, this study wasn't conclusive as it involved a lifestyle intervention with increased exercise, as well as errors due to recording bias especially as obese people are known to be prone to dietary under-reporting, both of which could be confounding variables.

Reducing dietary carbohydrates: Unlike polysaccharides, like starch and fibres, monosaccharide sugars are strongly associated with increased central adiposity. A randomized controlled multi-centre trial by Saris et al., (2000) [23] compared the carbohydrate types and found a relative weight loss of 1.7 kg in the high sugar diet and 2.6 kg in the high starch diet compared to the high fat diet (both statistically significant). However, the difference between carbohydrate types was not significant. This could be partly due to the hedonistic value and low satiety effect of sugars, which may lead to overconsumption. Hence, there is a need to consider the impact of sugar foods and drinks on central obesity.

An educational intervention program conducted by James et al., (2004) [24] associated a modest reduction in the consumption of carbonated drinks in the intervention group with a decrease of 0.2 percent in the BMI, for 644 children aged 7-11 years over a period of one year. Response bias was considered a major limitation in this study as drink diaries were not maintained by the subjects which raised doubts about the dietary data, and the randomization design may have been contaminated by transfer of knowledge between the participating schools.

The strongest association has been seen in the Planet Health Study by Ludwig et al., (2001) [25], among 548 children (12 years

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old) which reported a significant association between weight gain and soft drink consumption, estimating that a single serving was associated with a gain in BMI of 0.24 kg/m2 over 19 months (P =0.03) and a 60 percent increase in odds of obesity. While this study has widely influenced public opinion, it has been criticized for using raw BMI rather than BMI z-score, which is the preferred measure in children. The regression analysis adjusted for potentially confounding variables, such as baseline BMI, demographics, diet and lifestyle, doesn't account for dietary components that may influence weight, including milk, fruits, vegetables, whole grains and fiber.

Positive associations of carbonated sugar drinks with weight status may be more likely in different populations, including gender and ethnic groups [26]. For example, the Healthy Worker Project [27] among 3552 American adults, reported that women consuming one serving per week of soda were 0.21 kg heavier than non-consumers (P =0.03), but men consuming one serving were not significantly heavier (P =0.13)

Glycemic index

High carbohydrate, low Glycemic index (GI) foods, such as non-starchy vegetables, legumes, and fruits, increase cholecystokinin secretion and induce greater post-meal satiation, as well as promote fat oxidation and thus, decrease adiposity [28].

A study by Spieth et al., (2000) [28] among 107 obese children over 4 months, found that low GI diets may be more effective than reduced-fat diets in treating central adiposity. There were several limitations to this study, such as lack of diet records as diet was not monitored, short trial period (4 months), as well as presence of confounding variables like selection bias as participants were not formally randomized.

Animal model studies have the advantages of allowing long-term trials, and providing insight on the mechanism involved. A 32 week study by Pawlak et al., (2006) [29] on groups of rats fed high GI diets and low GI diets, found that the total body fat gained was significantly (40 percent) higher in the high-GI group (P < 0.05). Overall, current studies suggests an inverse association between GI and body weight, but long term human trials with changes in body weight are needed before definitive conclusions can be made.

Increased Plant Based Diet

Despite numerous studies examining the influence of dietary patterns, uncertainties remain with several studies [30] advocating that a high protein and low-carbohydrate diet promote weight loss and prevent obesity (for example, the Atkins diet). A randomized dietary intervention study [31] among 65 healthy, overweight and obese subjects (50 women, 15 men, aged 18 ± 55 y) over six months observed that the high-protein (protein at 25 percent of total energy) induces a larger weight loss in central adiposity than the high-carbohydrate (protein at 12 percent of total energy). However, this study is not conclusive as the long term health implications a protein-rich diet may have, such as osteoporosis, kidney function and colonic cancers, has not been evaluated.

The findings from several controlled trials do not support that the Atkins diet is effective beyond 6 months. For example, a randomized trial by Foster et al., (2003) [32] concluded that while a low-carbohydrate diet produced a greater weight loss than a conventional diet for the first six months, the differences were not significant at one year.

A National Health and Nutrition Examination Survey [33] among US adults over five years showed that higher intake of meat was associated with higher BMI and waist circumference, whereas intake of vegetables and fruits was inversely associated with BMI (P<0.05). The positive association between meat and obesity remained significant even after controlling for vegetables and fruits. The large sample size of the nationally representative data is a strong advantage; however the findings are limited by possible measurement error, as only 1-2 24 h dietary recalls were collected.

A Health Study [34] among 74,063 healthy female nurses aged 38-63 y over a 12 year follow-up, observed that those with the largest increase in plant based dietary intake had a 24 percent of lower risk of becoming obese (BMIZ-30 kg/m2) compared with those who had the largest decrease in intake. However, major drawbacks to this study are response bias, as the measurements were self-reported, and dietary data, as a change in diet (highly likely if participants perceive themselves as overweight during the 12 year follow up period) could lead to underestimation of the findings.

Dietary Interventions to Regulate Genetic Factors

Several dietary interventions [35, 36, 37] have been used to regulate adipose cytokines such as interleukin 6 (IL-6) [38], tumor necrosis factor α (TNFα) [38] and C-reactive protein [39] which are associated with metabolic disorders causing central obesity. Hypocaloric diets have proven effective [36, 37] but due to the dangerous side effects from prolonged use, there is increased focus on alternative dietary intervention, such as Mediterranean diets [40, 41, 42] to reduce the serum concentration of these biomarkers.

The Attica study [43], which included 1,514 men and 1,528 women from Attica, Greece concluded that adherence to a Mediterranean diet was associated with a reduction in the concentrations of these obesity-related inflammatory biomarkers. Further, a review by James et al., (2000) [44], determined that the increased levels of omega-3 polyunsaturated fatty acids (PUFA) of Mediterranean diets is instrumental in reducing obesity. However, there is a need for more long-term human studies with placebo-controlled, double-blinded RCTs to confirm the efficacy of increasing omega-3 intake to combat obesity.

Evidence-based recommendations

Several studies [45, 46] have shown that there is a tendency for under-reporting of energy intake, particularly in those who are overweight or obese. This reporting bias which diminishes the validity of the data, can be reduced by measuring the subject's body statistics and dietary adherence instead of relying on self-reported data.

Inadequate adjustment of confounding variables (for example, baseline BMI, ethnicity, baseline diet, misreporting, and physical activity) during statistical analysis and variation between studies in adjusting for these factors weakens the ability to compare results.

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The assessment of energy intake as well as energy expenditure (by physical activity) is important when studying weight change and may help to adjust for confounding resulting from under-reporting.

Conclusions

Despite the large number of studies on this topic, methodological weaknesses due to inconsistencies in study design, statistical analysis and interpretation result in inconclusive findings which cannot determine whether specified diet and lifestyle factors have contributed to weight change. Particular drawbacks in the evidence base are below:

•   Insufficient long-term interventions due to attrition bias or low follow ups.

•   Unreliable methodology design, such as low sample size and measurement errors, may result in type II error. Improvements in study designs, such as recognizing and adjusting for confounders in cross-sectional studies and longitudinal studies, may yield results consistent with cohort studies. Intervention studies are the strongest form of evidence as they infer causality. However there are several drawbacks such as difficulties in ensuring comparability of groups at baseline, compliance in the intervention group, non-contamination of the control group and adequate monitoring of diet and lifestyle during the trial.

•   Underpowered studies, where no conclusions can be drawn.

•   The possibility of a publication bias towards positive studies, with null studies often remaining unpublished, results in an overestimation of positive effects.

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