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The new total Western diet for rodents does not induce an overweight phenotype or alter parameters of metabolic syndrome in mice

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ARTICLE INFO

Article history:
Received 1 March 2016
Revised 25 May 2016
Accepted 1 June 2016

Keywords:
Mouse
Western diet
Macronutrient
Micronutrient
Metabolic disorder
Body composition
Liver triglycerides

ABSTRACT

In this study, we determined the impact of the total Western diet (TWD) for rodents and its macro- and micronutrient components on weight gain and biomarkers of metabolic function in mice compared to a 45% fat diet-induced obesity (DIO) diet and the standard AIN93G diet. We hypothesized that mice fed the TWD would have increased body fat with indicators of metabolic syndrome similar to mice consuming the DIO diet. As expected, DIO-fed mice acquired a metabolic syndrome phenotype typified by increased energy intake, increased body weight gain, increased fat mass, higher fasting glucose, impaired glucose tolerance, and higher plasma leptin relative to the AIN93G diet. Mice fed a macronutrient-modified (MM) diet (with standard vitamin and mineral composition) had a similar response, albeit to a lesser degree than mice fed the DIO diet. Mice fed a vitamin- and mineral-modified diet (with standard macronutrient composition) were not different from mice fed the AIN93G diet. Surprisingly, the TWD (with modified macronutrients, vitamins and minerals) did not significantly affect any of these parameters, despite the fact that the TWD macronutrient profile was identical to the MM diet. These data suggest that, in the context of the TWD, vitamin and mineral intakes in mice that reflect a Western dietary pattern inhibit the hyperphagia and resulting increased weight gain associated with the higher fat content of the TWD. In conclusion, these observations underscore the need to consider the influence of micronutrient intakes in pre-clinical models of obesity and metabolic syndrome.

Abbreviations: AIN, American Institute of Nutrition; AUC, area under the curve; DIO, diet-induced obesity; HOMA, homeostatic model assessment; IL-6, interleukin 6; MM, macronutrient-modified; MRI, magnetic resonance imaging; TWD, total Western diet; VMM, vitamin- and mineral-modified.

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http://dx.doi.org/10.1016/j.nutres.2016.06.002
0271-5317/

1. Introduction

The Western dietary pattern is thought to be involved in the etiology of several chronic diseases, including type II diabetes [1–3], non-alcoholic fatty liver disease [4], cardiovascular disease [5,6], and several cancers [3,7,8]. While it is common to implicate one dietary component as causing these diseases (such as an excess in saturated fat or a deficiency in vitamin D), their initiation and development is multifactorial and arises from interactions between many components. The Western diet is typified by high intakes of processed foods, added sugars, and refined grains coincident with comparatively low intakes of fruits, vegetables, and fish. As a result, this unbalanced diet contains excess amounts of energy, simple sugars, and sodium with an insufficient supply of fiber. In addition, some essential vitamins and minerals are consumed at levels below recommendations [1,3,9]. As a result, key nutritional factors increase risk of chronic disease, including such factors as glycemic load, fatty acid composition, macronutrient composition, micronutrient density, acid–base balance, the ratio of sodium to potassium, and the fiber content [9]. Therefore, experimental diets that are used in rodent studies to evaluate the influence of Western nutrition on health maintenance and disease risk should reproduce these basic features.

Researchers routinely employ standard diets that are formulated with respect to diet concentrations of macro- and micronutrients to sustain rodent health, such as the American Institute of Nutrition (AIN) diets [10]. Relative to diets consumed by average Americans, AIN93G/M diets are enriched in micronutrients, include more complex carbohydrates, contain less total and saturated fat, and have a lower n6-to-n3 ratio [11]. Commercial high fat diet formulations, often referred to as "Western diets," can be used to induce obesity in mice. These well-defined formulations allow for high reproducibility, but the fat content of these diets is at least 10% higher on a calorie basis that the average American diet. Currently, the most commonly used diet-induced obesity (DIO) diets contain 45% to 60% of energy as fat, most of which comes from lard. Consequently, these diets are significantly higher in saturated, monounsaturated and polyunsaturated fatty acids than the actual diets consumed in the US. Like the AIN93 diet [10], the macronutrient content of these high-fat diets is formulated to promote animal health. However, it is critical to note that these purified, standard rodent diets are not relevant to most human diets because their nutrient profile does not emulate typical dietary intakes, especially for populations that frequently consume energy dense, nutrient poor foods [11].

Importantly, none of the traditional approaches for modeling typical Western nutrition has appropriately considered the contribution of micronutrient intakes reflecting the Western dietary pattern in their disease models. In a study that partially addressed this problem, Newmark et al employed a nutrient density approach to partially model a Western type diet for colon cancer studies [12]. Calcium, vitamin D and contributors to one-carbon metabolism were provided to mice at the same mass per kcal as at risk human populations, emulating the lower one-fourth of the average American intakes for each of these micronutrients. Thus, intakes of these micronutrients could be provided at amounts analogous to human intakes on an energy density basis [13,14]. In another study that also employed the concept of translating human nutritional patterns to mouse diets based on energy density, Weldon and Whelan designed a diet formulation that contained nearly the same macronutrient distribution and percentage of saturated, monounsaturated and polyunsaturated fatty acids as the total Western diet (TWD) to investigate linoleic acid metabolism. However, unlike the TWD, long-chain polyunsaturated fatty acids were included in the diet formulation [15]. In the same investigation, it was also shown that nutrient density is the most appropriate method to translate human micronutrient intakes to rodents. However, our study is the first to consider the contribution of all the major macro-and micronutrients provided at levels that emulate the overall US dietary pattern.

To address this resource gap, our research team developed the new TWD for rodents with energy and nutrient profiles that emulate a typical Western diet using available US survey data (NHANES). The new TWD was formulated using a nutrient density approach, as devised by Newmark et al, and described in detail previously [11]. The TWD models median nutrient intakes for Americans and, thus, may be useful as a translational basal diet in preclinical animal studies investigating dietary interventions for prevention of various conditions, such as cancer, cardiovascular disease, metabolic syndrome, etc.

In this study, we hypothesized that mice consuming the TWD would have increased body fat with indicators of metabolic syndrome similar to mice consuming a typical 45% fat DIO diet. Our overall objective was to compare the impact of the TWD to that of a 45% fat DIO diet and the standard AIN93G diet on various health parameters, including weight gain, insulin resistance, and systemic inflammation in mice. Importantly, to determine the relative importance of macro- or micronutrients on health status, a secondary objective was to compare versions of the TWD that were formulated to mimic Western dietary intakes for either macro- or micronutrients only. The experimental approach employed to address these objectives was a standard feeding study in male C57BL/6J mice with five dietary treatments (described in detail below) with periodic assessment of several physiological parameters that are indicative of excess weight gain and development of metabolic syndrome, including food and energy intakes, body weight gain, body composition, fasting glucose and glucose tolerance and terminal assessment of insulin and various other hormones related to metabolic syndrome and/or systemic inflammation.

2. Methods and materials

2.1. *Animals*

The Utah State University Institutional Animal Care and Use Committee approved all procedures for the handling of mice (protocol #2063). Male C57BL/6J mice were obtained from Jackson Laboratory (Bar Harbor, ME) and housed in the AAALAC-approved Laboratory Animal Research Center. Mice