Soy Isoflavones

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Contributor: Agnieszka Baranska

After consumption of soy isoflavones, a study revealed statistically insignificant reduction in fasting glucose, insulin, HbA1c, and HOMA-IR (changes in glucose metabolism). The observed ability of both extracted isoflavone and soy protein with isoflavones to modulate the lipid profile suggests benefits in preventing cardiovascular events in diabetic subjects.

Keywords: T2DM ; soy isoflavones ; lipid profile ; total cholesterol ; HDL-C ; LDL-C ; triacylglycerol ; glycemic control ; HbA1c ; HOMA-IR

1. Introduction

Improvements in glycemic control have been demonstrated in adults with T2DM through a combination of pharmaceuticals and lifestyle changes, and with lifestyle changes alone [1][2]. Lifestyle factors such as diet and physical activity can be individually modified. It is important to choose a diet in relation to the quality of nutrients, including carbohydrates, protein, fats, minerals and vitamins, and to establish its health benefits [3][4]. A number of studies on animal models [5][6][7] and intervention studies in humans [8][9][10][11][12] have shown that soy protein with isoflavones can improve the parameters of glycemic control and lipid homeostasis. Recently, several new studies on this topic have appeared [13][14][15].

2. Effects of Soy Isoflavones on Glycemic Control and Lipid Profile in Patients with Type 2 Diabetes

It demonstrated a significant reduction in the concentration of TC (–0.21 mmol/L, $p = 0.0008$) and LDL-C (–0.20 mmol/L, $p < 0.0001$) in the plasma, while the levels of HDL-C (–0.02 mmol/L, $p = 0.2008$) and TAG (–0.19 mmol/L, $p = 0.1884$) did not change significantly after ingesting soy isoflavone supplements. Zhang et al. [16] also showed significant reduction in TC (–0.39, $p < 0.01$) and in LDL-C (–0.30, $p < 0.01$) and non-significant decrease in HDL-C (–0.05, $p = 0.55$) and TAG (–0.094, $p = 0.27$), while Yang et al. [17] noted significant reduction in TC (–0.42, $p < 0.05$), TAG (–0.22, $p < 0.05$), significant reduction in LDL-C (–0.30, $p = 0.05$) and significant increase in HDL-C (0.05, $p < 0.05$). Furthermore, Soltanipour et al. [18] observed significant reduction of TC (–0.47, $p < 0.01$). In addition, soy products consumption was seen to be beneficial in decreasing LDL-C and TAG, but had no significant effects on HDL-C (results not shown). Beyond the aforementioned, Giordano et al. revealed in their study that soy isoflavones increased plasma TC concentrations and decreased triglyceride ones—adding further evidence to the notion that soy isoflavones have assorted effects on cardiometabolic risk factors [19].

Simultaneously the effects on glycemic control revealed that soy protein and/or isoflavones are not significantly effective in reducing circulating glucose levels. In addition, the outcome of our meta-analysis of randomized controlled trials has indicated that soy protein and/or isoflavones supplementation has no statistical significance effect on glycemic control in T2DM (FBG: –0.30 mmol/L, $p = 0.28$; FI: –3.40 pmol/L, $p = 0.37$; HbA1c: –0.80%, $p = 0.13$; and HOMA-IR: –0.07, $p = 0.79$). These results are similar to those of Yang et al. [17], who, in 2011, also did not show any significant effect of soy protein and/or isoflavones on the level of FBG, FI and HbA1c. In turn, the meta-analysis by Zhang et al. [16], published in 2016 and based on eight trials with 13 comparisons revealed significant changes in the FBG, FI and HOMA-IR values after administering soy preparations (–0.207, $p = 0.015$; –0.29, $p = 0.01$; and –0.346, $p < 0.01$; respectively). Moreover, a recently published meta-analysis by Soltanipour et al. [18] reported that, according to the data from 14 RCTs, soy consumption had significant effects on HOMA-IR level (–0.25, $p < 0.01$), in the absence of significant effects on FBG (–0.14, $p = 0.09$; FI: –0.11, $p = 0.11$; and HbA1c: –0.22, $p = 0.18$).

The observed differences in outcomes can be result of differences in the inclusion criteria. We relied only on studies assessing the effects of isoflavones contained in soy protein or on the isoflavones alone. Yang et al. [17] used a study by Anderson et al. [20] in which only soy protein was used. In turn, the meta-analysis by Zhang et al. [16] included research with soy protein alone [20] or black soybean peptides [21], but also a study involving nondiabetic people with metabolic

syndrome [22]. Furthermore, Soltanipour et al. [18], in addition to including seven out of 16 studies using isolated soy protein and isoflavones [15][23][24][25][26][27][28][29], also analyzed studies using different types of soy products such as soy milk [30][31], bread fortified with soy flour [32], soy germ pasta enriched in isoflavones [12], multifilament soy protein-based diabetes-specific food [9], as well as other preparations containing native starch banana [33] or flavan-3-ols/isoflavones [34].

The molecular and physiological mechanisms underlying the metabolic action of phytoestrogens components containing in soybean have not yet been fully recognized. The studies conducted with soy dietary isoflavones and isoflavone alone in cell culture or in animal models and human studies have definitely demonstrated that isoflavones can improve some parameters associated with the course of diabetes. In addition, the structural similarity between soy isoflavones and endogenous 17-β-estradiol suggests that isoflavones, by binding to estrogen receptors (ERs), lead to gene activation and beneficial effects on glucose and lipid metabolism [35][36].

There is some evidence to intimate that estrogen receptor (ER) binding is only part of the isoflavone effect [37]. Genistein and daidzein (and its metabolite equol), improve glycemic control, and significantly alter glucose homeostasis through: (a) stimulating insulin secretion by inhibiting tyrosine kinase (TK) [38][39]; (b) activating adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK)—which results in decrease blood glucose in the liver, while stimulating glucose uptake independently of insulin in skeletal muscles and modulating glucose transport in peripheral tissue [40]; (c) activating the peroxisome proliferator-activated receptor gamma (PPARγ); thus, enhancing the expression and translocation of GLUT-1 and GLUT-4—which results in increased glucose uptake in adipocytes and muscle cells and subsequent reduction in plasma glucose levels [41]; (d) inhibiting alpha-glucosidase (AG)—which leads to slowing down the absorption of glucose in the gut [42]; and (e) directly modulating pancreatic beta-cell function and conferring protection against apoptosis through mechanisms that involve cyclic AMP/Protein Kinase A (cAMP/PKA) signaling [43][44].

Moreover, isoflavones can also regulate lipid metabolism without the mediation of estrogen receptors; increase expression of PPARα and activate AMPK—which results in increased activity of genes involved in lipoprotein metabolism; reduce TG-rich particle production and increase their lipolysis; promote HDL metabolism and promote the uptake, utilization and catabolism of fatty acid [45][46][47]. Furthermore, isoflavones can inhibit the expression and activity of the sterol regulatory element binding protein-1c (SREBP-1c) and carbohydrate regulatory element binding protein-1 (ChREBP)—proteins that enhance the expression of lipogenic genes and key enzymes involved in de novo lipogenesis [48][49]. Other possible mechanisms of soy isoflavones that may modulate lipoprotein metabolism, include their effects on several enzymes important in lipid transformation, including lipoprotein lipase (LPL), hepatic lipase (HL) also called hepatic triglyceride lipase (HTGL), and 7alpha-hydroxylase [50][51].

3. Conclusions

We found that consumption of soy isoflavones brought about a statistically significant reduction in total and LDL cholesterol, while simultaneously demonstrating no significant effects on HDL and TAG. Influence of soy isoflavones on glucose levels has been shown to be statistically insignificant. Moreover, the ability of both extracted isoflavone and soy protein with isoflavones to modulate the lipid profile suggests benefits in preventing cardiovascular events in people with type 2 diabetes. However, further multicenter studies based on a larger pool of research material and a well accurately defined dose of isoflavones are necessary to determine their beneficial effects on glucose and lipid metabolism.

References

1. Krook, A.; Holm, I.; Pettersson, S.; Wallberg-Henriksson, H. Reduction of risk factors following lifestyle modification programme in subjects with type 2 (non-insulin dependent) diabetes mellitus. Clin. Physiol. Funct. Imaging. 2003, 23, 21–30.
2. Kim, H.J.; Jung, T.S.; Jung, J.H.; Kim, S.K.; Lee, S.M.; Kim, K.Y.; Kim, D.R.; Seo, Y.M.; Hahm, J.R. Improvement of glycemic control after re-emphasis of lifestyle modification in type 2 diabetic patients reluctant to additional medication. Yonsei Med. J. 2013, 54, 345–351.
3. Brekke, H.K.; Lenner, R.A.; Taskinen, M.R.; Månsson, J.E.; Funahashi, T.; Matsuzawa, Y.; Jansson, P.A. Lifestyle modification improves risk factors in type 2 diabetes relatives. Diabetes Res. Clin. Pract. 2005, 68, 18–28.
4. Dailey, G. Early and intensive therapy for management of hyperglycemia and cardiovascular risk factors in patients with type 2 diabetes. Clin. Ther. 2011, 33, 665–678.
5. Bartke, A.; Peluso, M.R.; Moretz, N.; Wright, C.; Bonkowski, M.T.A.; Winters, T.A.; Shanahan, M.F.; Kopchick, J.J.; Banz, W.J. Effects of soy-derived diets on plasma and liver lipids, glucose tolerance, and longevity in normal, long-lived and short-lived mice. Horm. Metab. Res. 2004, 36, 550–558.

6. Lu, M.P.; Wang, R.; Song, X.; Chibbar, R.; Wang, X.; Wu, L.; Meng, Q.H. Dietary soy isoflavones increase insulin secretion and prevent the development of diabetic cataracts in streptozotocin-induced diabetic rats. Nutr. Res. 2008, 28, 464–471.
7. Nordentoft, I.; Jeppesen, P.B.; Hong, J.; Abudula, R.; Hermansen, K. Increased insulin sensitivity and changes in the expression profile of key insulin regulatory genes and beta cell transcription factors in diabetic KKAy-mice after feeding with a soy bean protein rich diet high in isoflavone content. J. Agric. Food Chem. 2008, 56, 4377–4385.
8. Shahbazian, H.; Reza, A.; Javad, S.; Heshmatollah, S.; Mahmood, L.; Ali, A.; Hosain, H.M. Beneficial effects of soy protein isoflavones on lipid and blood glucose concentrations in type 2 diabetic subjects. Saudi Med. J. 2007, 28, 652–654.
9. Vaisman, N.; Lansink, M.; Rouws, C.H.; van Laere, K.M.; Segal, R.; Niv, E.; Bowling, T.E.; Waitzberg, D.L.; Morley, J.E. Tube feeding with a diabetes-specific feed for 12 weeks improves glycaemic control in type 2 diabetes patients. Clin. Nutr. 2009, 28, 549–555.
10. Clerici, C.; Nardi, E.; Battezzati, P.M.; Asciutti, S.; Castellani, D.; Corazzi, N.; Giuliano, V.; Gizzi, S.; Perriello, G.; Di Matteo, G.; et al. Novel soy germ pasta improves endothelial function, blood pressure, and oxidative stress in patients with type 2 diabetes. Diabetes Care 2011, 34, 1946–1948.
11. Urita, Y.; Noda, T.; Watanabe, D.; Iwashita, S.; Hamada, K.; Sugimoto, M. Effects of a soybean nutrition bar on the postprandial blood glucose and lipid levels in patients with diabetes mellitus. Int. J. Food Sci. Nutr. 2012, 63, 921–929.
12. Setchell, K.D.; Nardi, E.; Battezzati, P.M.; Asciutti, S.; Castellani, D.; Perriello, G.; Clerici, C. Novel soy germ pasta enriched in isoflavones ameliorates gastroparesis in type 2 diabetes: A pilot study. Diabetes Care. 2013, 36, 3495–3497.
13. Konya, J.; Sathyapalan, T.; Kilpatrick, E.S.; Atkin, S.L. The effects of soy protein and cocoa with or without isoflavones on glycemic control in type 2 diabetes. A double-blind, randomized, placebo-controlled study. Front. Endocrinol. 2019, 10, 296.
14. Sathyapalan, T.; Rigby, A.S.; Bhasin, S.; Thatcher, N.J.; Kilpatrick, E.S.; Atkin, S.L. Effect of soy in men with type 2 diabetes mellitus and subclinical hypogonadism: A randomized controlled study. J. Clin. Endocrinol. Metab. 2017, 102, 425–433.
15. Chi, X.X.; Zhang, T.; Zhang, D.J.; Yu, W.; Wang, Q.Y.; Zhen, J.L. Effects of isoflavones on lipid and apolipoprotein levels in patients with type 2 diabetes in Heilongjiang Province in China. J. Clin. Biochem. Nutr. 2016, 59, 134–138.
16. Zhang, X.M.; Zhang, Y.B.; Chi, M.H. Soy protein supplementation reduces clinical indices in type 2 diabetes and metabolic syndrome. Yonsei Med. J. 2016, 57, 681–689.
17. Yang, B.; Chen, Y.; Xu, T.; Yu, Y.; Huang, T.; Hu, X.; Li, D. Systematic review and meta–analysis of soy products consumption in patients with type 2 diabetes mellitus. Asia Pac. J. Clin. Nutr. 2011, 20, 593–602.
18. Soltanipour, S.; Hasandokht, T.; Soleimani, R.; Mahdavi-Roshan, M.; Jalali, M.M. Systematic review and meta-analysis of the effects of soy on glucose metabolism in patients with type 2 diabetes. Rev. Diab. Stud. 2019, 15, 60–70.
19. Giordano, E.; Dávalos, A.; Crespo, M.C.; Tomé-Carneiro, J.; Gómez-Coronado, D.; Visioli, F. Soy isoflavones in nutritionally relevant amounts have varied nutrigenomic effects on adipose tissue. Molecules 2015, 20, 2310–2322.
20. Anderson, J.W.; Blake, J.; Turner, J.; Smith, B.M. Effects of soy protein on renal function and proteinuria in patients with type 2 diabetes. Am. J. Clin. Nutr. 1999, 68, 1347–1353.
21. Kwak, J.H.; Lee, J.H.; Ahn, C.W.; Park, S.H.; Shim, S.T.; Song, Y.D.; Han, E.N.; Lee, K.H.; Chae, J.S. Black soy peptide supplementation improves glucose control in subjects with prediabetes and newly diagnosed type 2 diabetes mellitus. J. Med. Food. 2010, 13, 1307–1312.
22. Azadbakht, L.; Kimiagar, M.; Mehrabi, Y.; Esmaillzadeh, A.; Padyab, M.; Hu, F.B.; Willett, W.C. Soy inclusion in the diet improves features of the metabolic syndrome: Used soy protein alone a randomized crossover study in postmenopausal women. Am. J. Clin. Nutr. 2007, 85, 735–741.
23. Gobert, C.P.; Pipe, E.A.; Capes, S.E.; Darlington, G.A.; Lampe, J.W.; Duncan, A.M. Soy protein does not affect glycemic control in adults with type 2 diabetes. Br. J. Nutr. 2010, 103, 412–421.
24. Azadbakht, L.; Atabak, S.; Esmaillzadeh, A. Soy protein intake, cardiorenal indices, and C-reactive protein in type 2 diabetes with nephropathy: A longitudinal randomized clinical trial. Diabetes Care 2008, 31, 648–654.
25. González, S.; Jayagopal, V.; Kilpatrick, E.S.; Chapman, T.; Atkin, S.L. Effects of isoflavone dietary supplementation on cardiovascular risk factors in type 2 diabetes. Diabetes Care 2007, 30, 1871–1873.
26. Teixeira, S.R.; Tappenden, K.A.; Carson, L.; Jones, R.; Prabhudesai, M.; Marshall, W.P.; Erdman, J.W., Jr. Isolated soy protein consumption reduces urinary albumin excretion and improves the serum lipid profile in men with type 2 diabetes

mellitus and nephropathy. J. Nutr. 2004, 134, 1874–1880.

27. Jayagopal, V.; Albertazzi, P.; Kilpatrick, E.S.; Howarth, E.M.; Jennings, P.E.; Hepburn, D.A.; Atkin, S.L. Beneficial effects of soy phytoestrogen intake in postmenopausal women with type 2 diabetes. Diabetes Care 2002, 25, 1709–1714.
28. Hermansen, K.; Søndergaard, M.; Høie, L.; Carstensen, M.; Brock, B. Beneficial effects of a soy-based dietary supplement on lipid levels and cardiovascular risk markers in type 2 diabetic subjects. Diabetes Care 2001, 24, 228–233.
29. Azadbakht, L.; Shakerhosseini, R.; Atabak, S.; Jamshidian, M.; Mehrabi, Y.; Esmaill-Zadeh, A. Beneficiary effect of dietary soy protein on lowering plasma levels of lipid and improving kidney function in type II diabetes with nephropathy. Eur. J. Clin. Nutr. 2003, 57, 1292–1294.
30. Miraghajani, M.S.; Mirlohi, M.; Esmaillzadeh, A.; Azadbakht, L.; Najafbadi, M.M. Soy milk consumption, inflammation, coagulation, and oxidative stress among type 2 diabetic patients with nephropathy. Diabetes Care 2012, 35, 1981–1985.
31. Chang, J.H.; Min Sun Kim, M.S.; Kim, T.W.; Lee, S.S. Effects of soybean supplementation on blood glucose, plasma lipid levels, and erythrocyte antioxidant enzyme activity in type 2 diabetes mellitus patients. Nutr. Res. Pract. 2008, 2, 152–157.
32. Salari Moghaddam, A.; Hassan Entezari, M.H.; Iraj, B.; Gholam Reza Askari, G.R.; Maracy, M.R. The effects of consumption of bread fortified with soy bean flour on metabolic profile in Type 2 diabetic women: A cross-over randomized controlled clinical trial. Int. J. Prev. Med. 2014, 5, 1529–1536.
33. Ble-Castillo, J.L.; Aparicio-Trápala, M.A.; Francisco-Luria, M.U.; Córdova-Uscanga, R.; Rodríguez-Hernández, A.; Méndez, J.D.; Díaz-Zagoya, J.C. Effects of native banana starch supplementation on body weight and insulin sensitivity in obese type 2 diabetics. Int. J. Environ. Res. Public Health 2010, 7, 1953–1962.
34. Curtis, P.J.; Sampson, M.; Potter, J.; Dhatariya, K.; Kroon, P.A.; Cassidy, A. Chronic ingestion of flavan-3-ols and isoflavones improves insulin sensitivity and lipoprotein status and attenuates estimated 10-year CVD risk in medicated postmenopausal women with type 2 diabetes: A 1-year, double-blind, randomized, controlled trial. Diabetes Care 2012, 35, 226–232.
35. Vitale, D.C.; Piazza, C.; Melilli, B.; Drago, F.; Salomone, S. Isoflavones: Estrogenic activity, biological effect and bioavailability. Eur. J. Drug Metab. Pharmacokinet. 2013, 38, 15–25.
36. Andres, S.; Hansen, U.; Niemann, B.; Palavinskas, R.; Lampen, A. Determination of the isoflavone composition and estrogenic activity of commercial dietary supplements based on soy or red clover. Food Funct. 2015, 6, 2017–2025.
37. Barnes, S.; Kim, H.; Darley-Usmar, V.; Patel, R.; Xu, J.; Boersma, B.; Luo, M. Beyond ERalpha and ERbeta: Estrogen receptor binding is only part of the isoflavone story. J. Nutr. 2000, 130, 656–657.
38. Liu, D.; Zhen, W.; Yang, Z.; Carter, J.D.; Si, H.; Reynolds, K.A. Genistein acutely stimulates insulin secretion in pancreatic beta-cells through a cAMP-dependent protein kinase pathway. Diabetes 2006, 55, 1043–1050.
39. Jonas, J.C.; Plant, T.D.; Gilon, P.; Detimary, P.; Nenquin, M.; Henquin, J.C. Multiple effects and stimulation of insulin secretion by the tyrosine kinase inhibitor genistein in normal mouse islets. Br. J. Pharmacol. 1995, 114, 872–880.
40. Vazirian, M.; Nabavi, S.M.; Jafari, S.; Manayi, A. Natural activators of adenosine 5’-monophosphate (AMP)-activated protein kinase (AMPK) and their pharmacological activities. Food Chem. Toxicol. 2018, 122, 69–79.
41. Ha, B.G.; Nagaoka, M.; Yonezawa, T.; Tanabe, R.; Woo, J.T.; Kato, H.; Chung, U.I.; Yagasaki, K. Regulatory mechanism for the stimulatory action of genistein on glucose uptake in vitro and in vivo. J. Nutr. Biochem. 2012, 23, 501–509.
42. Lee, D.S.; Lee, S.H. Genistein, a soy isoflavone, is a potent alpha-glucosidase inhibitor. FEBS Lett. 2001, 501, 84–86.
43. Fu, Z.; Zhang, W.; Zhen, W.; Lum, H.; Nadler, J.; Bassaganya-Riera, J.; Jia, Z.; Wang, Y.; Misra, H.; Liu, D. Genistein induces pancreatic beta-cell proliferation through activation of multiple signaling pathways and prevents insulin-deficient diabetes in mice. Endocrinology 2010, 151, 3026–3037.
44. Gilbert, E.R.; Liu, D. Anti-diabetic functions of soy isoflavone genistein: Mechanisms underlying its effects on pancreatic β-cell function. Food Funct. 2013, 4, 200–212.
45. Dang, Z.C.; Audinot, V.; Papapoulos, S.E.; Boutin, J.A.; Löwik, C.W.G.M. Peroxisome proliferator-activated receptor gamma (PPARgamma) as a molecular target for the soy phytoestrogen genistein. J. Biol. Chem. 2003, 278, 962–967.
46. Mezei, O.; Li, Y.; Mullen, E.; Ross-Viola, J.S.; Shay, N.F. Dietary isoflavone supplementation modulates lipid metabolism via PPARalpha-dependent and -independent mechanisms. Physiol. Genomics 2006, 26, 8–14.

47. Cederroth, C.R.; Vinciguerra, M.; Gjinovci, A.; Kühne, F.; Klein, M.; Cederroth, M.; Caille, D.; Suter, M.; Neumann, D.; James, R.W.; et al. Dietary phytoestrogens activate AMP-activated protein kinase with improvement in lipid and glucose metabolism. Diabetes 2008, 57, 1176–1185.
48. Mullen, E.; Brown, R.M.; Osborne, T.F.; Shay, N.F. Soy isoflavones affect sterol regulatory element binding proteins (SREBPs) and SREBP-regulated genes in HepG2 cells. J. Nutr. 2004, 134, 2942–2947.
49. Xu, X.; So, J.S.; Park, J.G.; Lee, A.H. Transcriptional control of hepatic lipid metabolism by SREBP and ChREBP. Semin. Liver Dis. 2013, 33, 301–311.
50. Demonty, I.; Lamarche, B.; Deshaies, Y.; Jacques, H. Role of soy isoflavones in the hypotriglyceridemic effect of soy protein in the rat. J. Nutr. Biochem. 2002, 13, 671–677.
51. Xue, Z.; Zhang, Q.; Yu, W.; Wen, H.; Hou, X.; Li, D.; Kou, X. Potential lipid-lowering mechanisms of biochanin A. J. Agric. Food Chem. 2017, 65, 3842–3850.72.