

Consumption of Fructose and High Fructose Corn Syrup: Is Fructositis triggered bronchitis, asthma, & auto-immune reactivity merely a side bar in the Etiology of Metabolic Syndrome II (to be defined)? – Evidence and a Hypothesis.

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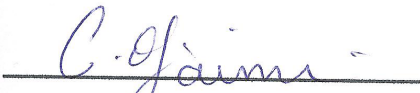
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**Consumption of Fructose and High Fructose Corn Syrup:
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reactivity merely a side bar in the Etiology of Metabolic
Syndrome II (to be defined)? – Evidence and a
Hypothesis.**



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Abstract

Consumption of Fructose and High Fructose Corn Syrup: Is Fructositis triggered bronchitis, asthma, & auto-immune reactivity merely a side bar in the Etiology of Metabolic Syndrome II (to be defined)? – Evidence and a Hypothesis.

A case history and prototype case report provide evidence of allergic reactivity to high fructose corn syrup (HFCS). Ingestion of the sweetener precipitates a cascade of symptoms associated with atypical pneumonitis and respiratory symptomology. Aside from an early onset dry cough, the symptoms do not follow the phenotype most often associated with food borne allergies. The allergic reaction is characterized by symptoms most associated with aero-allergens including bronchial mucus hypersecretion, low grade fever, airway hyper-reactivity, bronchitis triggered asthma, chronic bronchitis, wheezing, allergic rhinitis, eustachian tube dysfunction and inner ear infections. Fructose malabsorption is believed to contribute to the biochemical mechanisms likely involved in the syndrome. The allergenicity of HFCS was discovered during a strict elimination diet in a three to four year old child. Reactivity persists into young adulthood.

The factors contributing to why HFCS has remained an unknown allergen to date are explored including: flu symptom mimicry; the predominant focus by the medical community on native proteins in the main food allergens including peanut, tree nuts, crustacean shellfish, cow's milk, hen's egg, wheat and soy; the inordinate challenges of adherence to an elimination diet given the ubiquitous nature of a food such as HFCS; and the conventional wisdom that aero-allergens trigger respiratory symptomology not foods, and particularly not sugars.

Scientific research available to date indicates that 10% to 30% of “healthy” adults are fructose malabsorbers. Scant research has been done in children. What is available suggests children are at higher risk of being fructose malabsorbers (Riby, et al., 1993). The proposed fructositis hypothesis links the dramatic increases in rates of asthma amongst school aged, preschool and black children since 1984 (Asthma and Allergy Foundation of America (AAFA)), to the concomitant shift from sugar to HFCS occurring during the same time period (USDA). The proposed biochemical mechanisms are that high concentrations of intestinal fructose by those unable to adequately digest and absorb

fructose, leads to modifications and changes in dietary protein fragments (peptides) that turn them into “antigen” capable of triggering an adverse immune response via the AGE/ RAGE pathway (advanced glycation end-products and receptor). Modifications are proposed to occur via the non-enzymatic Maillard reaction, in the high fructose intestinal environment of fructose malabsorbers. The potential roles of IL-6, T helper 17 and gamma delta T cells are explored. Given the ubiquitous presence of HFCS in the US food supply, the fructositis hypothesis and related research raises questions as to its potential role in the many auto-immune diseases recently linked to the AGE/ RAGE pathway including Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA), Irritable Bowel Syndrome (IBS), Inflammatory Bowel Disease (IBD), COPD, Atherosclerosis, Psoriasis and other auto-immune system disorders.

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Revision 2. Corrections to current costs of asthma (over \$56 billion), pg. 73;
high-fructose foods correction: apples and watermelons, pg.27;
HFCS consumption date corrected from 1980 to 1982, pg. 14.

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References

USDA National Nutrient Database for Standard Reference, Release 24. Nutrient Data Laboratory Home Page. Available at: <http://www.ars.usda.gov/ba/bhnrc/ndl>. Accessed 01/15, 2012.

Trends in asthma morbidity and mortality. *American Lung Association*. Epidemiology & Statistics Unit, Research and Program Services. Available at http://www.epa.gov/asthma/pdfs/asthma_fact_sheet_en.pdf and <http://www.lung.org/finding-cures/our-research/trend-reports/asthma-trend-report.pdf>

Akinbami L. Asthma prevalence, healthcare use and mortality. *United States 2003 - 2005, CDC National Center for Health Statistics* [Akinbami]. 2006. Available at <http://www.cdc.gov/nchs/data/ad/ad381.pdf>

Asipu A, Hayward BE, O'Reilly J, Bonthron DT. Properties of normal and mutant recombinant human ketohexokinases and implications for the pathogenesis of essential fructosuria. *Diabetes*. 2003;52:2426-2432. Available at <http://diabetes.diabetesjournals.org/content/52/9/2426.full.pdf> and

Assimakopoulos SF, Papageorgiou I, Charonis A. Enterocytes' tight junctions: From molecules to diseases. *World J Gastrointest Pathophysiol*. 2011;2:123-137. <http://www.ncbi.nlm.nih.gov/pubmed/22184542>

Barone S, Fussell SL, Singh AK, Lucas F, Xu J, Kim C, Wu X, Yu Y, Amlal H, Seidler U, Zuo J, Soleimani M. Slc2a5 (Glut5) is essential for the absorption of fructose in the intestine and generation of fructose-induced hypertension. *J Biol Chem*. 2009;284:5056-5066. <http://www.ncbi.nlm.nih.gov/pubmed/19091748>

Bartling B, Fuchs C, Somoza V, Niemann B, Silber RE, Simm A. Lung level of HMBG1 is elevated in response to advanced glycation end product-enriched food in vivo. *Mol Nutr Food Res*. 2007;51:479-487. <http://www.ncbi.nlm.nih.gov/pubmed/17357979>

BeMiller JN. One hundred years of commercial food carbohydrates in the united states. *J Agric Food Chem*. 2009;57:8125-8129. <http://www.ncbi.nlm.nih.gov/pubmed/19719134>

Berg JM, Tymoczko JL, Stryer L. *Biochemistry. 5th edition*. New York: W H Freeman; 2002. Figure 16.15 Fructose Metabolism.

Bernstein JM. The role of IgE-mediated hypersensitivity in the development of otitis media with effusion: A review. *Otolaryngol Head Neck Surg*. 1993;109:611-620. <http://www.ncbi.nlm.nih.gov/pubmed/1549382>

Beyer PL, Caviar EM, McCallum RW. Fructose intake at current levels in the united states may cause gastrointestinal distress in normal adults. *J Am Diet Assoc*. 2005;105:1559-1566. <http://www.ncbi.nlm.nih.gov/pubmed/16183355>

Bonthron DT, Brady N, Donaldson IA, Steinmann B. Molecular basis of essential fructosuria: Molecular cloning and mutational analysis of human ketohexokinase (fructokinase). *Hum Mol Genet*.

1994;3:1627-1631. <http://www.ncbi.nlm.nih.gov/pubmed/7833921>

Bouteldja N, Timson DJ. The biochemical basis of hereditary fructose intolerance. *J Inherit Metab Dis*. 2010;33:105-112. <http://www.ncbi.nlm.nih.gov/pubmed/20162364>

Bovard J. The great sugar shaft. *Freedom Daily* [The Future of Freedom Foundation]. 1998.
Brett J, Schmidt AM, Yan SD, Zou YS, Weidman E, Pinsky D, Nowygrod R, Nepper M, Przysiecki C, Shaw A. Survey of the distribution of a newly characterized receptor for advanced glycation end products in tissues. *Am J Pathol*. 1993;143:1699-1712.

Buckley ST, Ehrhardt C. The receptor for advanced glycation end products (RAGE) and the lung. *J Biomed Biotechnol*. 2010;2010:917108. <http://www.ncbi.nlm.nih.gov/pubmed/20145712>

Bunn HF, Higgins PJ. Reaction of monosaccharides with proteins: Possible evolutionary significance. *Science*. 1981;213:222-224. <http://www.ncbi.nlm.nih.gov/pubmed/12192669>

Buttari B, Profumo E, Capozzi A, Facchiano F, Saso L, Sorice M, Rigano R. Advanced glycation end products of human β 2glycoproteinI modulate the maturation and function of DCs. *Blood*. 2011. <http://www.ncbi.nlm.nih.gov/pubmed/21498672>

Cardoso CR, Provinciatto PR, Godoi DF, Vieira TS, Ferreira BR, Teixeira G, Rossi MA, Cunha FQ, Silva JS. B cells are involved in the modulation of pathogenic gut immune response in food-allergic enteropathy. *Clin Exp Immunol*. 2008;154:153-161. <http://www.ncbi.nlm.nih.gov/pubmed/18778361>

Charrier L, Merlin D. The oligopeptide transporter hPepT1: Gateway to the innate immune response. *Lab Invest*. 2006;86:538-546. <http://www.ncbi.nlm.nih.gov/pubmed/16652110>

Chen Y, Akirav EM, Chen W, Henegariu O, Moser B, Desai D, Shen JM, Webster JC, Andrews RC, Mjalli AM, Rothlein R, Schmidt AM, Clynes R, Herold KC. RAGE ligation affects T cell activation and controls T cell differentiation. *J Immunol*. 2008;181:4272-4278. <http://www.ncbi.nlm.nih.gov/pubmed/18768885>

Cox TM. Aldolase B and fructose intolerance. *FASEB J*. 1994;8:62-71. <http://www.ncbi.nlm.nih.gov/pubmed/8299892>

Cox TM, O'Donnell MW, Camilleri M, Burghes AH. Isolation and characterization of a mutant liver aldolase in adult hereditary fructose intolerance. Identification of the enzyme variant by radioassay in tissue biopsy specimens. *J Clin Invest*. 1983;72:201-213. <http://www.ncbi.nlm.nih.gov/pubmed/6348085>

Cummings BP, Stanhope KL, Graham JL, Evans JL, Baskin DG, Griffen SC, Havel PJ. Dietary fructose accelerates the development of diabetes in UCD-T2DM rats: Amelioration by the antioxidant, alpha-lipoic acid. *Am J Physiol Regul Integr Comp Physiol*. <http://www.ncbi.nlm.nih.gov/pubmed/20147607> 2010;298:R1343-50.

Davis EA. Functionality of sugars: Physicochemical interactions in foods. *Am J Clin Nutr*. 1995;62:170S-177S. <http://ajcn.nutrition.org/content/62/1/170S.full.pdf> and <http://www.ncbi.nlm.nih.gov/pubmed/7598075>

- DeFrances C, Cullen K, Kozak L. National hospital discharge survey: 2005 annual summary with detailed diagnosis and procedure data. *National Center for Health Statistics* [DeFrances]. 2007; *Vital Health Statistics* 12:165. http://www.cdc.gov/nchs/data/series/sr_13/sr13_165.pdf
- Dekker MJ, Su Q, Baker C, Rutledge AC, Adeli K. Fructose: A highly lipogenic nutrient implicated in insulin resistance, hepatic steatosis, and the metabolic syndrome. *Am J Physiol Endocrinol Metab*. 2010;299:E685-94. <http://www.ncbi.nlm.nih.gov/pubmed/20823452>
- Deo P, Glenn JV, Powell LA, Stitt AW, Ames JM. Upregulation of oxidative stress markers in human microvascular endothelial cells by complexes of serum albumin and digestion products of glycated casein. *J Biochem Mol Toxicol*. 2009;23:364-372. <http://www.ncbi.nlm.nih.gov/pubmed/19827132>
- Dills WL, Jr. Protein fructosylation: Fructose and the maillard reaction. *Am J Clin Nutr*. 1993;58:779S-787S. <http://www.ncbi.nlm.nih.gov/pubmed/8213610>
- Donato R. RAGE: A single receptor for several ligands and different cellular responses: The case of certain S100 proteins. *Curr Mol Med*. 2007;7:711-724. <http://www.ncbi.nlm.nih.gov/pubmed/18331229>
- Fireman P. Otitis media and eustachian tube dysfunction: Connection to allergic rhinitis. *J Allergy Clin Immunol*. 1997;99:S787-97. <http://www.ncbi.nlm.nih.gov/pubmed/9042072>
- Foell D, Kucharzik T, Kraft M, Vogl T, Sorg C, Domschke W, Roth J. Neutrophil derived human S100A12 (EN-RAGE) is strongly expressed during chronic active inflammatory bowel disease. *Gut*. 2003;52:847-853. <http://www.ncbi.nlm.nih.gov/pubmed/12740341>
- Foell D, Roth J. Proinflammatory S100 proteins in arthritis and autoimmune disease. *Arthritis Rheum*. 2004;50:3762-3771. <http://www.ncbi.nlm.nih.gov/pubmed/15593206>
- Fujisawa T, Riby J, Kretchmer N. Intestinal absorption of fructose in the rat. *Gastroenterology*. 1991;101:360-367. <http://www.ncbi.nlm.nih.gov/pubmed/2065911>
- Fulgoni V, 3rd. High-fructose corn syrup: Everything you wanted to know, but were afraid to ask. *Am J Clin Nutr*. 2008;88:1715S. <http://www.ncbi.nlm.nih.gov/pubmed/19064535>
- Geissler S, Hellwig M, Zwarg M, Markwardt F, Henle T, Brandsch M. Transport of the advanced glycation end products alanylpyrraline and pyrallylalanine by the human proton-coupled peptide transporter hPEPT1. *J Agric Food Chem*. 2010;58:2543-2547. <http://www.ncbi.nlm.nih.gov/pubmed/20104847>
- Gibson PR, Newnham E, Barrett JS, Shepherd SJ, Muir JG. Review article: Fructose malabsorption and the bigger picture. *Aliment Pharmacol Ther*. 2007;25:349-363. <http://www.ncbi.nlm.nih.gov/pubmed/17217453>
- Haley S, Toasa J, Jerardo A. Sugar and sweeteners outlook. *United States Department of Agriculture* [A Report from the Economic Research Service]. 2008;SSS:253. <http://www.usda.gov/wps/portal/usda/usdahome?mode=simple&q=haley&sort=date:D:S:d1&num=10&ie=UTF-8&entqr=3&oe=UTF-8&ud=1&navid=SEARCH&start=90>

Helliwell PA, Richardson M, Affleck J, Kellett GL. Stimulation of fructose transport across the intestinal brush-border membrane by PMA is mediated by GLUT2 and dynamically regulated by protein kinase C. *Biochem J*. 2000;350 Pt 1:149-154.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1221236/>

Henle T. Protein-bound advanced glycation endproducts (AGEs) as bioactive amino acid derivatives in foods. *Amino Acids*. 2005;29:313-322. <http://www.ncbi.nlm.nih.gov/pubmed/15997413>

Herold K., Moser B, Chen Y, Zeng S, Yan SF, Ramasamy R, Emond J, Clynes R, Schmidt AM. Receptor for advanced glycation end products (RAGE) in a dash to the rescue: inflammatory signals gone awry in the primal response to stress. *J Leukoc Biol*. 2007, 82, 2, 204-212.

<http://www.ncbi.nlm.nih.gov/pubmed/17513693>

Hilmenyuk T, Bellinghausen I, Heydenreich B, Ilchmann A, Toda M, Grabbe S, Saloga J. Effects of glycation of the model food allergen ovalbumin on antigen uptake and presentation by human dendritic cells. *Immunology*. 2010;129:437-445. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2826688/>

Hinton DJ, Ames JM. Site specificity of glycation and carboxymethylation of bovine serum albumin by fructose. *Amino Acids*. 2006;30:425-434. <http://www.ncbi.nlm.nih.gov/pubmed/16583308>

Hoekstra JH, van den Aker JH, Kneepkens CM, Stellaard F, Geypens B, Ghoo YF. Evaluation of ¹³CO₂ breath tests for the detection of fructose malabsorption. *J Lab Clin Med*. 1996;127:303-309.

<http://www.ncbi.nlm.nih.gov/pubmed/9273364>

Hoekstra JH, van Kempen AA, Bijl SB, Kneepkens CM. Fructose breath hydrogen tests. *Arch Dis Child*. 1993;68:136-138. <http://www.ncbi.nlm.nih.gov/pubmed/8435000>

Hofmann MA, Drury S, Fu C, Qu W, Taguchi A, Lu Y, Avila C, Kambham N, Bierhaus A, Nawroth P, Neurath MF, Slattery T, Beach D, McClary J, Nagashima M, Morser J, Stern D, Schmidt AM. RAGE mediates a novel proinflammatory axis: A central cell surface receptor for S100/calgranulin polypeptides. *Cell*. 1999;97:889-901. <http://www.ncbi.nlm.nih.gov/pubmed/10399917>

Hofmann SM, Dong HJ, Li Z, Cai W, Altomonte J, Thung SN, Zeng F, Fisher EA, Vlassara H. Improved insulin sensitivity is associated with restricted intake of dietary glycoxidation products in the db/db mouse. *Diabetes*. 2002;51:2082-2089. <http://www.ncbi.nlm.nih.gov/pubmed/12086936>

Horiuchi S, Araki N, Morino Y. Immunochemical approach to characterize advanced glycation end products of the maillard reaction. evidence for the presence of a common structure. *J Biol Chem*. 1991;266:7329-7332. <http://www.ncbi.nlm.nih.gov/pubmed/2019568>

Jaffar Z, Ferrini ME, Shaw PK, FitzGerald GA, Roberts K. Prostaglandin promotes the development of IL-17-producing gammadelta T cells that associate with the epithelium during allergic lung inflammation. *J Immunol*. 2011;187:5380-5391. <http://www.ncbi.nlm.nih.gov/pubmed/21976777>

Jakas A, Katic A, Bionda N, Horvat S. Glycation of a lysine-containing tetrapeptide by D-glucose and D-fructose--influence of different reaction conditions on the formation of Amadori/Heyns products. *Carbohydr Res*. 2008;343:2475-2480. <http://www.ncbi.nlm.nih.gov/pubmed/18656854>

Johnson RJ, Perez-Pozo SE, Sautin YY, Manitius J, Sanchez-Lozada LG, Feig DI, Shafiu M, Segal M,

Glasscock RJ, Shimada M, Roncal C, Nakagawa T. Hypothesis: Could excessive fructose intake and uric acid cause type 2 diabetes? *Endocr Rev.* 2009;30:96-116.
<http://www.ncbi.nlm.nih.gov/pubmed/19151107>

Jones HF, Butler RN, Brooks DA. Intestinal fructose transport and malabsorption in humans. *Am J Physiol Gastrointest Liver Physiol.* 2011;300:G202-6. <http://www.ncbi.nlm.nih.gov/pubmed/21148401>

Kato S, Itoh K, Ochiai M, Iwai A, Park Y, Hata S, Takeuchi K, Ito M, Imaki J, Miura S, Yakabi K, Kobayashi M. Increased pentosidine, an advanced glycation end-product, in urine and tissue reflects disease activity in inflammatory bowel diseases. *J Gastroenterol Hepatol.* 2008;23 Suppl 2:S140-5.
<http://www.ncbi.nlm.nih.gov/pubmed/19120887>

Kellett GL, Brot-Laroche E. Apical GLUT2: A major pathway of intestinal sugar absorption. *Diabetes.* 2005;54:3056-3062. <http://www.ncbi.nlm.nih.gov/pubmed/16186415>

Kellett GL, Helliwell PA. The diffusive component of intestinal glucose absorption is mediated by the glucose-induced recruitment of GLUT2 to the brush-border membrane. *Biochem J.* 2000;350 Pt 1:155-162. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1221237/>

Koschinsky T, He CJ, Mitsuhashi T, Bucala R, Liu C, Buenting C, Heitmann K, Vlassara H. Orally absorbed reactive glycation products (glycotoxins): An environmental risk factor in diabetic nephropathy. *Proc Natl Acad Sci U S A.* 1997;94:6474-6479.
<http://www.ncbi.nlm.nih.gov/pubmed/9177242>

Laukoetter MG, Nava P, Nusrat A. Role of the intestinal barrier in inflammatory bowel disease. *World J Gastroenterol.* 2008;14:401-407. <http://www.ncbi.nlm.nih.gov/pubmed/18200662>

Leturque A, Brot-Laroche E, Le Gall M. GLUT2 mutations, translocation, and receptor function in diet sugar managing. *Am J Physiol Endocrinol Metab.* 2009;296:E985-92.
<http://www.ncbi.nlm.nih.gov/pubmed/19223655>

Lin L, Park S, Lakatta EG. RAGE signaling in inflammation and arterial aging. *Front Biosci.* 2009;14:1403-1413. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2661616/>

Liu H, Huang D, McArthur DL, Boros LG, Nissen N, Heaney AP. Fructose induces transketolase flux to promote pancreatic cancer growth. *Cancer Res.* 2010;70:6368-6376.
<http://www.ncbi.nlm.nih.gov/pubmed/20647326>

Lotze MT, Tracey KJ. High-mobility group box 1 protein (HMGB1): Nuclear weapon in the immune arsenal. *Nat Rev Immunol.* 2005;5:331-342. <http://www.ncbi.nlm.nih.gov/pubmed/15803152>

Makita Z, Vlassara H, Cerami A, Bucala R. Immunochemical detection of advanced glycosylation end products in vivo. *J Biol Chem.* 1992;267:5133-5138. <http://www.ncbi.nlm.nih.gov/pubmed/1371995>

Makita Z, Yanagisawa K, Kuwajima S, Yoshioka N, Atsumi T, Hasunuma Y, Koike T. Advanced glycation endproducts and diabetic nephropathy. *J Diabetes Complications.* 1995;9:265-268.
<http://www.ncbi.nlm.nih.gov/pubmed/8573743>

Maleki SJ, Chung SY, Champagne ET, Raufman JP. The effects of roasting on the allergenic properties

of peanut proteins. *J Allergy Clin Immunol*. 2000;106:763-768.
<http://www.ncbi.nlm.nih.gov/pubmed/11031348>

Merlin D, Si-Tahar M, Sitaraman SV, Eastburn K, Williams I, Liu X, Hediger MA, Madara JL. Colonic epithelial hPepT1 expression occurs in inflammatory bowel disease: Transport of bacterial peptides influences expression of MHC class I molecules. *Gastroenterology*. 2001;120:1666-1679.
<http://www.ncbi.nlm.nih.gov/pubmed/11375948>

Miyazawa N, Kawasaki Y, Fujii J, Theingi M, Hoshi A, Hamaoka R, Matsumoto A, Uozumi N, Teshima T, Taniguchi N. Immunological detection of fructated proteins in vitro and in vivo. *Biochem J*. 1998;336 (Pt 1):101-107. <http://www.ncbi.nlm.nih.gov/pubmed/9806890>

Morbini P, Villa C, Campo I, Zorzetto M, Inghilleri S, Luisetti M. The receptor for advanced glycation end products and its ligands: A new inflammatory pathway in lung disease? *Mod Pathol*. 2006;19:1437-1445. <http://www.ncbi.nlm.nih.gov/pubmed/16941014>

Morcos M, Sayed AA, Bierhaus A, Yard B, Waldherr R, Merz W, Kloeting I, Schleicher E, Mentz S, Abd el Baki RF, Tritschler H, Kasper M, Schwenger V, Hamann A, Dugi KA, Schmidt AM, Stern D, Ziegler R, Haering HU, Andrassy M, van der Woude F, Nawroth PP. Activation of tubular epithelial cells in diabetic nephropathy. *Diabetes*. 2002;51:3532-3544.
<http://www.ncbi.nlm.nih.gov/pubmed/12453911>

Murphy K. Allergy and allergic diseases. In: *Janeway's ImmunoBiology*. Vol 8th Edition. ; 2012:573.

Neeper M, Schmidt AM, Brett J, Yan SD, Wang F, Pan YC, Elliston K, Stern D, Shaw A. Cloning and expression of a cell surface receptor for advanced glycosylation end products of proteins. *J Biol Chem*. 1992;267:14998-15004. <http://www.ncbi.nlm.nih.gov/pubmed/1378843>

Orosz F, Olah J, Ovadi J. Triosephosphate isomerase deficiency: Facts and doubts. *IUBMB Life*. 2006;58:703-715. <http://www.ncbi.nlm.nih.gov/pubmed/17424909>

Pang DJ, Neves JF, Sumaria N, Pennington DJ. Understanding the complexity of gammadelta T cell subsets in mouse and human. *Immunology*. 2012. <http://www.ncbi.nlm.nih.gov/pubmed/22385416>

Qian BF, Wahl SM. TGF-beta can leave you breathless. *Curr Opin Pharmacol*. 2009;9:454-461.
<http://www.ncbi.nlm.nih.gov/pubmed/19467929>

Rabbani N, Godfrey L, Xue M, Shaheen F, Geoffrion M, Milne R, Thornalley PJ. Glycation of LDL by methylglyoxal increases arterial atherogenicity: A possible contributor to increased risk of cardiovascular disease in diabetes. *Diabetes*. 2011;60:1973-1980.
<http://www.ncbi.nlm.nih.gov/pubmed/21617182>

Ramakrishnan JB. The role of food allergy in otolaryngology disorders. *Curr Opin Otolaryngol Head Neck Surg*. 2010;18:195-199. <http://www.ncbi.nlm.nih.gov/pubmed/20168232>

Ramaswamy K, Malathi P, Caspary WF, Crane RK. Studies on the transport of glucose from disaccharides by hamster small intestine in vitro. II. characteristics of the disaccharidase-related transport system. *Biochim Biophys Acta*. 1974;345:39-48.

Ravich WJ, Bayless TM, Thomas M. Fructose: Incomplete intestinal absorption in humans. *Gastroenterology*. 1983;84:26-29. <http://www.ncbi.nlm.nih.gov/pubmed/6847852>

Rellos P, Sygusch J, Cox TM. Expression, purification, and characterization of natural mutants of human aldolase B. role of quaternary structure in catalysis. *J Biol Chem*. 2000;275:1145-1151. <http://www.ncbi.nlm.nih.gov/pubmed/10625657>

Riby JE, Fujisawa T, Kretchmer N. Fructose absorption. *Am J Clin Nutr*. 1993;58:748S-753S. <http://www.ncbi.nlm.nih.gov/pubmed/8213606>

Rumessen JJ, Gudmand-Hoyer E. Functional bowel disease: Malabsorption and abdominal distress after ingestion of fructose, sorbitol, and fructose-sorbitol mixtures. *Gastroenterology*. 1988;95:694-700. <http://www.ncbi.nlm.nih.gov/pubmed/3396816>

Rumessen JJ. Fructose and related food carbohydrates. sources, intake, absorption, and clinical implications. *Scand J Gastroenterol*. 1992;27:819-828. <http://www.ncbi.nlm.nih.gov/pubmed/1439534>

Srikrishna G, Turovskaya O, Shaikh R, Newlin R, Foell D, Murch S, Kronenberg M, Freeze HH. Carboxylated glycans mediate colitis through activation of NF-kappa B. *J Immunol*. 2005;175:5412-5422. <http://www.ncbi.nlm.nih.gov/pubmed/16210648>

Stanhope KL, Schwarz JM, Keim NL, Griffen SC, Bremer AA, Graham JL, Hatcher B, Cox CL, Dyachenko A, Zhang W, McGahan JP, Seibert A, Krauss RM, Chiu S, Schaefer EJ, Ai M, Otokoza S, Nakajima K, Nakano T, Beysen C, Hellerstein MK, Berglund L, Havel PJ. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. *J Clin Invest*. 2009;119:1322-1334. <http://www.ncbi.nlm.nih.gov/pubmed/19381015>

Simonian PL, Roark CL, Born WK, O'Brien RL, Fontenot AP. Gammadelta T cells and Th17 cytokines in hypersensitivity pneumonitis and lung fibrosis. *Transl Res*. 2009;154:222-227. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2766087/>

Suarez G, Rajaram R, Oronsky AL, Gawinowicz MA. Nonenzymatic glycation of bovine serum albumin by fructose (fructation). comparison with the maillard reaction initiated by glucose. *J Biol Chem*. 1989;264:3674-3679. <http://www.ncbi.nlm.nih.gov/pubmed/2537288>

Takeuchi M, Iwaki M, Takino J, Shirai H, Kawakami M, Bucala R, Yamagishi S. Immunological detection of fructose-derived advanced glycation end-products. *Lab Invest*. 2010;90:1117-1127. <http://www.ncbi.nlm.nih.gov/pubmed/20212455>

Tan D, Wang Y, Lo CY, Sang S, Ho CT. Methylglyoxal: Its presence in beverages and potential scavengers. *Ann N Y Acad Sci*. 2008;1126:72-75. <http://www.ncbi.nlm.nih.gov/pubmed/18448797>

Truswell AS, Seach JM, Thorburn AW. Incomplete absorption of pure fructose in healthy subjects and the facilitating effect of glucose. *Am J Clin Nutr*. 1988;48:1424-1430. <http://www.ncbi.nlm.nih.gov/pubmed/3202090>

Turk Z, Ljubic S, Turk N, Benko B. Detection of autoantibodies against advanced glycation endproducts and AGE-immune complexes in serum of patients with diabetes mellitus. *Clin Chim Acta*.

2001;303:105-115. <http://www.ncbi.nlm.nih.gov/pubmed/11163030>

Urbonaviciute V, Voll RE. High-mobility group box 1 represents a potential marker of disease activity and novel therapeutic target in systemic lupus erythematosus. *J Intern Med*. 2011;270:309-318. <http://www.ncbi.nlm.nih.gov/pubmed/21793951>

Ushijima K, Riby JE, Fujisawa T, Kretchmer N. Absorption of fructose by isolated small intestine of rats is via a specific saturable carrier in the absence of glucose and by the disaccharidase-related transport system in the presence of glucose. *J Nutr*. 1995;125:2156-2164. <http://www.ncbi.nlm.nih.gov/pubmed/7643250>

van Zoelen MA, Achouiti A, van der Poll T. RAGE during infectious diseases. *Front Biosci (Schol Ed)*. 2011;3:1119-1132. <http://www.ncbi.nlm.nih.gov/pubmed/21622260>

Vandenbroucke JP. In defense of case reports and case series. *Ann Intern Med*. 2001;134:330-334. <http://www.ncbi.nlm.nih.gov/pubmed/11182844>

Ventura EE, Davis JN, Goran MI. Sugar content of popular sweetened beverages based on objective laboratory analysis: Focus on fructose content. *Obesity (Silver Spring)*. 2011;19:868-874. <http://www.ncbi.nlm.nih.gov/pubmed/20948525>

Vos MB, Kimmons JE, Gillespie C, Welsh J, Blanck HM. Dietary fructose consumption among US children and adults: The third national health and nutrition examination survey. *Medscape J Med*. 2008;10:160. <http://www.ncbi.nlm.nih.gov/pubmed/18769702>

Wasserman D, Hoekstra JH, Tolia V, Taylor CJ, Kirschner BS, Takeda J, Bell GI, Taub R, Rand EB. Molecular analysis of the fructose transporter gene (GLUT5) in isolated fructose malabsorption. *J Clin Invest*. 1996;98:2398-2402. <http://www.ncbi.nlm.nih.gov/pubmed/8941659>

Watanabe M, Zingg BC, Mohrenweiser HW. Molecular analysis of a series of alleles in humans with reduced activity at the triosephosphate isomerase locus. *Am J Hum Genet*. 1996;58:308-316. <http://www.ncbi.nlm.nih.gov/pubmed/8571957>

Wolf R, Mascia F, Dharamsi A, Howard OM, Cataisson C, Bliskovski V, Winston J, Feigenbaum L, Lichti U, Ruzicka T, Chavakis T, Yuspa SH. Gene from a psoriasis susceptibility locus primes the skin for inflammation. *Sci Transl Med*. 2010;2:61ra90. <http://www.ncbi.nlm.nih.gov/pubmed/21148126>

Wu L, Ma L, Nicholson LF, Black PN. Advanced glycation end products and its receptor (RAGE) are increased in patients with COPD. *Respir Med*. 2011;105:329-336. <http://www.ncbi.nlm.nih.gov/pubmed/21112201>

Xue J, Rai V, Singer D, Chabierski S, Xie J, Reverdatto S, Burz DS, Schmidt AM, Hoffmann R, Shekhtman A. Advanced glycation end product recognition by the receptor for AGEs. *Structure*. 2011;19:722-732. <http://www.ncbi.nlm.nih.gov/pubmed/21565706>

Yan SF, Ramasamy R, Schmidt AM. Soluble RAGE: Therapy and biomarker in unraveling the RAGE axis in chronic disease and aging. *Biochem Pharmacol*. 2010;79:1379-1386. <http://www.ncbi.nlm.nih.gov/pubmed/20096667>

Yilmaz Y, Yonal O, Eren F, Atug O, Hamzaoglu HO. Serum levels of soluble receptor for advanced glycation endproducts (sRAGE) are higher in ulcerative colitis and correlate with disease activity. *J Crohns Colitis*. 2011;5:402-406. <http://www.ncbi.nlm.nih.gov/pubmed/21939913>

Yu LC. Intestinal epithelial barrier dysfunction in food hypersensitivity. *J Allergy (Cairo)*. 2012;2012:596081. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3170794/>