

Zone Diet Validation Studies

The Zone diet is patented (U.S. Patent No. 6,140,304) to treat insulin resistance, which is the underlying cause of many chronic disease conditions such as diabetes, heart disease, and Alzheimer's.

The Zone diet is a calorie-restricted dietary program consisting of adequate protein, moderate carbohydrates, and low in fat to stabilize blood sugar levels (by controlling insulin levels) and to maintain satiety (by increasing the release of GLP-1 from the gut).

The approximate percentage of macronutrients in the Zone diet is 40 percent carbohydrate, 30 percent protein, and 30 percent fat. The published research articles below compared the Zone diet to other dietary programs. In particular, the Zone diet leads to the remission of prediabetes (Reference 41) and is more effective than the Mediterranean diet in reducing insulin resistance (Reference 43). The Zone diet is also used by the Joslin Diabetes Center at Harvard Medical School for the management of type 2 diabetes (References 16, 20, 21, and 34).

References

1. Markovic TP, Jenkins AB, Campbell LV, Furler SM, Kraegen EW, and Chisholm DJ. "The determinants of glycemic responses to diet restriction and weight loss in obesity and NIDDM." *Diabetes Care* 21:687-694 (1998) doi: 10.2337/diacare.21.5.687.
2. Ludwig DS, Majzoub JA, Al-Zahrani A, Dallal GE, Blanco I, and Roberts SB. "High glycemic index foods, overeating, and obesity." *Pediatrics* 103: E26 (1999) doi: 10.1542/peds.103.3. e26.
3. Agus MS, Swain JF, Larson CL, Eckert EA, and Ludwig DS. "Dietary composition and physiologic adaptations to energy restriction." *Am J Clin Nutr* 71:901-907 (2000) doi: 10.1093/ajcn/71.4.901.
4. Dumesnil JG, Turgeon J, Tremblay A, Poirier P, Gilbert M, Gagnon L, St-Pierre S, Garneau C, Lemieux I, Pascot A, Bergeron J, and Despres JP. "Effect of a low-glycaemic index-low-fat-high protein diet on the atherogenic metabolic risk profile of abdominally obese men." *Br J Nutr* 86:557-568 (2001) doi: 10.1079/bjn2001427.
5. Parker B, Noakes M, Luscombe N and Clifton P. "Effect of a high-protein, high-monounsaturated fat weight loss diet on glycemic control and lipid levels

in type 2 diabetes” *Diabetes Care* 25:425-430 (2002) doi: 10.2337/diacare.25.3.425.

6. Layman DK, Shiue H, Sather C, Erickson DJ, and Baum J. “Increased dietary protein modifies glucose and insulin homeostasis in adult women during weight loss.” *J Nutr* 133:405-410 (2003) doi: 10.1093/jn/133.2.405.

7. Layman DK, Boileau RA, Erickson DJ, Painter JE, Shiue H, Sather C, and Christou DD. “A reduced dietary carbohydrate to protein ratio improves body composition and blood lipid profiles during weight loss in adult women.” *J Nutr* 133:411-417 (2003) doi: 10.1093/jn/133.2.411.

8. Gannon MC, Nuttall FQ, Saeed A, Jordan K, and Hoover H. “An increase in dietary protein improves the blood glucose response in persons with type 2 diabetes.” *Am J Clin Nutr* 78:734-741 (2003) doi: 10.1093/ajcn/78.4.734.

9. Pereira MA, Swain J, Goldfine AB, Rifai N, and Ludwig DS. “Effects of a low-glycemic load diet on resting energy expenditure and heart disease risk factors during weight loss.” *JAMA* 292:2482-2490 (2004) doi: 10.1001/jama.292.20.2482.

10. Johnston CS, Tjonn SL, and Swan PD. “High-protein, low-fat diets are effective for weight loss and favorably alter biomarkers in healthy adults.” *J Nutr* 134:586-591 (2004) doi: 10.1093/jn/134.3.586.

11. Pittas AG, Das SK, Hajduk CL, Golden J, Saltzman E, Stark PC, Greenberg AS, and Roberts SB. “A low-glycemic load diet facilitates greater weight loss in overweight adults with high insulin secretion but not in overweight adults with low insulin secretion in the CALERIE Trial.” *Diabetes Care* 28:2939-2941 (2005) doi: 10.2337/diacare.28.12.2939.

12. Fontani G, Corradeschi F, Felici A, Alfatti F, Bugarini R, Fiaschi AI, Cerretani D, Montorfano G, Rizzo AM, and Berra B. “Blood profiles, body fat and mood state in healthy subjects on different diets supplemented with omega-3 polyunsaturated fatty acids.” *Eur J Clin Invest* 35:499-507 (2005) doi: 10.1111/j.1365-2362.2005.01540.x.

13. Johnston CS, Tjonn SL, Swan PD, White A, Hutchins H, and Sears B. “Ketogenic low-carbohydrate diets have no metabolic advantage over non-ketogenic low-carbohydrate diets.” *Am J Clin Nutr* 83:1055-1061 (2006) doi: 10.1093/ajcn/83.5.1055.

14. Pittas AG, Roberts SB, Das SK, Gilhooly CH, Saltzman E, Golden J, Stark PC, and Greenberg AS. "The effects of the dietary glycemic load on type 2 diabetes risk factors during weight loss." *Obesity* 14:2200-2209 (2006) doi: 10.1038/oby.2006.258.
15. Gannon MC and Nuttall FQ. "Control of blood glucose in type 2 diabetes without weight loss by modification of diet composition." *Nutr Metab* 3:16 (2006) doi: 10.1186/1743-7075-3-16
16. Giusti J and Rizzott J. "Interpreting the Joslin Diabetes Center and Joslin Clinic clinical guideline for overweight and obese adults with type 2 diabetes." *Curr Diab Report* 6:405-408 (2006) doi: 10.1007/s11892-006-0014-y.
17. Johnston CS, Tjonn SL, Swan PD, White A, and Sears B. "Low-carbohydrate, high-protein diets that restrict potassium-rich fruits and vegetables promote calciuria." *Osteoporos Int* 17:1820-1821 (2006) doi: 10.1007/s00198-006-0214-y.
18. Ebbeling CB, Leidig MM, Feldman HA, Lovesky MM, and Ludwig DS "Effects of a low-glycemic load vs. low-fat diet in obese young adults: a randomized trial." *JAMA* 297:2092-2102 (2007) doi: 10.1001/jama.297.19.2092.
19. White AM, Johnston CS, Swan PD, Tjonn SL, Sears B. "Blood ketones are directly related to fatigue and perceived effort during exercise in overweight adults adhering to low-carbohydrate diets for weight loss: a pilot study." *J Am Diet Assoc* 107:1792-1796 (2007) doi: 10.1016/j.jada.2007.07.009.
20. Hamdy O. "Diabetes weight management in clinical practice—the Why Wait model," *US Endocrinology* 4:49–54 (2008) doi.org/10.17925/USE.2008.04.2.49.
21. Hamdy O and Carver C. "The Why WAIT program: improving clinical outcomes through weight management in type 2 diabetes." *Curr Diab Rep* 8:413-420 (2008) doi: 10.1007/s11892-008-0071-5.
22. Lasker DA, Evans EM, and Layman DK. "Moderate carbohydrate, moderate protein weight loss diet reduces cardiovascular disease risk compared to high carbohydrate, low protein diet in obese adults: A randomized clinical trial." *Nutr Metab* 5:30 (2008) doi: 10.1186/1743-7075-5-30.

23. Layman DK, Evans EM, Erickson D, Seyler J, Weber J, Bagshaw D, Griel A, Psota T, and Kris-Etherton P. "A moderate-protein diet produces sustained weight loss and long-term changes in body composition and blood lipids in obese adults." *J Nutr* 139:514-521 (2009) doi: 10.3945/jn.108.099440.
24. Jenkins DJ, Wong JM, Kendall CW, Esfahani A, Ng VW, Leong TC, Faulkner DA, Vidgen E, Greaves KA, Paul G, and Singer W. "The effect of a plant-based low-carbohydrate diet on body weight and blood lipid concentrations in hyperlipidemic subjects." *Arch Intern Med* 169:1046-1054 (2009) doi: 10.1001/archinternmed.2009.115.
25. Evangelista LS, Heber D, Li Z, Bowerman S, Hamilton MA, and Fonarow GC. "Reduced body weight and adiposity with a high-protein diet improves functional status, lipid profiles, glycemic control, and quality of life in patients with heart failure: a feasibility study." *J Cardiovasc Nurs* 24:207-215 (2009) doi: 10.1097/JCN.0b013e31819846b9.
26. Pearce KL, Clifton PM, and Noakes M. "Egg consumption as part of an energy-restricted high-protein diet improves blood lipid and blood glucose profiles in individuals with type 2 diabetes." *Br J Nutr* 105:584-592 (2011) doi: 10.1017/S0007114510003983.
27. Kitabchi AE, McDaniel KA, Wan JY, Tylavsky FA, Jacovino CA, Sands CW, Nyenwe EA, and Stentz FB. "Effects of high-protein versus high-carbohydrate diets on markers of β -cell function, oxidative stress, lipid peroxidation, proinflammatory cytokines, and adipokines in obese, premenopausal women without diabetes: a randomized controlled trial." *Diabetes Care* 36:1 919-1925 (2013) doi: 10.2337/dc12-1912.
28. Mamerow MM, Mettler JA, English KL, Casperson SL, Arentson-Lantz E, Sheffield-Moore M, Layman DK, and Paddon-Jones D. "Dietary protein distribution positively influences 24-h muscle protein synthesis in healthy adults." *J Nutr* 144:876-80 (2014) doi: 10.3945/jn.113.185280
29. Moosheer SM, Waldschütz W, Itariu BK, Brath H, and Stulnig TM. "A protein-enriched low glycemic index diet with omega-3 polyunsaturated fatty acid supplementation exerts beneficial effects on metabolic control in type 2 diabetes." *Prim Care Diabetes*. 8:308-314 (2014) doi: 10.1016/j.pcd.2014.02.004.

30. Mottalib A, Sakr M, Shehabeldin M, and Hamdy O. "Diabetes remission after nonsurgical intensive lifestyle intervention in obese patients with type 2 diabetes." *J Diabetes Res* 2015:468704 (2015) doi: 10.1155/2015/468704.
31. Stulnig TM. "The Zone diet and metabolic control in type 2 diabetes." *J Am Coll Nutr* 34 Suppl 1:39-41 (2015) doi: 10.1080/07315724.2015.1080110.
32. Stentz FB, Brewer A, Wan J, Garber C, Daniels B, Sands C, and Kitabchi AE. "Remission of pre-diabetes to normal glucose tolerance in obese adults with high protein versus high carbohydrate diet." *BMJ Open Diabetes Res Care* 4:e000258 (2016) doi: 10.1136/bmjdr-2016-000258.
33. Markova M, Pivovarova O, Hornemann S, Sucher S, Frahnw T, Wegner K, Machann J, Petzke KJ, Hierholzer J, Lichtinghagen R, Herder C, Carstensen-Kirberg M, Roden M, Rudovich N, Klaus S, Thomann R, Schneeweiss R, Rohn S, and Pfeiffer AF. "Isocaloric diets high in animal or plant protein reduce liver fat and inflammation in individuals with type 2 diabetes." *Gastroenterology* 152:571-585 (2017) doi: 10.1053/j.gastro.2016.10.007.
34. Hamdy O, Mottalib A, Morsi A, El-Sayed N, Goebel-Fabbri A, Arathuzik G, Shahar J, Kirpitch A, and Zrebiec J. "Long-term effect of intensive lifestyle intervention on cardiovascular risk factors in patients with diabetes in real-world clinical practice: a 5-year longitudinal study." *BMJ Open Diabetes Res Care* 5: e000259 (2017) doi: 10.1136/bmjdr-2016-000259.
35. Liu K, Wang B, Zhou R, Lang HD, Ran L, Wang J, Li L, Kang C, Zhu XH, Zhang QY, Zhu JD, Doucette S, Kang JX, and Mi MT. "Effect of combined use of a low-carbohydrate, high-protein diet with omega-3 polyunsaturated fatty acid supplementation on glycemic control in newly diagnosed type 2 diabetes: a randomized, double-blind, parallel-controlled trial." *Am J Clin Nutr* 108:256-265 (2018) doi: 10.1093/ajcn/nqy120.
36. Mateo-Gallego R, Marco-Benedí V, Perez-Calahorra S, Bea AM, Baila-Rueda L, Lamiquiz-Moneo I, de Castro-Orós I, Cenarro A, and Civeira F. "Energy-restricted, high-protein diets more effectively impact cardiometabolic profile in overweight and obese women than lower-protein diets." *Clin Nutr* 36:371-379 (2017) doi: 10.1016/j.clnu.2016.01.018.
37. Liu K, Wang B, Zhou R, Lang HD, Ran L, Wang J, Li L, Kang C, Zhu XH, Zhang QY, Zhu JD, Doucette S, Kang JX, and Mi MT. "Effect of combined use of a low-carbohydrate, high-protein diet with omega-3 polyunsaturated fatty acid supplementation on glycemic control in newly diagnosed type 2

diabetes: a randomized, double-blind, parallel-controlled trial.” *Am J Clin Nutr* 108:256-265 (2018) doi: 10.1093/ajcn/nqy120.

39. Xu C, Markova M, Seebeck N, Loft A, Hornemann S, Gantert T, Kabisch S, Herz K, Loske J, Ost M, Coleman V, Klauschen F, Rosenthal A, Lange V, Machann J, Klaus S, Grune T, Herzig S, Pivovarova-Ramich O, and Pfeiffer AFH. “High-protein diet more effectively reduces hepatic fat than low-protein diet despite lower autophagy and FGF21 levels.” *Liver Int* 40:2982-2997 (2020) doi: 10.1111/liv.14596.

40. Coussa A, Bassil M, Gougeon R, Marliss EB, and Morais JA. “Glucose and protein metabolic responses to an energy- but not protein- restricted diet in type 2 diabetes.” *Diabetes Obes Metab* 22:1278-1285 (2020) doi: 10.1111/dom.14026.

41. Stentz FB, Mikhael A, Kineish O, Christman J, Sands C. “High protein diet leads to prediabetes remission and positive changes in incretins and cardiovascular risk factors.” *Nutr Metab Cardiovasc Dis* 31:1227-1237 (2021) doi: 10.1016/j.numecd.2020.11.027.

42. Evangelista LS, Jose MM, Sallam H, Serag H, Golovko G, Khanipov K, Hamilton MA, and Fonarow GC. “High-protein vs. standard-protein diets in overweight and obese patients with heart failure and diabetes mellitus: Findings of the Pro-HEART trial.” *ESC Heart Fail* 8:1342-1348 (2021) doi: 10.1002/ehf2.13213.

43. Tettamanzi F, Bagnardi V, Louca P, Nogal A, Monti GS, Mambrini SP, Lucchetti E, Maestrini S, Mazza S, Rodriguez-Mateos A, Scacchi M, Valdes AM, Invitti C, Menni C. “A high protein diet is more effective in improving insulin resistance and glycemic variability compared to a Mediterranean diet: A cross-over controlled inpatient dietary study. *Nutrients* 13:4380 (2021) doi: org/10.3390/nu13124380.