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A Systematic Review of the Effects of Plant Compared with Animal Protein Sources on Features of Metabolic Syndrome[1–3]

Tristan Chalvon-Demersay,[4] Dalila Azzout-Marniche,[4] Judith Arfsten,[5] Léonie Egli,[5] Claire Gaudichon,[4] Leonidas G Karagounis,[5] and Daniel Tomé[4]*

[4]UMR Nutrition Physiology and Ingestive Behavior, AgroParisTech, INRA, Université Paris-Saclay, Paris, France; and [5]Nestlé Research Centre, Vers-Chez-Les Blanc, Lausanne, Switzerland

Abstract

Dietary protein may play an important role in the prevention of metabolic dysfunctions. However, the way in which the protein source affects these dysfunctions has not been clearly established. The aim of the current systematic review was to compare the impact of plant- and animal-sourced dietary proteins on several features of metabolic syndrome in humans. The PubMed database was searched for both chronic and acute interventional studies, as well as observational studies, in healthy humans or those with metabolic dysfunctions, in which the impact of animal and plant protein intake was compared while using the following variables: cholesterolemia and triglyceridemia, blood pressure, glucose homeostasis, and body composition. Based on data extraction, we observed that soy protein consumption (with isoflavones), but not soy protein alone (without isoflavones) or other plant proteins (pea and lupine proteins, wheat gluten), leads to a 3% greater decrease in both total and LDL cholesterol compared with animal-sourced protein ingestion, especially in individuals with high fasting cholesterol concentrations. This observation was made when animal proteins were provided as a whole diet rather than given supplementally. Some observational studies reported an inverse association between plant protein intake and systolic and diastolic blood pressure, but this was not confirmed by intervention studies. Moreover, plant protein (wheat gluten, soy protein) intake as part of a mixed meal resulted in a lower postprandial insulin response than did whey. This systematic review provides some evidence that the intake of soy protein associated with isoflavones may prevent the onset of risk factors associated with cardiovascular disease, i.e., hypercholesterolemia and hypertension, in humans. However, we were not able to draw any further conclusions from the present work on the positive effects of plant proteins relating to glucose homeostasis and body composition. *J Nutr* 2017;147:281–92.

Keywords: plant protein, animal protein, metabolic syndrome, blood pressure, cholesterol, body composition, glucose homeostasis

Introduction

Metabolic and physiologic dysfunctions, including hyperglycemia, abdominal obesity, hypertriglyceridemia, hypertension, and low-HDL cholesterolemia, are associated with an increased risk of type 2 diabetes and cardiovascular disease (1). Individuals presenting with ≥3 of these dysfunctions are diagnosed with metabolic syndrome. Patients with metabolic syndrome are 5 times more likely to develop type 2 diabetes and 3 times more likely to develop cardiovascular diseases over 5–10 y (2). Worldwide, the prevalence of metabolic syndrome is ~25%, but the distribution is heterogeneous and affected by various factors, including environmental, genetic, and cultural factors (1).

Lifestyle modifications that use physical activity and nutritional intervention are recommended for individuals who have or are at risk of developing metabolic syndrome. Indeed, some features of metabolic syndrome have been reported to be improved by dietary interventions such as low–glycemic index and low–glycemic load diets. The glycemic response of a diet is highly affected by its carbohydrate content and quality, but also by its fat and protein content (3). Indeed, the addition of dietary protein to a carbohydrate-based meal may reduce the ensuing glycemic response by delaying gastric emptying and stimulating

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*To whom correspondence should be addressed. E-mail: tome@agroparistech.fr.

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insulin secretion (4, 5). Therefore, such nutritional strategies may represent a way of reducing the glucose load in individuals with glucose homeostasis defects. In addition, high-protein diets have also been shown to be effective in preventing some features of metabolic syndrome (6) by reducing fat mass while also maintaining lean body mass during energy-deficient weight-loss diets (7), as well as by increasing HDL cholesterol (8).

Beyond the amount of protein intake, the source of dietary protein has also been shown to be an important factor influencing metabolic risk factors.

For example, Pan et al. (9) reported that a diet high in red meat was associated with an increased risk of cardiovascular disease, and that substitution with other products, such as plants, could lower this risk. However, whether or not this observed increase in risk is driven by protein per se is unclear and difficult to define. On the other hand, soy protein was claimed by the FDA (1999) to decrease cardiovascular disease risk through a cholesterol-lowering effect, whereas casein was thought to be hypercholesterolemic (10). In addition, given the current increased environmental impact of animal proteins, plant proteins are likely to be favored in the future for human consumption, given their lower environmental impact (11, 12).

In this context, this systematic review aimed to compare the effects of animal- and plant-sourced proteins on lipemia, blood pressure, glucose homeostasis, and body composition in healthy humans or in those with metabolic defects reported in both interventional and observational studies.

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (13). Prisma checklist is available in **Supplemental Table 1**. Ethical approval was not required because this was a secondary data analysis.

Literature search. A systematic search of the relevant literature was performed with the use of PubMed in order to identify interventional and observational studies investigating the relation between plant- and animal-sourced proteins on markers of lipemia, blood pressure, and glucose homeostasis (glycemia and insulinemia), as well as body composition, published before March 2016. The structured search strategies used the combination of an animal- and a plant-sourced protein with an outcome related to metabolic syndrome features: [animal protein OR dairy protein OR meat OR whey OR casein OR meat OR milk OR different sources of protein] AND [vegetable protein OR plant-based protein OR soy OR gluten OR cereal OR rice] AND [insulin OR glucose OR body OR weight OR lipids OR triglycerides OR HDL OR LDL OR cholesterol OR blood pressure].

Articles retrieved were then included or excluded based on the criteria outlined below.

Inclusion criteria:

- Articles published in a peer-reviewed journal
- Cross-sectional, cohort, and interventional studies
- Studies conducted in both children and adults
- Studies conducted in healthy humans, or those with metabolic impairment (overweight, obese, hypercholesterolemic, prehypertensive, hypertensive, or with type 2 diabetes)
- Studies assessing the relation of the source of dietary protein on one of the following factors—
    - Fasting or postprandial TGs, and total, HDL, and LDL cholesterol
    - Systolic or diastolic blood pressure
    - Fasting or postprandial glucose and/or insulin, measures of insulin sensitivity
    - Body weight, body composition, fat and fat-free mass

Exclusion criteria:

- Case studies
- Letters, commentaries, conference papers, narrative reviews
- Studies conducted in infants
- Studies not conducted in humans

The search was limited to literature presented in the English language. Only studies comparing the effect of both animal and plant proteins were included. A second systematic search was performed in parallel with the use of the electronic search tool ProQuest Dialog, with which we searched in 4 different databases: BIOSIS Previews, CAB ABSTRACTS, Embase, and MEDLINE. The same inclusion and exclusion criteria were used. The keywords used to retrieve literature are presented in **Supplemental Table 2**. The selection of the articles was performed by a second reviewer, and results from the 2 systematic searches were combined.

Quality assessment. Each study was assessed with the use of a quality score methodology as illustrated in **Supplemental Table 3**. The methodology was derived from a quality score recently used by Voortman et al. (14) and adapted for acute intervention studies and measurements related to body composition. A score ranging from 0 to 2 was allocated for each of the 5 following characteristics: study design, population size, exposure, adjustment for potential confounders, and subject characteristics. The score of these 5 characteristics was summed up, with a score of 10 representing the highest quality and a score of 0 representing the lowest quality. High quality was assigned to studies with a score of $\geq$6, whereas low quality was assigned to studies with a score <6.

Data extraction. Data on study design, population size, exposure (description of the dietary intervention), adjustment for potential confounders or subject characteristics, and outcome measurements were extracted for the quality assessment. The results of each comparison between plant- and animal-sourced proteins were reported for each of the following outcomes:

- Fasting total, LDL, and HDL cholesterol; LDL:HDL cholesterol ratio; fasting TGs; postprandial TGs after a protein-based meal
- Systolic and diastolic blood pressure
- Fasting glucose and insulin, postprandial glucose and insulin after a protein-based meal, homeostasis model assessment index
- BMI, waist circumference, body weight, and lean body mass

The percentage difference between groups was extracted when the comparison was statistically significant. Additional data on study design, number of participants, population characteristics (including age, sex, and health status), protein form and supply, and isoflavone quantity were extracted and taken into account for subsequent data analysis. A qualitative synthesis of the evidence was performed.

Specifically, we deemed evidence to be strong if at least one-half of the higher-quality studies or two-thirds of the lower-quality studies reported consistent results and moderate if at least one-third of the higher-quality studies or one-half of the lower-quality studies reported consistent results. Below these thresholds, findings were considered to be inconclusive.

Results of high-quality studies (i.e., with a score $\geq$6) and low-quality studies (i.e., with a score <6) were also analyzed separately to evaluate whether or not different conclusions would be drawn depending on the quality of the study.

Results

Characteristics of the included studies. The systematic search in PubMed retrieved a total of 11,008 titles, of which 103 articles fulfilled the inclusion criteria. The details of the number of references retrived during systematic search is available in **Supplemental Table 4**. The second literature search yielded 20 additional articles, resulting in a total final inclusion of 123 articles: 107 intervention studies, 7 cross-sectional studies, and 9 longitudinal studies (**Figure 1**). In all, the 123 studies included a total number of 516,330 participants. Studies included healthy participants, as well as obese or overweight, diabetic, hypercholesterolemic, and hypertensive participants of all ages.

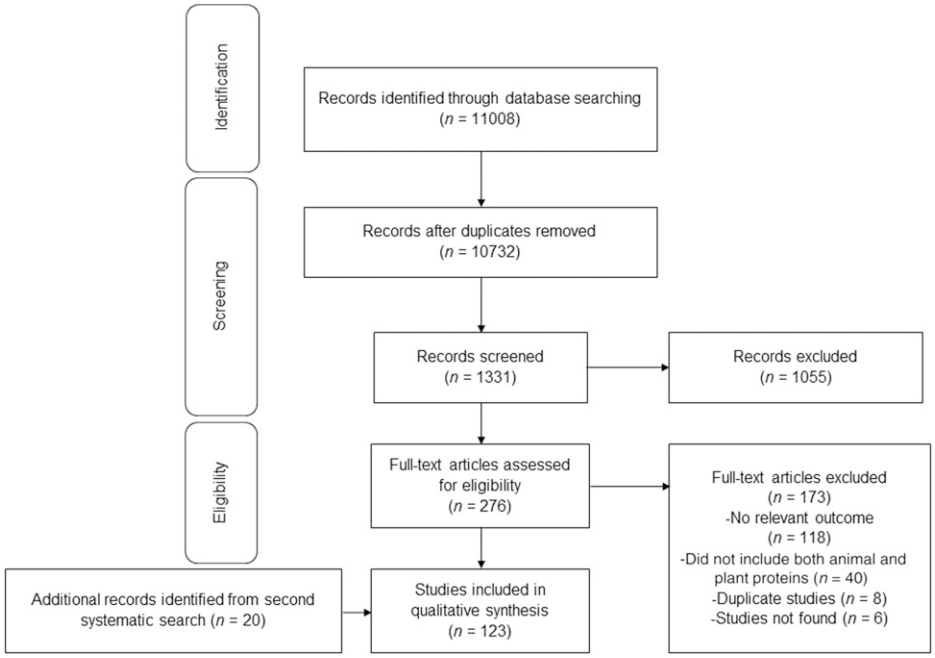

FIGURE 1 Flow chart of the study selection.

The plant-sourced proteins used in the trials were mainly soy proteins, both those associated with and those not associated with isoflavones, in addition to lupine, barley, pea, rice, and fava bean proteins, as well as the protein fraction of wheat referred to as wheat gluten.

With respect to animal-sourced proteins, casein was often used as a control, but trials also tested the effect of total milk, whey, meat (beef and pork), cod, cottage cheese, and egg protein. The overall quality score of the included studies ranged between 3 and 10, with a mean score of 6.6 indicating that the studies included herewith were of good quality, on average. Details of all the included studies can be found in **Supplemental Table 5**.

Cholesterolemia and triglyceridemia. In total, 96 comparisons from 66 articles investigated the effects of plant- compared with animal-sourced proteins and their effects on ≥1 of the following outcomes: fasting total cholesterol, fasting LDL and HDL cholesterol, fasting LDL:HDL cholesterol ratio, fasting TGs, and postprandial TGs. Although numerous studies (32 of 66 studies) reported no difference between plant- and animal-sourced proteins on lipemia, 12 comparisons from 10 high-quality studies reported that soy protein with isoflavones resulted in a greater reduction in total cholesterol (15–24), whereas 12 comparisons reported a greater reduction in LDL cholesterol (15, 16, 19, 21, 22, 25–28).

In those positive studies, the soy protein was mainly provided as soy protein isolate (16 of 17 comparisons), and the referent animal proteins used were either total milk protein or casein (12 of 17 comparisons), and, more marginally, animal and meat protein. However, the proportion of significant differences between plant- and animal-sourced proteins was higher when animal proteins were provided as a whole diet rather than as supplementation (20 out of 33 comparisons compared with 10 out of 60 comparisons) (19, 25, 29–38). The amount of protein provided ranged between 25 and 117 g/d, and the duration of the intervention period ranged between 4 wk and 4 y, but no dose or duration effect could be observed. The same results were also observed with low-quality studies (29–42) and are available in **Supplemental Table 6**. In addition, no difference was observed when whey protein was used as the referent animal-sourced protein and compared with soy (43–46) (**Table 1**). Only a few high-quality interventional studies reported an improved LDL: HDL cholesterol ratio (25, 47, 54), decreased TGs (15, 18, 20, 47), and increased HDL cholesterol concentrations (20, 26, 28, 48) with a soy protein–based diet (or supplemented with soy protein with isoflavones) compared with animal-sourced protein (meat, milk, casein, or whey), as reported in Supplemental Table 6. With regard to these variables, no effect was observed relating to either the amount or type of protein, the intervention duration, or the animal referent protein. In addition, no difference was reported on postprandial plasma TG responses to the ingestion of a milk protein (total, whey, or casein) and soy protein with isoflavones (in 5 studies), suggesting no additional effect of plant proteins on this risk factor, as shown in Supplemental Table 6. Because isoflavones are thought to display both serum cholesterol–lowering and arterial-vasodilation effects compared with animal protein (63, 64), some studies attempted to establish the role of soy protein isolate (void of isoflavones through alcoholic extraction during the protein solation phase) on the above variables. Interestingly, soy protein without isoflavones (18, 43, 46, 49, 54–56) had no beneficial effect on cholesterolemia and triglyceridemia compared with whey and milk proteins Table 1).

Similarly to soy protein isolate (without isoflavones), other plant protein sources, such as pea, barley, and fava bean proteins and wheat gluten (62, 65–71), had no further beneficial effect on fasting lipemia compared with animal-sourced protein (Table 1). However, 3 different studies reported that wheat gluten ingestion resulted in a higher postprandial TG response compared with whey protein (65, 67, 68), as reported in Supplemental Table 6. Interestingly, most comparisons showing a differential effect between plant- and animal-sourced proteins were observed in trials lasting between 42 and 84 d, which may define a critical period for supplementation (Table 1).

Blood pressure. In 6 different observational studies (of 23 studies), an inverse relation between the intake of plant-sourced protein and diastolic and/or systolic blood pressure was reported,

TABLE 1 Comparison between the effects of the intake of plant and animal proteins on circulating total and LDL cholesterol in healthy humans and in those with metabolic dysfunctions[1]

Reference	Score	*n*	Population characteristics	Female, %	Age,[2] y	Duration, wk	Comparison	Soy protein form	Isoflavones	Protein quantity	Total cholesterol		LDL cholesterol	
											Final value[3]	Change[4]	Final value[3]	Change[4]
Soy + isoflavones (showing an effect)														
(15)	6	41	Diabetic adults	56	62.1	208	Animal vs. soy	Soy protein isolate	Yes (42 mg/d)	0.8 g/kg BW	→	↓ (15)	→	↓ (19)
(25)	6	26	Hypercholesterolemic men	0	20–50 (38)	5	Animal vs. soy	Soy protein isolate	Yes (NA)	75 g/d	→	NA	↓ (6)	NA
(25)	6	26	Normocholesterolemic men	0	20–50 (38)	5	Animal vs. soy	Soy protein isolate	Yes (NA)	75 g/d	→	NA	↓ (6)	NA
(26)	6	11	Healthy adults	55	28–54 (42)	4	Casein vs. soy	Soy protein isolate	Yes (NA)	140 g/d	→	→	→	↓ (15)
(22)	8	156	Hypercholesteroemic adults	40	53	9	Casein vs. soy	Soy protein isolate	Yes (3, 27, 37, and 62 mg/d)	25 g/d	↓ (4)	NA	↓ (6)	NA
(16)	7	52	Hypercholesterolemic adults	40	35–70 (55)	6	Casein vs. soy	Soy protein isolate	Yes (96.2 mg/d)	52 g/d	NA	↓ (3)	NA	↓ (5)
(23)	10	32	Hypercholesterolemic adults	47	NA	24	Casein vs. soy	Soy protein isolate	Yes (100 mg/d)	30 g/d	→	↓ (16)	→	↓ (14)
(17)	6	81	Moderately hypercholesterolemic adults	0	23–74 (45)	6	Casein vs. soy	Soy protein isolate	Yes (95 mg/d)	50 g/d	NA	↓ (7)	NA	NA
(18)	6	36	Moderately hypercholesterolemic adults	55	62.6	6	Casein vs. soy	Soy protein isolate	Yes (46 mg/d)	55 (F) or 71 (M) g/d	↓ (4)	NA	→	NA
(19)	6	42	Postmenopausal women	100	NA	8	Meat vs. soy	Soy protein isolate	Yes (84 mg/d)	30 g/d	↓ (5)	NA	↓ (5)	NA
(19)	6	42	Postmenopausal women	100	NA	8	Meat vs. soy	Soy nut	Yes (102 mg/d)	30 g/d	↓ (8)	NA	↓ (12)	NA
(27)	7	29	Diabetic adults	45	NA	8	Milk vs. soy	Soy protein isolate	Yes (88 mg/d)	40 g/d	→	NA	↓ (4)	NA
(28)	10	352	Healthy adults	42	47.5	8	Milk vs. soy	Soy protein isolate	Yes (84 mg/d)	40 g/d	→	→	↓ (2)	NA
(21)	7	88	Hypercholesterolemic adults	61	35–70 (54.6)	8	Milk vs. soy	Soy protein isolate	Yes (NA)	25 g/d	→	↓ (6)	→	→
(21)	7	88	Hypercholesterolemic adults	61	35–70 (54.6)	8	Milk vs. soy	Soy nondenatured isolate	Yes (NA)	25 g/d	→	↓ (11)	→	↓ (9)
(20)	8	58	Moderately hypercholesterolemic adults	55	51	4	Milk vs. soy	Soy protein isolate	Yes (23–26 mg/d)	25 g/d	NA	↓ (4)	NA	NA
(24)	7	52	Overweight adults	NA	18–65 (NA)	12	Milk vs. soy	Soy protein isolate	Yes (NA)	90 g/d	→	↓ (7)	→	→
Soy + isoflavones (showing no effect)														
(23, 47–53)							Casein vs. soy							
(54–59)							Milk vs. soy							
(60)							Whey + egg vs. soy							
(43, 44, 46)							Whey vs. soy							
Soy without isoflavones or other vegetable protein (no effect)														
(61)							Casein vs. lupine							
(18, 49)							Casein vs. soy							
(18)							Casein vs. soy							
(54, 55, 62)							Milk vs. lupine							
(54–56)							Milk vs. soy							
(43, 46)							Whey vs. soy							

[1] BW, body weight; NA, not specified.
[2] Values are means or ranges (means).
[3] ↑ indicates increase with plant protein compared with animal protein (percentage of difference); → indicates no difference between plant and animal protein; ↓ indicates decrease with plant protein compared with animal protein (percentage of difference).
[4] ↑ indicates higher increase with plant protein than with animal protein (difference in the percentage change); → indicates similar change between plant and animal proteins; ↓ indicates higher decrease with plant protein than with animal protein (difference in the percentage change).

whereas no effect was reported for the intake of animal-sourced protein (72–77). One longitudinal study reported that the intake of both animal- and plant-sourced protein was associated with a decrease in blood pressure (78). Moreover, one cross-sectional study showed that a 19.9-g/d increase in the intake of animal protein was associated with and a decrease in both systolic and diastolic blood pressure, whereas a 13.1-g/d increase in the intake of plant protein was associated with a decrease in diastolic blood pressure without any improvement on systolic blood pressure (79). Other studies reported no effect from the intake of animal- and plant-sourced protein on blood pressure in children (80, 81) (**Tables 2** and **3**).

Results from intervention studies mainly reported no differential effect on blood pressure from plant-sourced proteins (soy, lupine) and animal-sourced proteins (milk, casein) when provided either as a meal or as a supplement to a meal (24, 50, 62, 69, 82–86) (Tables 2 and 3, **Supplemental Table 7**). In addition, 3 other intervention studies reported inconsistent results: one study in middle-aged adults reported that a group supplemented with 40 g soy protein/d had a greater decrease in diastolic and systolic blood pressure than did a group consuming animal protein (47), and 2 studies that used whey, egg, or milk protein as the animal protein source reported that soy protein intake resulted in higher systolic or diastolic blood pressure post-intervention (57, 60) (Tables 2 and 3).

Glucose homeostasis. Most intervention studies did not show any difference in fasting insulin, glucose, or homeostasis model assessment index between plant and animal sourced proteins (24, 30, 37, 39, 49, 51, 60, 61, 67, 86–91), as shown in **Supplemental Table 8**. With respect to these 3 variables, no particular effect was observed relating to the amount or type of protein provided, the intervention duration, or the animal referent protein. In one high-quality intervention study, postmenopausal women on a hypertension prevention diet substituted 30 g red meat with either a soy protein isolate or soy nuts, and both (soy protein isolate and soy nuts) resulted in significantly lower homeostasis model assessment index and insulinemia, with no effect on glycemia (19), as reported in Supplemental Table 8. Other high-quality intervention studies reported lower fasting glycemia in diabetic adults who consumed a soy protein–based diet than in a group that consumed an animal protein–based diet (15), and lower fasting glycemia in obese adults who received a 4-d supplementation of 45-g wheat gluten than in a group supplemented with cod protein (67). In contrast, a low-quality study reported higher fasting glycemia after 2 wk of a soy-based high-protein diet than that with a meat-based high-protein diet (36).

Studies evaluating insulin and glucose responses subsequent to the ingestion of a mixed meal containing either plant-sourced protein or whey protein reported a lower insulinotropic effect with wheat gluten (65–67, 92) and soy protein when provided in isolate (45, 93) or hydrolysate (93) form, and this was associated with a higher postprandial glucose response in only one study (67). However, no difference was observed in either postprandial insulinemia or glycemia when pea or rice proteins were compared with whey protein (94, 95) (Supplemental Table 5). Finally, various high-quality studies that can be found in Supplemental Table 8 reported that wheat gluten intake in obese or diabetic subjects induced a higher postprandial glucose response than did whey (67, 68), cod, or casein (68) intake.

Body composition. One high-quality observational study reported a negative association between the intake of plant-sourced protein and BMI or waist circumference, whereas the intake of animal-sourced protein was positively associated with these 2 outcomes (96). One longitudinal study showed that increasing dietary plant-sourced proteins by 5% at the expense of animal-sourced protein in an isoenergetic diet reduced weight gain by nearly 1 kg in men over a 5-y period, but not in women (97). Two longitudinal studies (**Supplemental Table 9**) reported an increase in body weight or BMI in parallel with an increased intake of animal-sourced protein, whereas no changes in these markers were observed with the intake of plant-sourced proteins (98, 99). Interestingly, 3 studies performed in children reported that the consumption of animal-sourced protein at the age of 1 y was positively associated with increased BMI and body fat at the age of 6 (81, 100) or 7 y (101). This last study also reported that the consumption plant-sourced protein between the ages of 5 and 6 y was associated with a decrease in body fat at the age of 7 y, as shown in Supplemental Table 9.

Results from intervention studies are mostly inconsistent, and most studies did not report any differential effect from plant and animal protein on BMI, body weight, fat, or waist circumference (Supplemental Table 9). In postmenopausal women presenting

TABLE 2 Comparison between the effects of the intake of plant and animal proteins on diastolic and systolic blood pressure in healthy humans and those with metabolic dysfunctions, observational studies[1]

Reference	Score	*n*	Study design	Population characteristics	Female, %	Age,[2] y	Duration, mo	Comparison	Isoflavones	DBP		SBP	
										Plant[3]	Animal[4]	Plant[3]	Animal[4]
Plant protein (showing an effect)													
(72)	7	20,820	Cross-sectional study	General population	46	20–65 (42)	—	Animal vs. plant	No	→	→	↓	→
(75)	9	810	Longitudinal study	General population	61.7	50	18	Animal vs. plant	No	↓	→	↓	→
(73)	8	1714	Longitudinal study	Healthy men	0	40–55 (48)	96	Animal vs. plant	No	↓	→	↓	→
(74)	7	272	Longitudinal study	Older adults	0	70.1	60	Animal vs. plant	No	↓	→	↓	→
(79)	6	7585	Cross-sectional study	General population	54	40–69 (52)	—	Animal vs. plant	No	→	↓	↓	↓
(78)	8	1361	Longitudinal study	General population	58	30–54 (44)	124	Animal vs. plant	No	↓	↓	↓	↓
(76)	7	2195	Cross-sectional study	General population	50	40–59 (49)	—	Animal vs. plant	No	↓	→	↓	→

[1] DBP, diastolic blood pressure; SBP, systolic blood pressure.
[2] Values are means or ranges (means).
[3] ↑ indicates increase with plant protein intake; → indicates no effect of plant protein; ↓ indicates decrease with plant protein intake.
[4] ↑ indicates increase with animal protein intake; → indicates no effect of animal protein; ↓ indicates decrease with animal protein intake.

TABLE 3 Comparison between the effects of the intake of plant and animal proteins on diastolic and systolic blood pressure in healthy humans and those with metabolic dysfunctions, interventional studies[1]

Reference	Score	*n*	Study design	Population characteristics	Female, %	Age,[2] y	Duration, mo	Comparison	Soy protein form	Isoflavones	Protein quantity	DBP		SBP	
												Final value[3]	Change[4]	Final value[3]	Change[4]
Plant protein (showing an effect)															
(47)	9	179	Chronic intervention study	Middle-aged adults	46	50–75 (NA)	3	Casein vs. soy	Soy protein isolate	Yes (84 mg/d)	40 g/d	↓ (3)	NA	↓ (3)	NA
(57)	8	202	Chronic intervention study	Postmenopausal women	100	66.7	12	Milk vs. soy	Soy protein isolate	Yes (99 mg/d)	25.6 g/d	↑ (3)	NA	→	NA
(60)	8	25	Chronic intervention study	Obese adults	88	60–79 (68.4)	3	Whey + egg vs. soy	Soy protein–based food	Yes (60–135 mg/d)	44 g/d	→	NA	↑ (4)	NA
Plant protein (showing no effect)															
(81)			Longitudinal study					Animal vs. plant (age 1 y)							
(24, 82, 83)			Chronic intervention study					Milk vs. soy							
(62)			Chronic intervention study					Milk vs. lupine							
(50, 84)			Chronic intervention study					Casein vs. soy							

[1] DBP, diastolic blood pressure; NA, not specified; SBP, systolic blood pressure.
[2] Values are means or ranges (means).
[3] ↑ indicates increase with plant protein compared with animal protein (percentage of difference); → indicates no difference between plant and animal proteins; ↓ indicates decrease with plant protein compared with animal protein (percentage of difference).
[4] ↑ indicates lower decrease with plant protein compared with animal protein (difference in the percentage change); → indicates similar change between plant and animal proteins; ↓ indicates higher decrease with plant protein compared with animal protein (difference in the percentage change).

with hyperglycemia, soy protein supplementation was more potent than milk protein in reducing BMI, body fat, and body mass (49). In postmenopausal women, a 3-mo supplementation with soy protein induced a 9% greater decrease in abdominal fat than did casein (87). In contrast, 2 high-quality studies reported that soy was less potent than milk or whey proteins in reducing body fat (102, 103).

Most of the studies reported no difference in lean body mass maintenance or increase when individuals were supplemented with or consumed animal or plant proteins (43, 44, 49, 51, 60, 87, 102, 104–110), as shown in Supplemental Table 9. One high-quality study reported that overweight or obese men supplemented for 12 wk with whey protein exhibited a higher gain in lean body mass than did a group supplemented with soy protein (111).

Influence of age and health status. Previous studies have shown that the efficiency of protein in decreasing cholesterolemia and blood pressure depends on the severity of the hypercholesterolemia or hypertension of the individuals included in the study (72, 112, 113). Moreover, high protein intake can either reduce adiposity in adults (7) or be positively associated with obesity when provided during early childhood (114, 115). These observations suggest that both age and health status need to be taken into account in data analysis.

Four studies investigated the effect of both plant and animal proteins on metabolic syndrome features in children (80, 81, 100, 101). Therefore, the effect of age could only be assessed in adults, and the results do not provide evidence that the differential physiologic responses from plant and animal dietary proteins are age specific. Similarly, filtering the results on the health characteristics of the subjects did not provide substantial evidence that health status affects the outcomes of the comparisons relating to blood pressure, glycemic control, and body composition. In contrast, 15 of 31 comparisons performed in subjects with high cholesterol or TG concentrations showed a more potent lowering effect of plant-protein on total cholesterol and LDL cholesterol than that of animal protein, although this ratio fell to 15 of 53 when subjects without cholesterolemia or triglyceridemia impairments were considered (Table 1).

Discussion

The aim of the present systematic review was to compare the effect of animal- and plant-sourced proteins on markers related to metabolic syndrome, including cholesterolemia, triglyceridemia, blood pressure, glucose homeostasis, and body composition, and aimed to define potential differences between animal and plant proteins.

It is widely accepted that both low LDL and HDL cholesterol and low plasma TG concentrations are associated with a lower risk of cardiovascular disease (116), and that postprandial TGs are also associated with the risk of cardiovascular diseases (68). The extraction of data on these variables provides evidence that subjects at high risk of cardiovascular disease could benefit from increasing their intake of plant-sourced proteins and, more particularly, soy protein with isoflavones, as part of a complete diet. Indeed, our results show that the intake of plant protein was associated with a decrease in systolic and diastolic blood pressure, whereas the intake of animal protein had no effect. Moreover, the consumption of soy protein with isoflavones resulted in lower total and LDL cholesterol than did the consumption of animal protein, with the exception of whey isolate. The mechanisms of the cholesterol-lowering effect of soy

protein and isoflavones have been widely studied, and it has been shown that isoflavones increase the expression of sterol regulatory element binding protein 2, a transcription factor that senses the intracellular cholesterol concentration and is involved in serum cholesterol clearance (117). In line with these results, it is reported that soy or isoflavone extracts induce an increase in the mature form of sterol regulatory element binding protein 2 in HepG2 in vitro (118). Accordingly, in vivo studies also reported that soy protein also decreases hepatic TGs and plasma LDL cholesterol concentrations (117).

Our analysis indicates that statistically significant results were mostly observed in the context of a whole diet rather than with protein supplementation. This may be attributed in part to a lower intake of total dietary fibers and polyunsaturated fats, as well as a higher intake of dietary cholesterols and saturated fats usually associated with animal- or meat-based diets, which, in turn, are known to have direct elevating effects on plasma cholesterol and TG concentrations (119). In addition, greater amounts of protein are usually consumed in a normal diet than when a single dietary supplement is consumed (71 compared with 36 g, respectively, in the studies included), and this may therefore lead to greater physiologic adaptations. Furthermore, most of the differential effects of plant- and animal-sourced proteins were observed in hypercholesterolemic subjects, something that probably is due to the magnitude of the decrease, which is greater in these individuals than in healthy ones (112). Interestingly, the results showed that, in numerous studies, soy protein without isoflavones, as well as other plant proteins, had no additional effect on cholesterolemia and triglyceridemia compared with animal proteins. This suggests that the effect of soy and isoflavones when taken separately may not be sufficient enough to induce a cholesterol-lowering effect, and, therefore, any effects on cholesterolemia attributed to soy protein with isoflavones probably are due to the synergy between these 2 nutritional components (112, 120). This said, soy proteins are thought to modulate fecal sterol excretion, and several animal studies reported that the consumption of soy protein increased the amount of excreted sterols in rats (121–123) and rabbits (124) independently of isoflavone content (122, 123). However, a study in humans does not support this hypothesis, because it reported no difference in fecal bile acids and neutral sterol excretion between groups supplemented with soy and milk protein (20).

Another proposed mechanism explaining the cholesterol-lowering effect of soy protein is its amino acid pattern, particularly its low leucine-to-arginine ratio compared with that of animal proteins, and this difference is thought to be related to hypercholesterolemia and atherosclerosis (125). Indeed, high postprandial plasma concentrations of arginine are thought to have a hypocholesterolemic effect (126), whereas leucine is a cholesterol precursor in man (127) and also has a strong insulinotropic effect, which can stimulate the activity of β-hydroxy-β-methylglutaryl coenzyme A reductase, the rate-limiting step in cholesterol synthesis (128). In addition, several studies showed that wheat gluten intake results in a higher TG response when ingested in a mixed meal than when ingested as whey protein (65, 67, 68). In line with these observations, one study reported that a gluten-based diet stimulates liver lipogenesis in rats (129). However, the observation could originate from a specific effect of whey protein or a combination of the effects of both types of protein, because it was reported that whey protein, possibly through a lipid absorption–lowering effect, reduced plasma TGs (130).

Hypertension is a risk factor for coronary heart disease and the single most important risk factor for stroke (131). The effect of dietary protein on blood pressure has been reviewed several times, and it was concluded that increasing dietary protein intake could reduce blood pressure, although results from intervention studies are scarce (132, 133). Taken together, the results from observational studies suggest a slight but significant effect of plant-sourced proteins on blood pressure, whereas the intake of animal protein does not seem to affect blood pressure. However, no direct relation between the intake of plant protein and blood pressure has been reported in interventional studies. The discrepancy between the 2 types of studies could originate from confounding factors in observational studies or from the duration of the intervention studies, which, by nature, are much shorter than long-term observational studies. However, some evidence suggests that the amino acid pattern of plant-sourced proteins could mediate the blood pressure–lowering effect. Indeed, plant proteins have a lower ratio of methionine and alanine to threonine and histidine than do animal proteins.

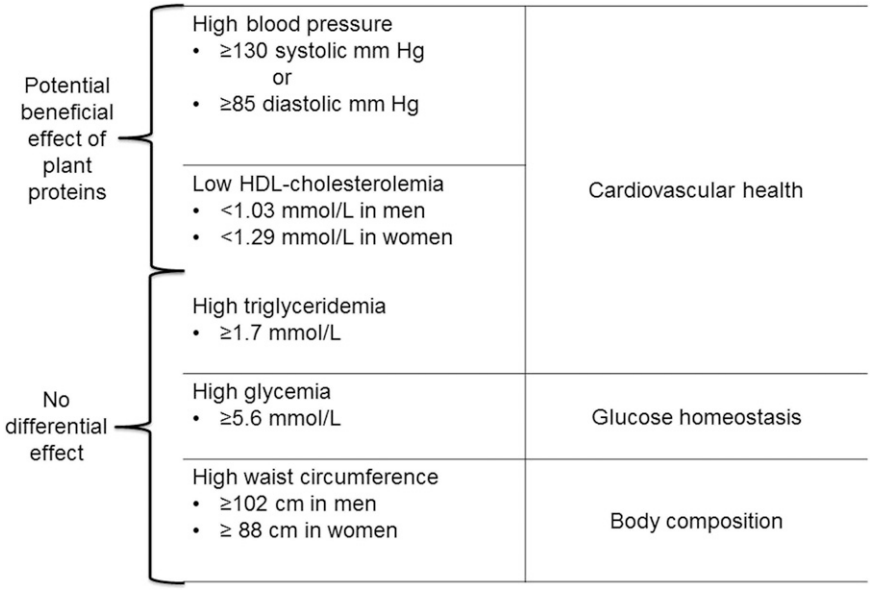

FIGURE 2 Tools for the clinical diagnosis of metabolic syndrome.

Methionine and alanine intake has previously been positively associated with increased blood pressure, whereas threonine and histidine intake has previously been reported to be inversely associated with blood pressure (133, 134).

High insulin and glucose concentrations are directly associated with cardiovascular disease and mortality (135). Moreover, a recent study reported that the insulin index, which is the postprandial insulin response to a test food, is considered to be an independent risk factor for the development of insulin resistance (136). Therefore, fasting and postprandial insulin and glucose are important outcomes on which to focus. Several studies in rodents previously reported that isoflavones or soy protein can improve glycemic control and insulin sensitivity (137–139). In line with these results, several observational studies reported that soy intake could lower the risk of diabetes (140, 141). However, in a meta-analysis, no significant effect of soy intake was reported on fasting glucose and insulin concentrations (142). Moreover, the insulin response after protein intake may result in the prevention and management of obesity (143) and type 2 diabetes (144), although this is equivocal. Data extraction, however, did not show any difference between animal- and plant-sourced proteins on either fasting glucose or insulin, despite a higher postprandial insulin response with whey protein ingestion than with wheat gluten and soy protein, but not with rice or pea proteins. This discrepancy between the observations on glucose and insulin may result from the fact that, unlike glucose, insulinemia may be increased up to 10-fold in response to a meal, whereas the glycemic response rarely increases >2-fold. Thus, a comparison of insulin values can result more easily in significant differences (145).

Whey protein, a mixture of globular proteins (α-lactalbumin, lactoferrin, and β-lactoglobulin), is rapidly digested (146) and contains high concentrations of BCAAs, which may be partly responsible for its high insulinotropic effect. In line with these results, a drink containing a mixture of BCAAs (leucine, isoleucine, and valine) was sufficient to reproduce the insulinotropic effect of a whey protein drink (147). Moreover, the whey protein effect on insulinemia could also be mediated by the increase in the secretion of glucagon-like peptide 1 and glucose-dependent insulinotrophic polypeptide, which are known to increase insulin secretion, after its intake (147, 148). However, no significant change in glycemia was observed in our analysis of the literature. This may be due to the simultaneous stimulation of glucagon secretion induced by whey ingestion, as reported by Anderson et al. (112).

Dairy-sourced proteins such as whey and casein contain a high amount of BCAAs. Both of these are known to stimulate muscle protein synthesis (149); therefore, high intake of such proteins may affect body composition (7). However, to our knowledge, the long-term effect of animal- compared with plant-sourced proteins on body composition has not been studied extensively up to now. This systematic review does not show strong evidence of a differential effect of animal and plant proteins on body composition. To our knowledge, only a few observational studies reported previously that the intake of animal protein was associated with an increase in BMI, waist circumference, and body weight in adults, and that, in children, intake of a high amount of animal-sourced protein at an early age could have deleterious effects on body composition at the age of 6 or 7 y. However, most studies that used meal-based protein intake or protein supplementation failed to show any effect on body composition. However, given the shorter duration (<6 mo) of the intervention studies, it is likely that they do not last long enough for significant differences in body composition to be observed. Furthermore, it may be the case that confounding factors, such as energy expenditure and physical activity, may not have been taken into account in observational studies. The effects of plant proteins compared with animal proteins on the markers of metabolic syndrome are summarized in **Figure 2**.

Strengths and limitations of the present review. The present systematic review provides an overview of the comparisons between plant and animal proteins on metabolic syndrome features and related outcomes. The assessment of the quality of the studies allowed us to report that low- and high-quality studies were overall consistent in their findings. Our present analysis is very wide and is not restricted to a particular sex, age range, health status, or protein form or source. On this last point, the present work is particularly relevant because it was not limited to the study of the effects of soy protein, but also explored the effects of other plant proteins, such as pea, rice, and fava bean proteins and wheat gluten. Moreover, a special effort was made to distinguish the effects of soy protein alone from those of soy protein associated with isoflavones. The large number of included articles is also a limitation of the review, because the discussion of the results had to be restricted to a limited number of outcomes. Thus, for example, it was decided not to extract data on glucagonemia, even though it may play an important role in glycemic control, or plasma lipoprotein(a) concentration, which is identified as a cardiovascular risk factor.

Conclusion

This systematic review provides some evidence that the intake of plant-sourced proteins and, in particular, soy protein associated with isoflavones, may prevent the onset of risk factors associated with cardiovascular disease, i.e., hypercholesterolemia and hypertension. However, no additional effect of plant proteins on glucose homeostasis and body composition was observed, as reported in Figure 2. Additional long-term studies are required to evaluate the effects of soy protein and isoflavones separately in humans.

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TC-D, DA-M, JA, LE, and LGK designed the research; TC-D and LE conducted the research; TC-D, DA-M, LE, LGK, and DT analyzed the data; TC-D wrote the paper; and JA, CG, LGK, and DT had primary responsibility for the final content. All authors read and approved the final manuscript.

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