Immune Health and Food: The good, the bad, and the ugly

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Overview

- What is celiac disease
- Why is the celiac model important
  - Early infections
  - Seasonality of birth
  - GFD effect on microbiome

- Food's impact on the gut in general
  - Negative impact
  - Positive

Celiac Disease

- Historically
  - Thought celiac disease was rare
  - Childhood disorder
  - “grew out of”

- Today we understand:
  - Autoimmune disease that is genetic
  - Affects 1% of the population (Estimated 3.1 million Americans)
  - Primarily affects the gastrointestinal tract causing
    - Villous atrophy
    - Chronic inflammation
  - Can affect the skin; Dermatitis Hepetiformis (DH)
    - Itchy inflamed rash
  - If untreated – associated with the development of other disease such as diabetes, hypothyroidism, cancers, downs syndrome

Infections and development of CD

- Infections in early childhood

- 10 infections before age 10 >> 32% higher risk of Celiac
  - 72,921 children born between 2000 and 2009
  - 581 diagnosed with celiac by 2013
  - Parental questionnaire
    - Gathered data on minor infections as well as hospitalizations
    - Risk increased with each additional infection

Birth Seasonality

- Season of birth related to celiac diagnosis
  - Compared records from 2 Italian hospitals from 2003 - 2010
  - 596 children diagnosed with celiac
  - 28% of individuals with celiac born in summer
  - 23% of general population born in summer

- Potential causes
  - Heat stress during pregnancy
  - Infants increased exposure to viruses in winter
  - Weaning and gluten introduction in winter with increased virus exposure

Celiac and Asthma

- Increased risk of asthma 1.6-fold in celiac disease
- Swedish Cohort study – followed from 1969 – 2008
  - 28,281 individuals with celiac
  - 140,295 controls –
  - matched for sex, age calendar period of study entry
  - Risk remained 5 years after diagnosis
  - Adjusted for smoking, BMI and C sections

- Additional 1.7-fold increase risk for:
  - Allergic conjunctivitis
  - Allergic rhinitis
  - Eczema

Celiac Disease: Systemic Autoimmune Disorder

+

Hadjivassiliou et al.
Lancet, Neuro 2010

Dermatitis Herpetiformis

Human TGs
B4-2
TG5
TG7
TG3
TG6
TG2
TG4
FXIIIa
TG1

+Gluten

Classic coeliac disease

Gliadin-specific CD4+ T cell
TCR
Activation
MHC II
Endocytosis
TG-specific B cell
Neurological dysfunction*
B-cell differentiation
TG–gliadin peptide complex
Plasma cell
Autoantibody production

Classic Celiac +
Manifestations in:
Lung, Liver,
Kidney,
Blood Vessels,
Placenta, etc.

Lane Hamilton Syndrome
IgA Nephropathy
MPGN
Cardiomyopathy, IHD
Fertility

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Inflammation and the Gut

- Intestine is an important gatekeeper
  - Tight cell junctions
  - Enteroendocrine cells functions
- Maintains balance between absorption of nutrients and elimination of “toxins”
  - Pro-inflammatory responses disrupts barrier and immune function
  - Bacteria to pass through junctions – increasing inflammatory response
- Disruption of this balance results increases
  - Infection
  - inflammation

Inflammation and the Gut

- Inflammation is a normal physiologic process
  - good thing when helping the body to heal

- BUT
- Chronic inflammation actually interrupts the normal healing process
- Chronic inflammation is associated with
  - Cardiovascular disease
  - Cancers (colon, gastric, esophageal, breast, gallbladder etc)
  - Diabetes
  - Dementia
  - Arthritis
  - Osteoporosis……

Persistent inflammation associated with CD

- Inflammation may exacerbate nutrient deficiencies in the GFD

Hallert et al (2002)

- Population 30 adults
- On diet for 8 to 12 years
- Reviewed both lab data and 4 day food diary
- **Results**
  - **Increased body weight**
    - Males increased 9.8 kg (from 70.4 to 79.2 kg)
    - Females increased 9.9 kg (from 62.1 to 71.0 kg)
  - **56% had signs of nutritional deficiency**

- **Increased homocysteine level – poor vitamin status**
  - Biopsy proven remission – villous recovery
- **Number of bread servings comparable to controls**

- **Shepard & Gibson (2012)**
  - Population 55 adults - On diet for more than 2 years
  - 50 newly diagnosed – followed for 12 months prospectively
  - Compared intake to Australian general population
  - **Results**
    - **Newly diagnosed and experienced GF women – deficient in thiamine, folate, Vit A, magnesium & calcium**
    - > 10% of men in both GF groups – deficient in thiamin, folate, vit A magnesium, calcium and iron
    - **Inadequate intake of folate, calcium, iron and zinc compared to general population**
    - **Number of starch servings decreased over first 12 months on diet**

Inflammation; negative effect on nutrients

- Iron absorption
  - Inflammation decreases iron absorption and metabolism
  - 36 – 76% of IBD patients have iron deficiency anemia
  - Inflammation associated with infections decrease iron absorption
    - Decrease absorption response to inflammatory cytokines

- Osteoporosis
  - Bone resorption and high fracture risk associated with
  - RA, IBD, celiac, cystic fibrosis, and chronic obstructive pulmonary disease
  - Association is independent of common risk factors of inactivity, low vitamin D, poor nutritional status and calcium intake
  - Association is linked to pro-inflammatory cytokines

Foods: negative association with inflammation

- Refined carbohydrates
  - Less fiber and more sugar increases inflammation
- Gluten exposure in celiac patients
  - Decrease of immune response regulators
- IBD risk factor – diet high in:
  - Sugar
  - Animal fat
- High saturated fat diet
  - Mouse model; high saturated fat diet was associated with;
    - Weight gain
    - Insulin resistance
    - Mesenteric fat inflammation
- Omega 6 fatty acids are pro- inflammatory
  - Increasing use of omega-6 fats in processed food for shelf stability

Environment: negative association with gut flora

- Gut microbiome associated with various cancers
  - Microbial interrelationship with inflammation
  - Specific microbiota associated with different cancers
    - H-pylori – gastric and esophageal
    - Decreased diversity – colorectal (decrease in protective bacteria)
    - Salmonella infection – gall bladder cancer

- Hygiene hypothesis
    - Older siblings associated with increased gut micro diversity
    - Increased bacterial diversity (p=0.03)
    - Bacterial richness (p=0.006)

- Antibiotic use
  - Decreases total diversity and richness
  - Effects persist long after treatment

Foods: negative association with microbiome

- Paleo diet – (not Paleolithic but modern adaptation of high protein – low carbohydrate)
  - Decreased microbes
  - Increased bilophila
    - Associated with increased bile production
    - Associated with increased inflammation and colitis in mice
- Gluten ingestion (general population – 10 subjects GFD 1 month)
  - Healthy gut bacteria decreased
  - Unhealthy bacteria increased – mirroring low fiber, simple carbohydrate intake changes
- Gluten ingestion (in celiac disease)
  - Intake associated with increased gut permeability
  - Increased inflammation
- Vitamin D deficiency
  - Deficiency associated with gut dysbiosis and inflammation

Foods – Negative effect on the microbiome

- Refined carbohydrates
- Fried foods – French fries
- Red meats; processed meats
- Margarine
- Soda; sweetened beverages
- **Actually – the GFD**

Standard Gluten Free Products

- Traditionally used starches not whole grain flours
- Typically use white rice, potato, tapioca and corn
- Additional ingredients
  - Added oils and fat (commonly palm oil for texture)
  - Added sugar
  - Added salt
  - Added gums for stability and moisture (guar, xanthum, cellulose)
  - Poor nutritional quality

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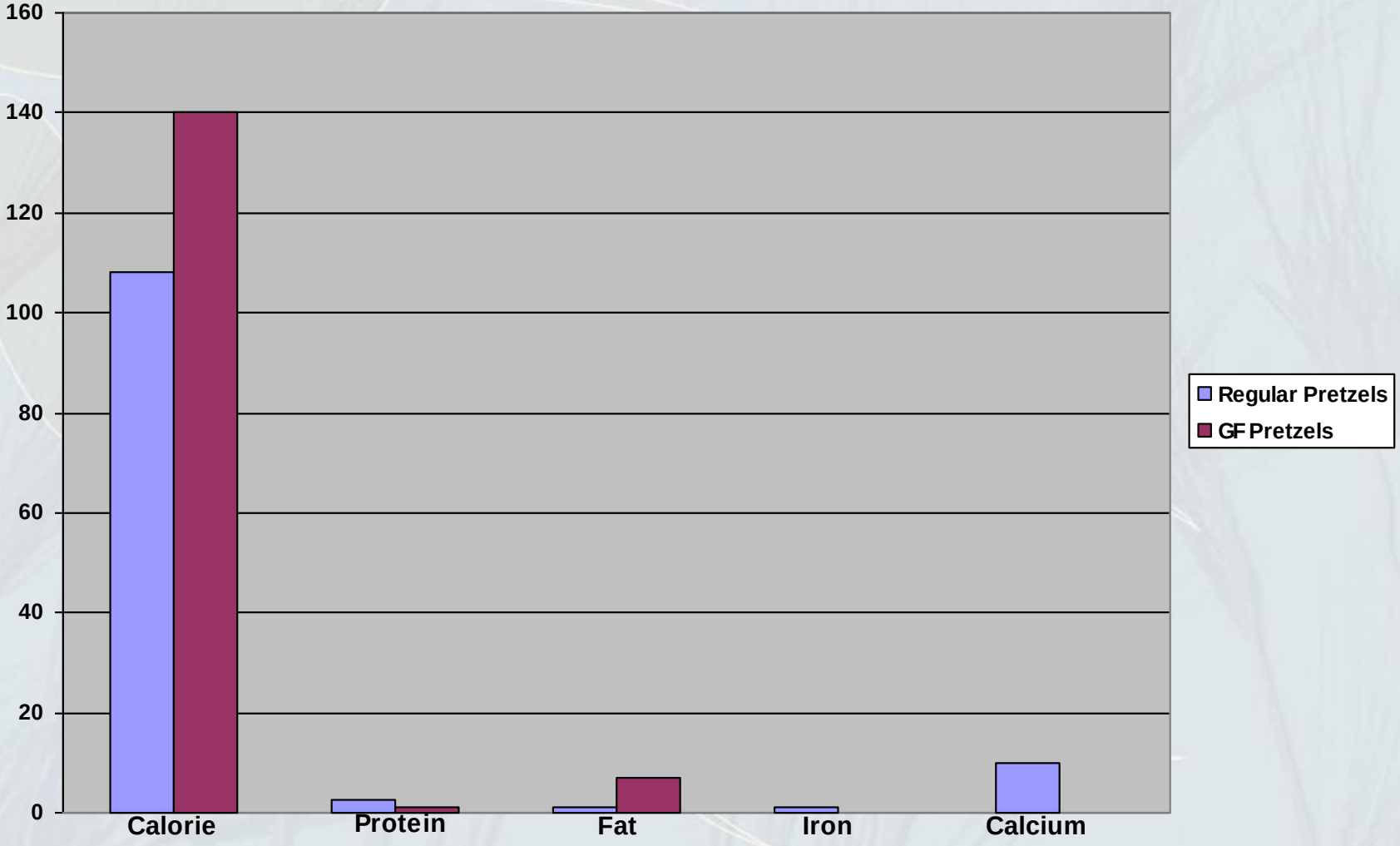
Comparison of Regular & GF Pretzels



Nutritional Deficiencies of Gluten-Free Diet

- Thompson, et al
  - Population 47 adults
  - Review of three day food intake records
  - Results:
  - RDA's:
    - Fibre: 46% females, 88% males
    - Calcium: 31% females, 63% males
    - Iron: 44% females, 100% males
  - Grain consumption below recommendations
    - **Majority of grain foods consumed were quick breads (donuts and muffins) followed by cold cereals and savory snacks**
    - **Rice was main side dish consumed**

» Thompson, 2005. Consumption Patterns of Americans, previously unreported data

Nutritional Deficiencies of Gluten-Free Diet

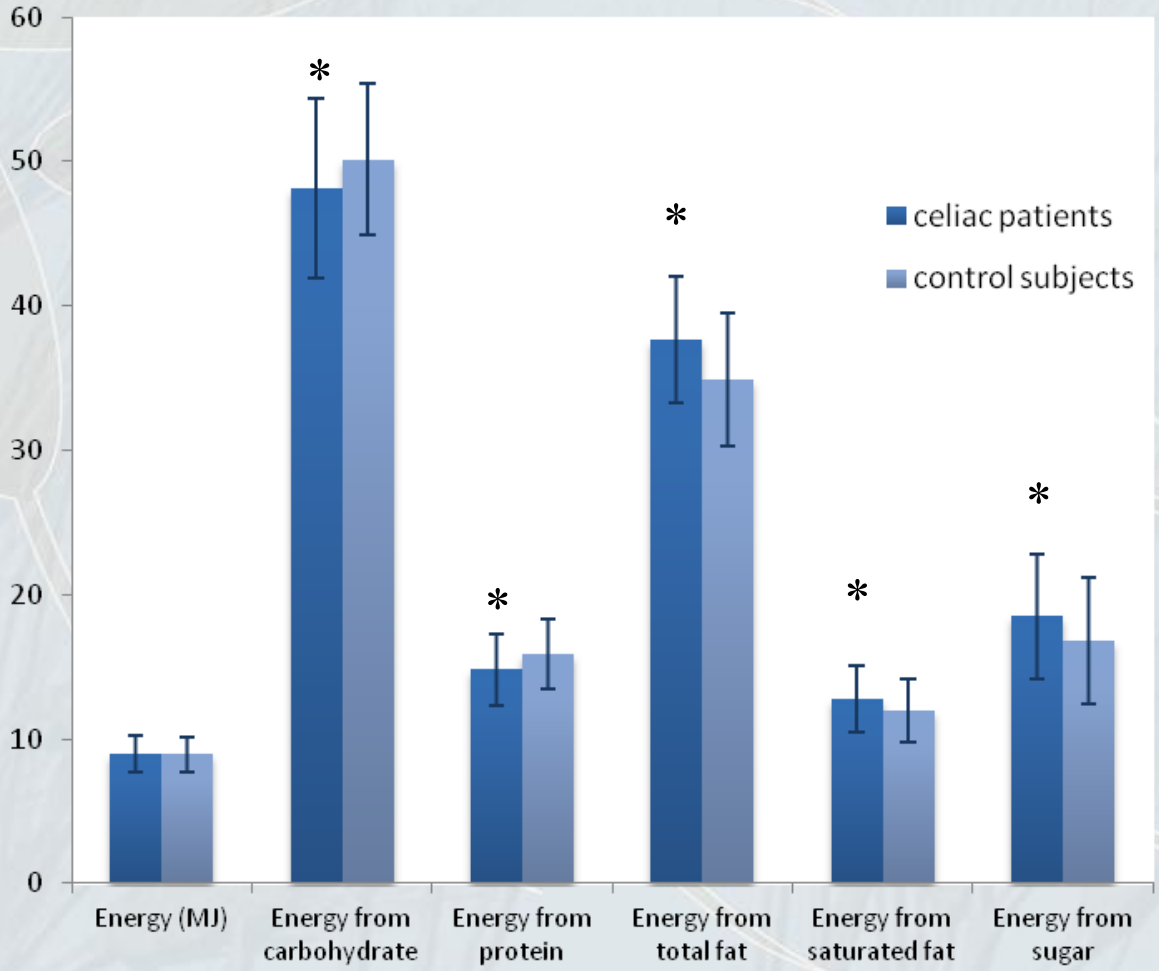
- Dickey:
  - Population: 371 diagnosed over ten year period
  - Compared BMI at diagnosis and at two year follow up
  - **Results:**
    - 4% underweight (BMI<18.5)
    - 57% normal BMI (18.5-24.9)
    - 39% overweight (BMI >25)
    - 13% of these were obese (BMI>30)
  - **Two year follow up:**
    - **Mean BMI rose from 24.4 to 25.9**
    - **Weight gain in 81%**
    - **82% of the initial overweight patients gained more**

Preliminary results from an ongoing Italian study

- 150 celiac patients from the Lombardy region (Northern Italy) in association with University of Milan Celiac Center;
- 150 healthy non-CD control subjects;
- Dietary habits recorded by means of a food frequency questionnaire (FFQ) and a 7-day weighed food record (7-d record).

Energy Comparison:

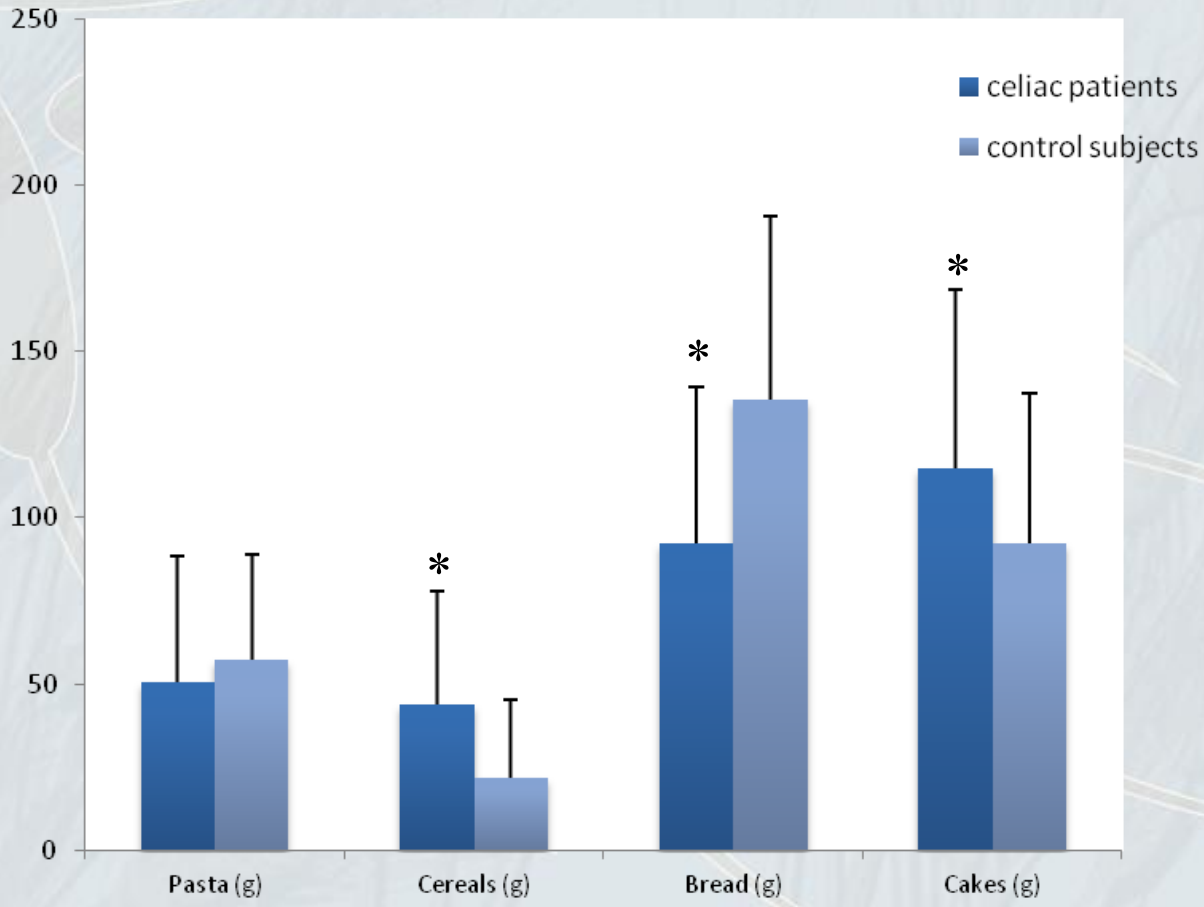
intake of celiac patients and control subjects: data from the 7-day records



- * Significantly different ($p < 0.05$) from control subjects.
- Mean ± SD

Grain Comparison:

intake of celiac patients and control subjects: data from the 7-day records



- * Significantly different ($p < 0.05$) from control subjects.
- Mean ± SD

- Similar intake of **calcium sodium, iron, zinc** and **phosphorus**.

Gluten-free version

- Less fiber
- Less whole grains

Nutrition Facts

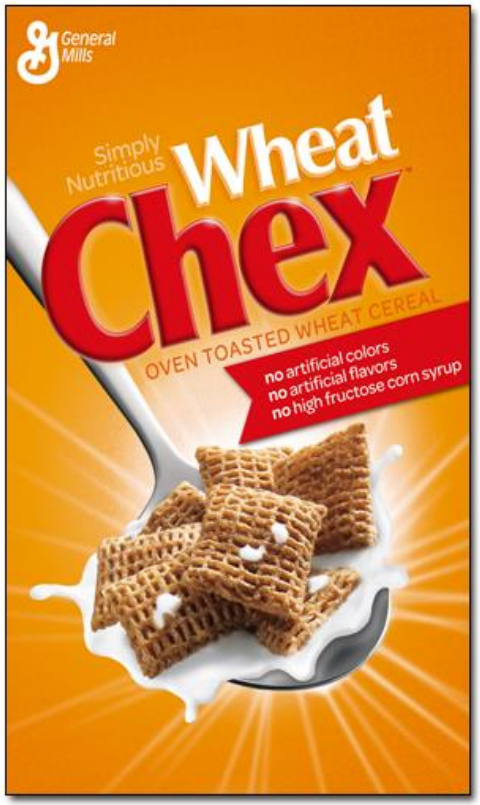
Serving Size 1 cup (27g)
Servings Per Container about 12

Amount Per Serving	Rice Chex	with ½ cup skim milk
Calories	100	140
Calories from Fat	5	5
	% Daily Value**	
Total Fat 0.5g*	1%	1%
Saturated Fat 0g	0%	0%
Trans Fat 0g		
Polyunsaturated Fat 0g		
Monounsaturated Fat 0g		
Cholesterol 0mg	0%	1%
Sodium 220mg	9%	12%
Potassium 50mg	1%	7%
Total Carbohydrate 23g	8%	10%
Dietary Fiber 1g	4%	4%
Sugars 2g		
Other Carbohydrate 21g		
Protein 2g		
Vitamin A	10%	15%
Vitamin C	10%	10%
Calcium	10%	25%
Iron	50%	50%
Vitamin D	10%	25%
Thiamin	25%	30%
Riboflavin	25%	35%
Niacin	25%	25%
Vitamin B_6	25%	25%
Folic Acid	50%	50%
Vitamin B_{12}	25%	35%
Phosphorus	4%	15%
Magnesium	2%	6%
Zinc	25%	30%

* Amount in cereal. A serving of cereal plus skim milk provides 0.5g total fat, less than 5mg cholesterol, 280mg sodium, 250mg potassium, 29g total carbohydrate (8g sugars), and 6g protein.

** Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:

	Calories	2,000	2,500
Total Fat	Less than	65g	80g
Sat Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Potassium		3,500mg	3,500mg
Total Carbohydrate		300g	375g
Dietary Fiber		25g	30g



Nutrition Facts

Serving Size ¾ cup (47g)
Servings Per Container About 8

Amount Per Serving	Wheat Chex	with ½ cup skim milk
Calories	160	200
Calories from Fat	10	10
	% Daily Value**	
Total Fat 1g*	1%	1%
Saturated Fat 0g	0%	0%
Trans Fat 0g		
Polyunsaturated Fat 0.5g		
Monounsaturated Fat 0g		
Cholesterol 0mg	0%	1%
Sodium 270mg	11%	14%
Potassium 170mg	5%	11%
Total Carbohydrate 39g	13%	15%
Dietary Fiber 6g	24%	24%
Soluble Fiber 1g		
Sugars 5g		
Other Carbohydrate 28g		
Protein 5g		
Vitamin A	10%	15%
Vitamin C	10%	10%
Calcium	10%	25%
Iron	80%	80%
Vitamin D	10%	25%
Thiamin	25%	30%
Riboflavin	25%	35%
Niacin	25%	25%
Vitamin B_6	25%	25%
Folic Acid	100%	100%
Vitamin B_{12}	25%	35%
Phosphorus	15%	30%
Magnesium	10%	15%
Zinc	35%	40%

* Amount in cereal. A serving of cereal plus skim milk provides 1g total fat, less than 5mg cholesterol, 330mg sodium, 380mg potassium, 45g total carbohydrate (10g sugars, 29g other carbohydrate), and 9g protein.

** Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:

	Calories	2,000	2,500
Total Fat	Less than	65g	80g
Sat Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Potassium		3,500mg	3,500mg
Total Carbohydrate		300g	375g
Dietary Fiber		25g	30g

Ingredients: Whole Grain Wheat, Sugar, Salt, Molasses. BHT Added to Preserve Freshness.

Vitamins and Minerals: Calcium Carbonate, Iron and Zinc (mineral nutrients), **Vitamin C** (sodium ascorbate), **A B Vitamin** (niacinamide), **Vitamin B_6** (pyridoxine hydrochloride), **Vitamin B_2** (riboflavin), **A B Vitamin** (folic acid), **Vitamin B_1** (thiamin mononitrate), **Vitamin A** (palmitate), **Vitamin B_{12}**, **Vitamin D_3**.

CONTAINS WHEAT INGREDIENTS.

DIST. BY GENERAL MILLS SALES, INC., MINNEAPOLIS, MN 55440 USA

F 3859660559 SSG 3869920559

May be mfg. under U.S. Pat. No. 7,021,525

Exchange: 2½ Starch

Based on Academy of Nutrition and Dietetics and American Diabetes Association criteria

This package is sold by weight, not by volume. You can be assured of proper weight even though some settling of contents normally occurs during shipment and handling.

Wheat Chex™ is not gluten free.

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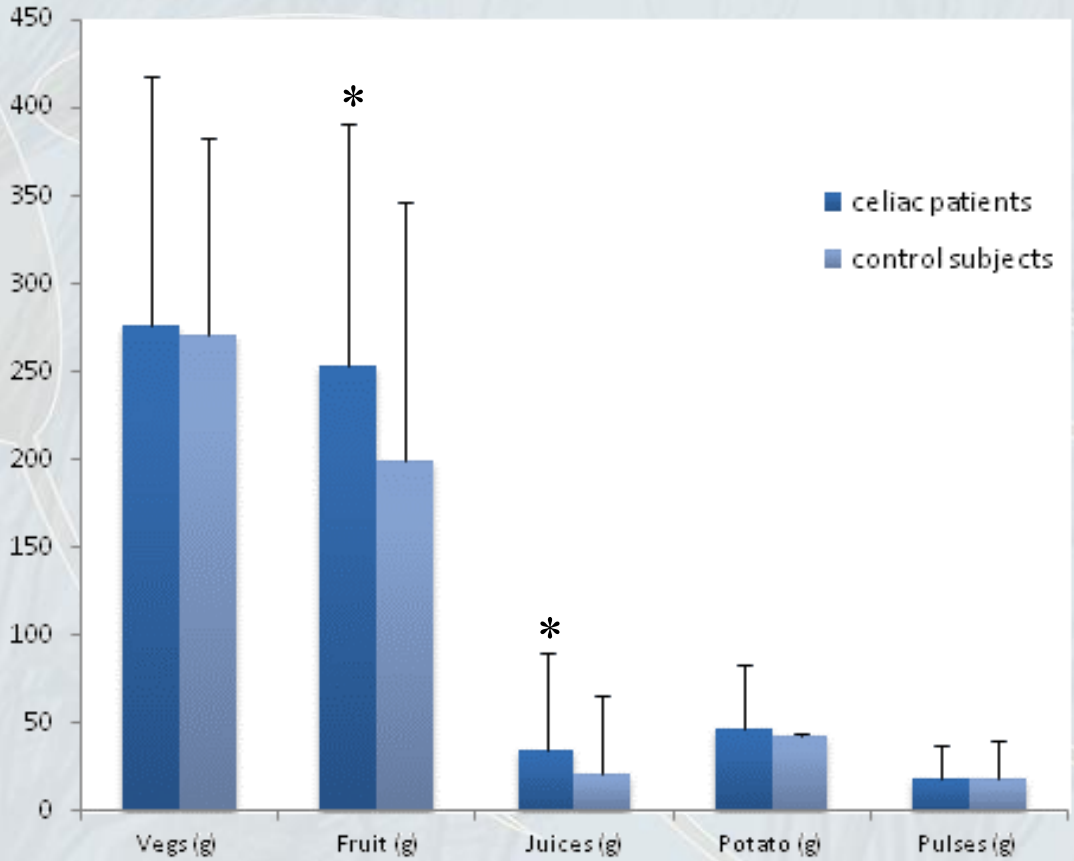
Fruit and Vegetable Comparison:

intake of celiac patients and control subjects: data from the 7-day records



- * Significantly different ($p < 0.05$) from control subjects.
- Mean ± SD

- Similar intake of meat, fish, eggs, milk and cheese;
- Higher intake of **vitamin C** and **E** in celiac patients;
- Similar intake of folate, β–carotene, B group vitamins (B1, B2, B3, B6) and potassium.

Nutritional adequacy of celiac diet

	Celiac patients	Control subjects	*Dietary reference values#*	Adequate intake celiacs	Adequate intake controls
Energy from total fats (%)	**37.7**	34.9	*20-35*	26.0%	60.0%
Energy from saturated fats (%)	**12.8**	**12.0**	*< 10*	9.0%	12.0%
Folate (µg/day)	**321.0**	**339.8**	*400*	23.0%	23.0%
Calcium (mg/day)	**885.2**	**848.8**	*1000*	31.0%	27.0%
Iron (mg/day)	**11.6**	**12.5**	*10 men* *18 women*	90.9% 5.1%	96.8% 8.7%
Fiber (g/MJ)	**2.6**	**2.7**	*3-4*	22.0%	29.0%
Potassium (g/day)	**3.3**	**3.2**	*3.9*	18.0%	15.0%
Sodium (g/day)	**2.9**	**2.8**	*1.5*	6.0%	3.0%
Zinc (mg/day)	**10.3**	**11.3**	*11 men* *8 women*	45.4% 96.1%	45.2% 98.6%

Dietary reference intakes for the Italian population: http://www.sinu.it/html/pag/nuovi_larn.asp

Foods: negative association with microbiome

- Fast Foods
  - High sat fat diet increased colonic permeability
  - Increased mesenteric fat inflammation

- High saturated fat diet
  - Mouse model; high saturated fat diet was associated with;
    - Increase in hydrogen sulfide producing bacteria

So what are the alternatives?

- Good news – There are many alternatives
  - New research on the microbiome
  - Renewed interest in food and health
  - Evolving and increasing understanding of the role of food in the gut

Role of pro and pre-biotics

- Role of food as an integral part of over all health is not new

- 1907 - Elie Mutchnikov father of the microbiome
  - Developed the framework for the understanding of the positive use of microbes (pro and pre-biotics

- Work continues to develop in the concept of multiple protective pathways
  - Stimulation of immunity
  - Suppression of immunity
  - Promotion of intestinal epithelia cell development
  - Enhanced recovery from infection
  - Antimicrobial functions

Probiotics

- Stimulate the immunity (adaptive and innante)

- Macaubas et al 2003 and Prescott et al 2008
  - Significant effect of maternal probiotic use
    - Mothers took B lactis or L rhamnosus
    - Breast milk had significantly higher levels of Immunoglobulin A
    - Increased levels were detected at weei 1, 3 mos
    - At 6 mos no effect

Probiotics

- Promotion of intestinal epithelium
  - Increasing the health of the intestinal lining associated with reduction of disease

- Predis et al 2012
  - Found that gut bacteria can prevent rotavirus associated with gastroenteritis in mouse model.
    - Treated mice with lactobacillus
    - 1 day reduction of disease vs control mice

Comparison of Five Commercial Probiotic Preparations on Duration of Diarrhea in Children

NOTE: *N* = 571 children aged 3–36 months presenting with acute diarrhea; 5-day treatment period. CI = confidence interval; IQR = interquartile range.

SOURCE: Canani et al., 2007

Treatment	Median (IQR) Duration (hours)	Estimated Difference (95% CI)	*P*-Value
Oral rehydration solution alone	115.5 (95.2–127)	—	—
Lactobacillus casei subp *rhamnosus* GG	78.5 (56.5–104.5)	−32 (−41 to −23)	<0.001
Saccharomyces boulardil	105.0 (90–104.5)	−5 (−13 to 5)	0.38
Bacillus clausii	118.0 (95.2–128.7)	1 (−7 to 8)	0.76
L. delbrueckii var. *bulgaricus, L. acidophilus, Streptococcus thermophilus, B. bifidum*	70.0 (49–101)	−37 (−47 to −25)	<0.001
Enterococcus faecium SF 68	115.0 (89–144)	2 (−5 to 11)	0.61

Prebiotics

- Prebiotics
  - The foods that feed the probiotics in the gut
    - Resistant starch
    - Inulin
    - Polyosaccharides

- Martinez et al 2010
  - 10 healthy human subjects
  - 17 week double blind cross over study
  - Subjects were fed crackers containing different compositions of carbohydrate
  - Crackers with resistant starch increased production of bifidobacterium
  - Significant increase over crackers with wheat starch

Historically knew certain foods were associated with health

- Framingham and Nurses study pointed to the positive effect of fruits and vegetables on overall health
  - Tomatoes
  - Olive oil
  - Green leafy vegetables
  - Nuts; almonds
  - Fruits: blueberries, strawberries cherries
  - Whole grains

- Asian culture has attributed health to various foods as well
  - Green Tea
  - Kimchi

Natural sources of pre and probiotics

- Prebiotics
- Fiber
  - Inulin, resistant starch found in:
  - Artichoke
  - Asparagus
  - Beans and legumes
  - cabbage
  - Chicory
  - Garlic
  - Leek
  - Oatmeal and bran:
    - High fiber bran from rice, soy etc.
  - Root vegetables:
    - beets, sweet potato, turnips, carrots, onion

- Probiotics
- Fermented foods
  - Cheeses
  - Kefir
  - Kimchi
  - Kombucha
  - Miso
  - Sauerkraut
  - Sour Cream
  - Tempheh

How do we translate this into gluten free diet

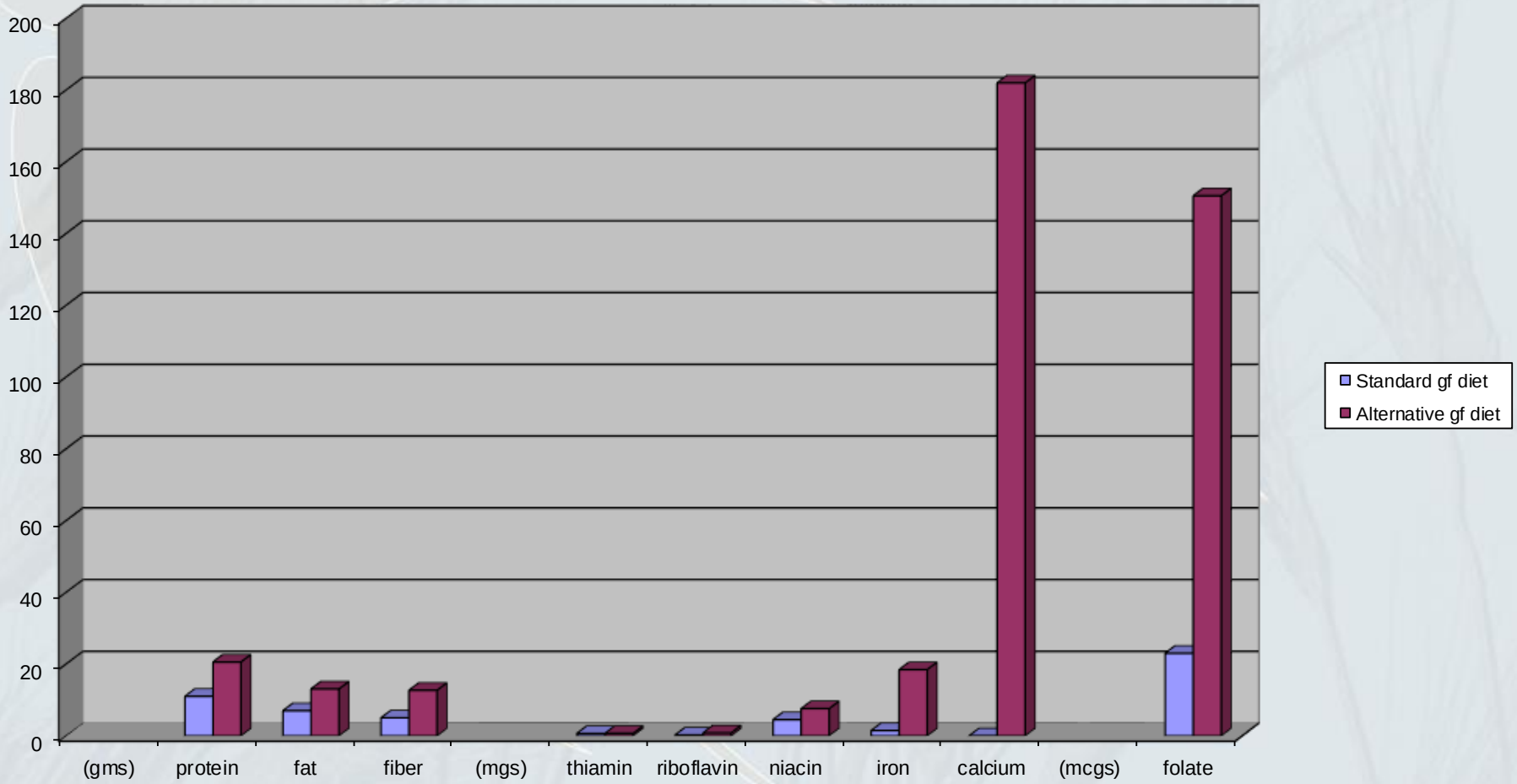
- Choose foods wisely
  - Naturally gluten free over processed foods
  - Add yogurt, kefir or cheese to your daily routine
  - Use root vegetables in soups stews
  - Add onions, leeks to salads and sauces
  - Meatless Monday – use legumes, and beans
  - Whole gluten free grains –
    - a significant difference in the overall nutrient profile of the diet

Alternate Grain Study

- Current GF diet is a cause for concern on two levels
  - Nutrient deficiencies
  - High concentration of processed foods

- Study premise:
  - Substituting the commonly used grains in the gluten-free diet should improve the nutrient profile of diet
  - Substituted the only the grain selection
  - Compared nutrient analysis

Nutrient comparison of standard vs alternate diet



Practical approach and recommendations

- Good control of the GFD is starting point – need to heal!!

- Diet alone will not reverse long term deficiencies or meet nutritional needs
- Changes need to be made slowly –
  - especially for children

- Minimize use of processed foods
  - The more processed the fewer nutrients
  - Higher fat and sugar content

- Reserve prepared foods for a quick meal or treat
  - Hectic days deserve a **balance**
  - Combine a new food with a prepared favorite
    - **It takes 10 exposures to a new food for it to be familiar and accepted**

Recommendations:
Eat, play, enjoy

- Eat like the French
- Go out side and get dirty
- Enjoy what you do and what you eat

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