Background information pertaining to diethyl azelate as it relates to insulin resistance

Elzbieta Izbicka
Robert T. Streeper

New Frontier Labs LLC
San Antonio, TX, USA

Correspondence to:
info@newfrontierlabs.com

Azelaic acid, a medium chain fatty acid, and its esters, azelates, occur naturally in plants, animals, and humans. We have discovered a novel use of diethyl azelate (DEA) (1), for the treatment of diet- and ethanol-induced insulin resistance (IR), the hallmark of metabolic syndrome, prediabetes and Type 2 diabetes (T2D). A number of studies (2-4) have shown a correlation of metabolic diseases with increased risk of cancer, especially liver, pancreatic and endometrial (5-7).

The Western diet combined with a sedentary lifestyle results in chronic metabolic inflammation (8, 9). A diet consisting of ~50% carbohydrates with high levels of fructose has been shown to induce insulin resistance in healthy non-obese men within 2-7 days (10). The detrimental health effects of dietary fructose are similar to those of ethanol (11). The diabetogenic effects of ethanol consumption, either acute (12) or chronic (13) strongly correlate with the development of insulin resistance in a dose-dependent manner (14, 15).

Insulin resistance develops when the tissues of the body that are normally responsive to insulin (liver, muscles, etc.) become less sensitive to insulin, a hormone the pancreas releases to help maintain healthy levels of glucose (8). This subsequently causes sugar to quickly accumulate in the blood, an issue that can be detrimental to health.

Under healthy circumstances, insulin has several functions that include:

- Directing glucose in the blood to travel into fat, liver, and muscle cells where it can be used for energy or stored as an energy reserve.
- Ensuring that the pancreas produces less insulin in response to decreasing glucose levels in the bloodstream as it begins to enter cells.

For many reasons, fat, muscle, and liver cells may respond inappropriately to insulin or not at all. If this happens, the cells cannot take up glucose from the bloodstream or store it. Due to the cells' insulin resistance, the pancreas continues to produce more of this hormone in an attempt to combat increased blood glucose levels.

If the pancreas can produce sufficient amounts of insulin that overcome cells' poor responses to insulin, blood sugar levels will remain in a healthy range. However, if the cells become increasingly resistant to insulin, blood sugar may rise to dangerous levels, a problem that can lead to metabolic difficulties.

New Frontier Labs LLC
MAIMS RESEARCH & DEVELOPMENT

Current T2D treatments do not reduce the incidence of or cure T2D and have side effects that range from mild to life-threatening, in some cases warranting 'Black Box' warnings mandated by the Federal Drug Administration in the United States of America (US FDA). Therapies available to patients with type T2D after metformin failure have been shown to induce weight gain, cause hypoglycemia or show poor long-term efficacy (16). No T2D drugs address the progressive nature of the disease and the underlying causes of insulin resistance. There is a need for agents with prolonged efficacy, superior disease modification power, and improved safety.

DEA and other azelates are metabolic products occurring naturally in humans and other mammals (17, 18). Azelates are also present in grains and grain-derived products including liquors (19), and in fermented foods due to bacterial degradation of acyl glycerol fatty acids and esterification of the resulting medium chain fatty acids (20). Fermentation of olives by Lactobacilli to render them edible has been practiced for at least 6 millennia in the Mediterranean basin (21). The Lactobacilli destroy bitter alkaloids contained in olive fruits, converting them to table olives (22). In addition, the Lactobacilli ferment some of the oleic acid contained in the olives into azelaic acid and azelates. The rind of olives also contains appreciable quantities of azelaic acid. Fermented soybean products, produced by humans for over 3 millennia (23), may help prevent or attenuate the progression of T2D (24). Notably, nonfermented soybean products have no effect on insulin resistance (24). Azelaic acid and azelate ethyl esters are present in douchi, a fermented black bean product (25).

Although not currently used as drugs, azelates and similar fatty acid esters are used as food additives. DEA is approved as a flavoring additive in the European Union (26, 27) and diethylhexyl azelate is approved for food contact packaging in the United States. A closely related ester, diethyl sebacate, which differs from DEA in that sebacic acid is one methylene unit longer than azelaic acid, is on the list of Generally Regarded As Safe (GRAS) compounds (28) and the Inactive Ingredients List (29) of the US FDA.

The New Frontier Labs' human study evaluate the effects of DEA on certain surrogate markers of insulin resistance, namely, blood plasma glucose, insulin and lipids (30), when administered orally to overweight or obese adult male volunteers. The cohort spanned from normal to prediabetic subjects based on the levels of the blood marker glycated hemoglobin A1c (A1c), which is considered a longer-term gauge of blood glucose control (31). The American Diabetes Association defines prediabetes as an A1c of 5.7%-6.4%, but also states that patients with an A1c just below the 5.7% threshold are at risk of developing diabetes (32). Our study has demonstrated that DEA can significantly improve the condition of subjects with IR.

For example, at 21days patients showed a 38% decrease in fasting insulin levels, 5.9% decrease in fasting plasma glucose levels, and an 8% reduction in cholesterol/HDL in subjects with high A1c levels.

Each of these results was statistically significant.

Concluding Remarks

The use of DEA in oral formulations shows great promise in supporting healthy markers of insulin resistance such as fasting plasma glucose, insulin, and cholesterol. DEA can help maintain healthy insulin sensitivity and glucose tolerance – and supports cardiovascular health. It has been shown to have a very favorable side effect profile, which is paramount in assuring routine compliance.

References

1. Streeper R, Izbicka E, inventors; New Frontier Labs, LLC, assignee. United States Patent No. US10,251,857 B2. Azelaic acid esters in the treatment of insulin resistance. USA 2019.
2. Esposito K, Chiodini P, Colao A, Lenzi A and, Giugliano D:. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. Diabetes Care. 2012;35(11): 2402-2411, 2012. Epub 2012/10/25. doi: 35/11/2402 [pii] 10.2337/dc12-0336. PubMed PMID: 23093685.; PubMed Central PMCID: PMC3476894. DOI: 35/11/2402 (pii) 10.2337/dc12-0336
3. Moghaddam AA, Woodward M and, Huxley R:. Obesity and risk of colorectal cancer: a meta-analysis of 31 studies with 70,000 events. Cancer Epidemiol Biomarkers Prev. 2007;16(12): 2533-2547, 2007. Epub 2007/12/19. doi: 16/12/2533 [pii] 10.1158/1055-9965.EPI-07-0708. PubMed PMID: 18086756. DOI: 16/12/2533 (pii) 10.1158/1055-9965
4. Huang Y, Cai X, Qiu M, Chen P, Tang H, Hu Y. Prediabetes and the risk of cancer: a meta-analysis. Diabetologia. 2014;57(11):2261-9. Epub 2014/09/12. doi: 10.1007/s00125-014-3361-2. PubMed PMID: 25208757.
5. Koo D, Han K, Park C. The Incremental Risk of Pancreatic Cancer According to Fasting Glucose Levels: Nationwide Population-Based Cohort Study. The Journal of Clinical Endocrinologu and Metabolism. 2019; 104(10):4594-99. Epub 2019/09/10. doi: 10.1210/jc.2019-00033
6. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. Diabetes Care. 2010;33(7):1674-85. Epub 2010/07/01. doi: 33/7/1674 [(pii]) 10.2337/dc10-0666. PubMed PMID: 20587728; PubMed Central PMCID: PMC2890380.
7. Hernandez AV, Pasupuleti V, Benites-Zapata VA, Thota P, Deshpande A, Perez-Lopez FR. Insulin resistance and endometrial cancer risk: A systematic review and meta-analysis. Eur J Cancer. 2015;51(18):2747-58. Epub 2015/11/26. doi: S0959-8049(15)00851-5 [(pii]) 10.1016/j.ejca.2015.08.031. PubMed PMID: 26597445.
8. Caputo T, Gilardi F, Desvergne B. From chronic overnutrition to metaflammation and insulin resistance: adipose tissue and liver contributions. FEBS Lett. 2017;591(19):3061-88. Epub 2017/07/06. doi: 10.1002/1873-3468.12742. PubMed PMID: 28677122.
9. Christ A, Latz E. The Western lifestyle has lasting effects on metaflammation. Nat Rev Immunol. 2019;19(5):267-8. Epub 2019/03/27. doi: 10.1038/s41577-019-0156-1 10.1038/s41577-019-0156-1 [(pii]). PubMed PMID: 30911129.
10. Boden G, Homko C, Barrero CA, Stein TP, Chen X, Cheung P, et al. Excessive caloric intake acutely causes oxidative stress, GLUT4 carbonylation, and insulin resistance in healthy men. Sci Transl Med. 2015;7(304):304re7. Epub 2015/09/12. doi: 7/304/304re7 [(pii]) 10.1126/scitranslmed.aac4765. PubMed PMID: 26355033; PubMed Central PMCID: PMC5600191.
11. Lustig RH. Fructose: it's "alcohol without the buzz". Adv Nutr. 2013;4(2):226-35. Epub 2013/03/16. doi: 4/2/226 [(pii]) 10.3945/an.112.002998. PubMed PMID: 23493539; PubMed Central PMCID: PMC3649103.
12. Shelmet JJ, Reichard GA, Skutches CL, Hoeldtke RD, Owen OE, Boden G. Ethanol causes acute inhibition of carbohydrate, fat, and protein oxidation and insulin resistance. J Clin Invest. 1988;81(4):1137-45. Epub 1988/04/01. doi: 10.1172/JCI113428. PubMed PMID: 3280601; PubMed Central PMCID: PMC329642.
13. Kim SJ, Ju A, Lim SG, Kim DJ. Chronic alcohol consumption, type 2 diabetes mellitus, insulin-like growth factor-I (IGF-I), and growth hormone (GH) in ethanol-treated diabetic rats. Life Sci.

2013;93(21):778-82. Epub 2013/10/03. doi: S0024-3205(13)00553-5 [(pii)] 10.1016/j.lfs.2013.09.018. PubMed PMID: 24084046.
14. Hirakawa M, Arase Y, Amakawa K, Ohmoto-Sekine Y, Ishihara M, Shiba M, et al. Relationship between Alcohol Intake and Risk Factors for Metabolic Syndrome in Men. Intern Med. 2015;54(17):2139-45. Epub 2015/09/04. doi: 0.2169/internalmedicine.54.2736. PubMed PMID: 26328637.
15. Carr RM, Dhir R, Yin X, Agarwal B, Ahima RS. Temporal effects of ethanol consumption on energy homeostasis, hepatic steatosis, and insulin sensitivity in mice. Alcohol Clin Exp Res. 2013;37(7):1091-9. Epub 2013/02/13. doi: 10.1111/acer.12075. PubMed PMID: 23398239; PubMed Central PMCID: PMC3657580.
16. Sterrett JJ, Bragg S, Weart CW. Type 2 Diabetes Medication Review. Am J Med Sci. 2016;351(4):342-55. Epub 2016/04/16. doi: S0002-9629(15)41058-4 [(pii)] 10.1016/j.amjms.2016.01.019. PubMed PMID: 27079339.
17. Smilowitz JT, O'Sullivan A, Barile D, German JB, Lonnerdal B, Slupsky CM. The human milk metabolome reveals diverse oligosaccharide profiles. J Nutr. 2013;143(11):1709-18. Epub 2013/09/13. doi: jn.113.178772 [(pii)] 10.3945/jn.113.178772. PubMed PMID: 24027187; PubMed Central PMCID: PMC4083237.
18. Matsubara T, Tanaka N, Krausz KW, Manna SK, Kang DW, Anderson ER, et al. Metabolomics identifies an inflammatory cascade involved in dioxin- and diet-induced steatohepatitis. Cell Metab. 2012;16(5):634-44. Epub 2012/11/13. doi: S1550-4131(12)00406-8 [(pii)] 10.1016/j.cmet.2012.10.006. PubMed PMID: 23140643; PubMed Central PMCID: PMC3496181.
19. Fan H, Fan W. Characterization of key odorants in Chinese chixiang aroma-type liquor by gas chromatography-olfactometry, quantitative measurements, aroma recombination, and omission studies. J Agric Food Chem 2015;63(14):3660-8
20. Saerens SM, Delvaux F, Verstrepen KJ, Van Dijck P, Thevelein JM, Delvaux FR. Parameters affecting ethyl ester production by Saccharomyces cerevisiae during fermentation. Appl Environ Microbiol. 2008;74(2):454-61. Epub 2007/11/13. doi: 10.1128/AEM.01616-07. PubMed PMID: 17993562; PubMed Central PMCID: PMCPMC2223249.
21. Kostelenos G, Kiritsakis A. Olive tree history and evolution. In: Kiritsakis A, Shahidi F, editors. Olives and olive oil as functional foods. Oxford, UK: John Wiley & Sons Ltd; 2017. p. 1-12.
22. Rahmani M. Food hazards and quality control in table olive processing with a special reference to functional compounds. In: Kiritsakis A, Shahidi F, editors. Olives and olive oil as functional foods. Oxford, UK: John Wiley & Sons Ltd; 2017. p. 347-52.
23. Hymowitz T. The history of the soybean. Soybeans Chemistry, Production, Processing and Utilization: AOCS Press 2008. p. 1-31.
24. Kwon DY, Daily JW, 3rd, Kim HJ, Park S. Antidiabetic effects of fermented soybean products on type 2 diabetes. Nutr Res. 2010;30(1):1-13. Epub 2010/02/02. doi: S0271-5317(09)00245-0 [(pii)] 10.1016/j.nutres.2009.11.004. PubMed PMID: 20116654.
25. Kim J, Chung H. Components in Commercial Douchi a Chinese Fermented Black Bean Product by Supercritical Fluid Extraction. J Food Sci Nutr 2008;13:12-7.
26. European Food Safety Authority (EFSA). Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food (AFC) on a request from the Commission related to Flavouring Group Evaluation 10: Aliphatic primary and secondary saturated and unsaturated alcohols, aldehydes, acetals, carboxylic acids and esters containing an additional

oxygenated functional group and lactones from chemical groups 9, 13 and 30 (Commission Regulation (EC) No 1565/2000 of 18 July 2000) The EFSA Journal 2005;246:1-110.
27. European Commission. Available from: https://ec.europa.eu/food/safety/food_improvement_agents/additives/database_en.
28. Food and Drug Administration (FDA) of the United States of America. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=172.515.
29. Food and Drug Administration (FDA) of the United States of America. Available from: https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm?event=BasicSearch.page.
30. Singh B, Saxena A. Surrogate markers of insulin resistance: A review. World J Diabetes. 2010;1(2):36-47. Epub 2011/05/04. doi: 10.4239/wjd.v1.i2.36. PubMed PMID: 21537426; PubMed Central PMCID: PMC3083884.
31. Bonora E, Tuomilehto J. The pros and cons of diagnosing diabetes with A1C. Diabetes Care. 2011;34 Suppl 2:S184-90. Epub 2011/05/06. doi: 34/Supplement_2/S184 [(pii)] 10.2337/dc11-s216. PubMed PMID: 21525453; PubMed Central PMCID: PMC3632159.
32. American, Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2013;36 Suppl 1:S67-74. Epub 2013/01/04. doi: 10.2337/dc13-S067. PubMed PMID: 23264425; PubMed Central PMCID: PMCPMC3537273.