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Low glycemic load diets protect against metabolic syndrome and Type 2 diabetes mellitus in the male Nile rat

Julia Bolsinger, Michelle Landstrom, Andrzej Pronczuk, Andrew Auerbach, KC Hayes*

Foster Biomedical Research Laboratory, Brandeis University, 415 South Street, Waltham, MA 02454, USA

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Abstract

Background: Dietary modification helps prevent and manage Metabolic Syndrome (MetS) and Type 2 Diabetes Mellitus (T2DM) in humans and Nile rats. Specifically fibrous legumes, like lentils, benefit humans, but whether this reflects a specific change in the Glycemic Load (GLoad) remains controversial. Accordingly, low-GLoad foods were tested in the glucose-sensitive Nile rat.
Methods: 131 male Nile rats aged 3 weeks to 15 months were challenged during four experiments with 15 dietary exposures that varied Glycemic Index (GI, 36–88), GLoad (102–305/2000 kcal), and cumulative GLoad (*Cum* GLoad=days×GLoad, 181–537g total glucose).
Results: Lentil diets with low GLoads (102, 202) prevented, delayed, reduced, even reversed the progress of MetS and T2DM as measured by blood glucose (fasting, random, and oral glucose tolerance test) and plasma lipid parameters (plasma cholesterol and triglycerides) plus necropsy findings (liver and kidney pathology plus adipose reserves). The benefit from lentils exceeded dietary factors such as macronutrient composition (%Energy from carbohydrate:fat:protein, between 70:10:20 to 40:40:20), total fiber (0–24%), or dietary caloric density (2.9–4.7 kcal/g). The benefit of a low GLoad applied equally to rats inherently *susceptible* or *resistant* to T2DM, based on random glucose above or below 75 mg/dl, respectively, during interventions of 7-17 weeks.
Conclusions: Measuring total food intake and the novel concept of *Cum* GLoad during growth generated strong correlations (up to r=0.93) between *Cum* GLoad and parameters of MetS and T2DM, especially during sexual maturation. The present experiments confirm the applicability of male Nile rats to diet-induced human T2DM, and suggest dietary compositions to deter MetS and T2DM in humans.

Keywords: Diabetes; Metabolic syndrome; Glycemic load; Glycemic index; Nile rat; Carbohydrate; Insulin resistance

1. Background

The increasing worldwide prevalence of metabolic diseases such as diabetes, metabolic syndrome (MetS), and related long-term consequences continues to pose a challenge to health care systems and professionals [1]. Diet is considered a major environmental insult contributing to the increase in metabolic disease incidence, especially in younger individuals. An animal model realistically mimicking most features of human diabetes would be an important asset for better understanding the diet x disease interaction, with the potential for indicating further dietary guidelines for prevention and management of the disease [2]. Determining the relative influence of dietary fiber, caloric density, macronutrient composition, Glycemic Index (GI), and Glycemic Load (GLoad) on T2DM and related metabolic parameters in such a model would offer an advantage over more costly, long-term human studies. The growing world population of subjects with diabetes and pre-diabetes would be well served by such insight.

The male Nile rat (*Arvicanthis niloticus)* is proving to be an effective model for the study of T2DM and MetS, expressing a natural genetic susceptibility to these conditions and their modification by diet. The pathogenesis, as well as the response to nutritional manipulation, conforms to the human disease [3–6]. Preliminary studies in Nile rats demonstrated that neutralizing the GLoad of a standard high carbohydrate (hiCHO) diet by adding Acarbose™ or enhancing insulin sensitivity by supplementing Metformin™ exerted significant anti-diabetic effects in the model, further emphasizing the similarities between Nile rat and human metabolism (unpublished data). Even as new classes of oral anti-diabetic drugs are being developed and designed [7], establishing a diet-based approach to delay or completely prevent the need for such anti-diabetic medication would be a useful adjunct for individuals suffering from T2DM or impaired glucose tolerance.

Abbreviations: CHO, carbohydrate; *Cum* GLoad, cumulative Glycemic Load; F, fiber; FBG, fasting blood glucose; GI, Glycemic Index; GLoad, Glycemic Load; hiCHO, high carbohydrate; HOMA-IR, homeostatic model assessment of insulin resistance; Ltl, lentil; modCHO, moderate carbohydrate; MetS, Metabolic Syndrome; OGTT, oral glucose tolerance test; RBG, random blood glucose; T2DM, Type 2 diabetes mellitus.

* Corresponding author.
E-mail addresses: bolsinger.julia@gmail.com (J. Bolsinger), mlandstrom@brandeis.edu (M. Landstrom), pronczuk@brandeis.edu (A. Pronczuk), aa1991@brandeis.edu (A. Auerbach), kchayes@brandeis.edu (K.C. Hayes).

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Table 1
Diet composition summary for male Nile rats in Expts 1, 2, 3, and 4

Diet name	hiCHO-Ltl-20%F	modCHO-0%F	hiCHO-0%F	hiCHO-16%F	hiCHO-Ltl-6%F	hiCHO-24%F
Expt # (Diet #)	1, 3 (Diet 112)	3 (Diet 77)	2, 3, 4 (Diet 73 MB)	4 (Diet 73MBF)	2, 4 (Diet 106A)	2 (Diet 120)
CHO:Fat:Prot (% Energy)	57:20:23	40:40:20	70:10:20	70:10:20	74:9:17	70:10:20
kcal/g	3.1	4.7	3.9	3.2	3.4	2.9
Glycemic Index	36	88	85	85	55	88
GLoad/2000 kcal	102	170	304	305	202	305
Ingredient	g/kg					
Green lentil flour (@ 89.0% solids for energy)	720 (641)	0	0	0	550 (490)	0
water and ash from lentil flour @ 11.0%	(79)	0	0	0	(61)	0
Methionine	3	0	0	0	0	0
Casein	0	120	100	83	4	75
Lactalbumin	0	120	100	83	4	75
Protein from lentil flour @ 24.6%	(177)	0	0	0	(135)	0
Dextrose	0	240	350	292	0	265
Cornstarch *	60	236	347	290	370	265
available CHO from cornstarch @ 90%	(54)	(212)	(312)	(261)	(333)	(238)
total CHO from lentil flour@ 63.4%	(456)	0	0	0	(349)	0
available CHO from lentil flour @ 52.6%	(379)	0	0	0	(289)	0
fiber from lentil flour @ 10.7% (of flour)	(77)	0	0	0	(60)	0
Psyllium Husks	20	0	0	0	0	0
Cellulose	100	0	0	165	0	242
Fat						
Margarine B (fat only) †	60	214	45	37	27	33
Fat from lentil flour @ 1.1%	(8)	0	0	0	(6)	0
Mineral mix (Ausman-Hayes)	28	53	44	37	34	33
Vitamin mix (Hayes-Cathcart)	7	13	11	9	8	8
Choline chloride	3	3	3	3	3	3
Cholesterol 0.06%	0	0.4 (+0.2) [1]	0.6	0.6	0.6	0.6

* 60 g cornstarch added to 800 ml water to form gel.

† Margarine B composition: 24% milk fat+40% tallow+20% chicken fat+16% soybean oil.

[1] Cholesterol contributed by Margarine B.

Reducing the GI and/or GLoad, or the addition of cereal fiber [8–10], or citrus or legume fibers [11], is associated with reduced risk for MetS and T2DM in humans. A recent meta-analysis of 14 studies suggests that GI and GLoad of foods are meaningful predictors of T2DM risk in younger subjects when the diet GLoad data are updated periodically [10]. Similar results have been reported for children with MetS [12] or for cardiovascular risk [13]. However, other epidemiological studies that included older subjects or relied on a single baseline nutritional dataset, found GI and GLoad to be poorly predictive risk factors [10,14]. Calorie restriction, another means of reducing carbohydrate (CHO) intake, is known to have positive effects on T2DM, but is more readily achieved in humans by reducing nutrient density than by limiting food intake [15]. In this regard dietary fiber has proved beneficial, including large global clinical trials focused on fruit and legume intake that improved blood glucose dynamics and other metabolic parameters [16–20].

Green lentils are rich in complex carbohydrates and fiber, providing an easily accessible, low-glycemic index food. They also provide phytosterols and polyphenols [21], factors known to exert additional beneficial effects on plasma lipids and energy metabolism [22–25]. Polyphenol-rich fruit juice has specifically been demonstrated to protect the Nile rat against T2DM [6]. Both rodent and human studies have shown anti-diabetic effects of green lentils [26,27]. Accordingly, green lentils were utilized in a series of four Nile rat experiments. Six diets plus lab chow were designed to vary the GI, GLoad, caloric density, macronutrient composition, and dietary fiber content. Objectives were to modulate the dietary GLoad for its effects on MetS and T2DM, to compare the relevance of the model to the human experience, and to identify further avenues for diabetes management through dietary modification in humans.

2. Methods

2.1. Animals and diets

A total of 131 male wild-type Nile rats from the Brandeis University breeding colony were fed special diets in four different experiments to test the hypothesis that GLoad would effectively predict T2DM outcomes from weaning into maturity. Males are studied because they are much more sensitive to T2DM than females for ill-defined reasons. It may be growth rate, and it likely reflects gender and/or testosterone-estrogen differences. Females are diet-sensitive for the first 5–6 weeks of life, but become "resistant" as they sexually mature (estrogen/progesterone). Also, males grow at a more rapid rate between 3–10 weeks of age, and even among males the individuals that grow more rapidly (gain the most weight) develop the most severe diabetes, in part because they consume more calories and, thus, process more glucose. Females eventually express the diabetes, but it can take up to a year, which is an unrealistic experimental time frame.

Diets were modified to control nutritional parameters such as macronutrient composition (% Energy from CHO:fat:protein), caloric density, fiber content (F), glycemic index (GI) and glycemic load (GLoad), and the newly introduced measure of cumulative glycemic load (*Cum* GLoad). Diet descriptors and details of formulation are provided in Table 1. Metabolic effects were assessed with three measures of blood glucose, plasma insulin and lipids, food intake and efficiency, as well as body and organ weights. Nile rats with a wide range of starting ages (between 3 weeks [weanling] and 15 months [mature adults]) were evaluated, and intervention periods lasted between 3 weeks and 17 weeks. All experiments and procedures were approved by the Brandeis University Institutional Animal Care and Use Committee (IACUC).

2.2. Hyperglycemia: RBG is better indicator than FBG

In these experiments elevated blood glucose (hyperglycemia) was ascertained by impaired fasting blood glucose (FBG), random blood glucose (RBG), or a 2-h oral glucose tolerance test (OGTT), typically measured in the same rat. Extensive experimentation in more than 1300 young male Nile rats in the past 3 years ([5] and unpublished data) has determined that the normal FBG is 40–60 mg/dl with pre-diabetes indicated by FBG rising into the 60–80 mg/dl range. On the