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Review

Effect of diet composition on insulin sensitivity in humans

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S U M M A R Y

Diet composition has a marked impact on the risk of developing type 2 diabetes and cardiovascular disease. Prospective studies show that dietary patterns with elevated amount of animal products and low quantity of vegetable food items raise the risk of these diseases. In healthy subjects, animal protein intake intensifies insulin resistance whereas plant-based foods enhance insulin sensitivity. Similar effects have been documented in patients with diabetes. Accordingly, pre-pregnancy intake of meat (processed and unprocessed) has been strongly associated with a higher risk of gestational diabetes whereas greater pre-pregnancy vegetable protein consumption is associated with a lower risk of gestational diabetes. Population groups that modify their traditional dietary habit increasing the amount of animal products while reducing plant-based foods experience a remarkable rise in the frequency of type 2 diabetes. The association of animal protein intake with insulin resistance is independent of body mass index. In obese individuals that consume high animal protein diets, insulin sensitivity does not improve following weight loss. Diets aimed to lose weight that encourage restriction of carbohydrates and elevated consumption of animal protein intensify insulin resistance increasing the risk of developing type 2 diabetes and cardiovascular disease. The effect of dietary components on insulin sensitivity may contribute to explain the striking impact of eating habits on the risk of type 2 diabetes and cardiovascular disease. Insulin resistance predisposes to type 2 diabetes in healthy subjects and deteriorates metabolic control in patients with diabetes. In nondiabetic and diabetic individuals, insulin resistance is a major cardiovascular risk factor.

1. Introduction

Diet composition has a crucial effect on the risk of developing type 2 diabetes (T2D) and cardiovascular disease although the specific nutrients responsible for this effect remain undefined. Prospective studies have shown that elevated consumption of animal products and low intake of plant-based food items increase the risk of T2D [1,2] and cardiovascular disease [3–8]. Insulin resistance is a metabolic condition that has been linked to T2D and cardiovascular disease [9–11]. Diet composition has a major effect on insulin sensitivity that may contribute to explain the striking effect of nutritional factors on the risk of T2D and cardiovascular disease. In 1935, Himsworth and Marshall observed that a dietary pattern with elevated content of animal products and low intake of plant-based food increased the risk of T2D. They stated, "This type of dietary pattern would favor the appearance of diabetes in the potential diabetic" [12]. Since then, accumulated evidence confirms that dietary habits with animal protein consumption and low intake of vegetable food promote insulin resistance both in healthy subjects and in patients with diabetes [13]. Glucagon opposes insulin action in the liver. In healthy humans, animal protein ingestion and the infusion of amino acids such as arginine and alanine activate glucagon secretion [14–16]. The increase in plasma glucagon is maintained for at least 4 h after the intake of animal protein [17]. The rise in plasma glucagon associated to animal protein ingestion is intensified in patients with diabetes [14,18–22]. Sustained hyperglucagonemia that follows animal protein ingestion may induce insulin resistance that in turn predisposes to T2D,

Abbreviations: BMI, body mass index; EPIC, European Prospective Investigation into Cancer and Nutrition; HDL-c, cholesterol associated to high-density lipoprotein; HOMA-IR, homeostasis model assessment-insulin resistance; HPFS, Health Professionals Follow-up Study; LDL-c, cholesterol associated to low-density lipoprotein; NHS, Nurses' Health Study; T1D, type 1 diabetes; T2D, type 2 diabetes.

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deteriorates the metabolic control in patients with type 1 diabetes (T1D), and induces vascular injury both in healthy subjects and in patients with diabetes (Fig. 1).

2. Differential effect of animal versus vegetable food items on insulin sensitivity in nondiabetic subjects

2.1. Animal protein intake intensifies insulin resistance in nondiabetic subjects

The ingestion of animal protein has been consistently associated with insulin resistance, assessed by its clinical expression (the metabolic syndrome or its components) and by laboratory evaluation, such as hyperinsulinemic euglycemic clamps or the homeostasis model assessment of insulin resistance (HOMA-IR) [23–29].

In the Finnish and Dutch cohorts of the Seven Countries Study, baseline intake of animal products was independently associated with insulin resistance at follow-up (evaluated by an oral glucose tolerance test) [23].

Cross-sectional studies also find an independent association between animal protein intake and insulin resistance, assessed by the HOMA-IR index. The association of animal protein consumption and insulin resistance is independent of the body mass index (BMI) [24–26,39].

A randomized controlled trial investigated the effect of animal protein intake on whole-body insulin sensitivity in obese postmenopausal women, assessed by measuring insulin-stimulated whole-body glucose disposal rate (M value) during a hyperinsulinemic euglycemic clamp. Participants achieved 10% weight loss with a hypocaloric diet containing either 0.8 g/kg/day of animal protein or 1.2 g/kg/day. Despite the same degree of weight loss, insulin sensitivity improved only in the low-protein group after weight loss. The M value remained unchanged from baseline in the high-protein group. The same extent of weight loss improved insulin sensitivity only in the group consuming a low animal protein diet while failed to improve insulin sensitivity in the high-protein group. Animal protein in a weight loss diet has profound negative effects on glucose metabolism [38]. Accordingly, carbohydrate-restricted dietary patterns that encourage animal protein consumption promote insulin resistance and greater risk of T2D [40].

A number of studies have documented that animal protein intake promotes hepatic insulin resistance in healthy subjects. Insulin promotes hepatic glycogen accumulation and inhibits gluconeogenesis (reducing hepatic glucose output) while glucagon has the opposite effects.

In healthy volunteers, high animal protein intake increases gluconeogenesis and hepatic glucose output compared with normal protein consumption [27]. Accordingly, animal protein restriction decreases gluconeogenesis and hepatic glucose output in normal subjects [28]. Furthermore, the normal suppression of hepatic glucose production by insulin is impaired in subjects consuming a high animal protein diet compared to a normal protein diet [27]. The effect of high animal protein intake increasing hepatic glucose output has been observed in overweight subjects as well. Hepatic glucose output rises in overweight subjects that consume a high animal protein diet compared to those on a high cereal and fiber diet [41]. An interventional study investigated the long-term influence of dietary animal protein on hepatic insulin sensitivity. Healthy volunteers received either a diet high in animal protein or a diet with normal amount of protein. After 6 months of intervention, hepatic insulin sensitivity was enhanced in the volunteers who received a normal protein diet compared to those fed a high protein diet. Animal protein intake stimulated hepatic gluconeogenesis and increased hepatic glucose output [29]. These findings suggest that animal protein intake intensifies hepatic insulin resistance, probably by activating glucagon secretion, in healthy and overweight individuals [27,28,41].

The metabolic syndrome is a cluster of clinical features that reflects insulin resistance and includes hyperinsulinemia, hypertension, obesity, and dyslipidemia characterized by low cholesterol associated to high-density lipoprotein (HDL-c) and hypertriglyceridemia. Animal protein intake has been linked to clinical manifestations of insulin resistance (Table 1).

Cross-sectional, prospective and interventional studies consistently find an association of animal protein consumption and hyperinsulinemia, independently of BMI and other confounders. A meta-analysis confirms the association [25,28,30–35]. A cross-sectional analysis of the Nurses' Health Study (NHS), a large cohort of US women, showed that greater intake of unprocessed and processed meat was associated with higher fasting insulinemia after adjustment for confounders. BMI accounted only for a proportion of the association [30]. Further, fasting insulinemia fell after reducing red meat intake at the expense of alternative protein food [28,30]. In healthy subjects from the Attica area of Greece, a cross-sectional study showed that red meat consumption was positively associated with hyperinsulinemia after adjusting for BMI and other potential confounders. Higher intake of red meat is associated to increased plasma insulin level in nondiabetic subjects [25]. Prospective studies including the Normative Aging Study [31], the San Luis Valley Diabetes Study [32], and the Kuopio Ischemic Heart Disease Risk Factor Study [33] confirm the independent association between dietary animal protein and hyperinsulinemia. Elevated intake of animal products at baseline is related to higher insulinemia at follow-up after adjusting for confounders [31–33]. An interventional study with a crossover design examined the effect of animal protein on insulin levels. Obese subjects were fed a weight-maintaining diet with 170 g protein for 14 days. Then, they consumed an isocaloric diet containing 6 g protein for 14 more days. Mean basal insulin levels decreased after the low-protein diet.

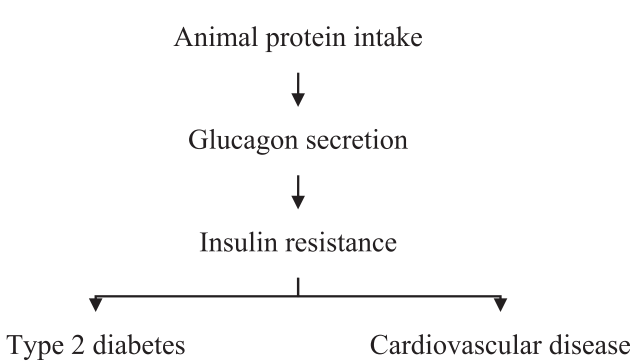

Fig. 1. Animal protein intake increases the risk of type 2 diabetes and cardiovascular disease by intensifying insulin resistance.

Table 1
Differential effects of animal protein versus vegetable protein consumption on clinical manifestations of insulin resistance and lipid profile.

	Animal protein	Vegetable protein
Body mass index	↑	↓
Waist circumference	↑	↓
Plasma total cholesterol	↑	↓
Plasma LDL-c	↑	↓
Plasma triacylglycerol	↑	↓
Fasting insulin	↑	↓
Blood pressure	↑	↓
Metabolic syndrome	↑	↓

Animal protein deprivation lowers basal plasma insulin levels in obese subjects even in the presence of sufficient calories to maintain weight, indicating that animal protein intake plays a crucial role in the development of insulin resistance and hyperinsulinemia in obesity [34]. A meta-analysis of 14 epidemiologic studies concludes that intake of red meat is associated with higher fasting insulinemia in nondiabetic Caucasians after adjustment for potential confounders. Additional adjustment by BMI only attenuated the association [35].

An independent association between animal protein consumption and obesity has been consistently documented by cross-sectional and prospective studies across ethnic groups [33,36,37,39,42–45]. In healthy subjects, a cross-sectional study examined whether the same amount of energy intake had different consequences on BMI depending on the source of energy from specific macronutrients. Changes of BMI per increments of energy intake from animal protein and plant-based foods were calculated controlling for confounders. Animal protein intake was positively associated with BMI controlling for energy intake while plant-based food intake had no positive association with obesity [36]. Other cross-sectional investigations have also found an independent association between animal protein intake and higher BMI and waist circumference [39,42]. Prospective analyses of data from the NHS with 8-year follow-up showed that increased intake of animal fat was associated with weight gain while increased consumption of vegetable fat was not associated with weight gain. Overall percent of calories from fat had only a weak positive association with weight gain, but percentage of calories from animal fat had stronger association with weight gain in nondiabetic women [37]. In a prospective cohort study of French women with a median follow-up of 13.8 years, both processed meat and unprocessed meat were independently associated with higher BMI [43]. The association between meat consumption and weight gain was investigated in the European Prospective Investigation into Cancer and Nutrition (EPIC)-PANACEA (Physical Activity, Nutrition, Alcohol, Cessation of Smoking, Eating Out of Home and Obesity) after 5 years of follow-up. On multivariable models after adjustment for potential confounders, annual weight gain was positively associated with intake of total meat, poultry, red meat, and processed meat in both normal weight and overweight subjects. Meat consumption at baseline was positively associated with weight gain, suggesting that a decrease in meat consumption may facilitate weight management [44]. The Kuopio Ischemic Heart Disease Risk Factor Study is a prospective cohort trial of Finnish men with 19.3 years of follow-up. Elevated animal protein intake at baseline was associated with higher BMI after multivariable adjustments [33]. In the EPIC-InterAct study, a case-cohort analysis showed that participants with high intake of animal protein had higher mean BMI and waist circumference [45].

2.2. *Vegetable food consumption enhances insulin sensitivity in nondiabetic subjects*

Observational and interventional investigations provide evidence that vegetable food intake enhances insulin sensitivity, evaluated either by laboratory estimates or by clinical features.

Cross-sectional studies, including the Isle of Ely study [46], the Japan Multi-Institutional Collaborative Cohort study [47], the Mediators of Atherosclerosis in South Asians Living in America study [42], and the Inter99 study [26], show an independent association between consumption of vegetable protein and enhanced insulin sensitivity.

The Finnish and Dutch cohorts of the Seven Countries Study investigated the prospective association between baseline intake of plant-based foods and incident insulin resistance. After adjustment for covariates, habitual intake of vegetables and legumes was inversely related to the incidence of insulin resistance assessed by an oral glucose tolerance test [23].

A number of interventional studies document a beneficial effect of vegetable food consumption on insulin sensitivity independently of BMI. Randomized controlled trials in healthy subjects [48] and overweight/obese individuals [49–51], show that consumption of plant-based diets improves insulin sensitivity compared to eucaloric control diets that include animal products, regardless of weight [48–51]. A randomized crossover trial in obese postmenopausal women shows that the intake of soy products at the expense of meat improves insulin sensitivity (evaluated by a frequently-sampled intravenous glucose tolerance test), contributing to prevent the metabolic syndrome [52]. In postmenopausal women with the metabolic syndrome, a randomized crossover trial shows that soy-nut intake as a replacement for red meat improves insulin resistance (evaluated by HOMA-IR values) and glycemic control [53]. In women with insulin resistance, insulin sensitivity (assessed by a frequently-sampled intravenous glucose tolerance test) improved after the administration of a resistant starch compared to placebo in a randomized crossover study. Consumption of dietary fiber improved insulin sensitivity in women with insulin resistance [54].

Frequent consumption of plant-based food items improves the clinical expression of insulin resistance, including hyperinsulinemia, dyslipidemia, hypertension, obesity, and the metabolic syndrome [13,32,48,50,52,55–72].

Normal weight vegetarians show lower fasting insulinemia compared to normal weight subjects consuming a western-type diet [55]. In the San Luis Valley Diabetes Study, high intake of plant-based food at baseline was inversely associated with fasting insulin level at follow-up, suggesting that plant-based dietary habits improve insulin sensitivity [32].

Randomized controlled trials confirm that plant-based diets decrease fasting insulinemia compared to control diets that include animal products, regardless of weight [48,50].

Consumption of plant-based foods reduces plasma level of triglycerides due to enhanced insulin sensitivity. In addition, vegetarian diets reduce total cholesterol and cholesterol associated to low-density lipoprotein (LDL-c) probably due to the absence of cholesterol in the vegetable kingdom. Plasma levels of total cholesterol, LDL-c, and triglycerides are lower in vegetarians, compared to nonvegetarians consuming the usual western diet, typically high in animal products, independently of weight. Overall intake of animal products was directly related to the levels of total cholesterol and LDL-c. Consistently, the HDL-c/LDH-c ratio of vegetarians is elevated [56]. In a systematic review of the literature, the evidence is assessed as probable to convincing regarding the effect of soy protein lowering LDL-c in healthy adults [57]. Interventional studies conducted in healthy subjects, obese postmenopausal women, and patients with coronary heart disease show that plant-based diets reduce serum triglycerides, LDL-c and total cholesterol compared to control diets [52,58–60].

In healthy persons consuming a vegetarian diet, systolic and diastolic blood pressure levels are lower than those recorded for omnivorous individuals. Blood pressure is positively associated with the amount of animal products consumed, independently of BMI. Likewise, in patients with coronary artery disease, lifestyle changes including a vegetarian diet reduced blood pressure compared with usual care [58]. A systematic review and meta-analysis of observational studies and controlled clinical trials on the association between vegetarian diets and blood pressure concluded: “consumption of vegetarian diets is associated with lower blood pressure. Such diets could be a useful nonpharmacologic mean for reducing blood pressure” [61].

Plant-based diets promote weight loss and reduce BMI [13]. Consistently, a number of investigations have reported that body weight, waist circumference, and BMI are lower in vegetarians compared to nonvegetarians, independently of confounding factors [56,62–65].

Subjects in the earliest stages of becoming vegetarian were observed for 6 months. On changing to a self-selected vegetarian diet, the subjects became leaner. There was a reduction in body fat, waist circumference and hip circumferences [66]. The NHS1 cohort [67], the Insulin Resistance Atherosclerosis Study [68], the Oxford cohort of the EPIC study [69,70], and the Adventist Health Study [71] have reported that increased intake of vegetable food items is associated with decreased BMI and waist circumference after full multivariate adjustment [67–71]. In overweight postmenopausal women, a randomized controlled trial shows that adherence to a vegan diet is associated with weight loss despite the absence of limits on energy intake compared to a control diet. Body weight, waist circumference and BMI decreased more in the intervention group (vegan diet) than in the control group [50]. In patients with ischemic heart disease, a randomized controlled trial showed that a lifestyle change including a vegetarian diet reduced weight compared to the control group (standard care) in which the weight remained unchanged [58]. The Adventist Health Study-2 shows that BMI is lowest in vegetarians, intermediate in semi-vegetarians and highest in nonvegetarians. Further, a vegetarian diet is independently associated with lower risk of having metabolic syndrome when compared with a nonvegetarian diet [72].

2.3. Differential effect of animal versus vegetable protein on insulin resistance in nondiabetic subjects

Investigations that compare the effect of animal versus vegetable food items on sensitivity to insulin confirm that intake of plant-based foods improves insulin sensitivity while animal protein intake intensifies insulin resistance [41,55,59,72,73].

In normal weight individuals, a vegetarian diet improved insulin sensitivity (assessed by the HOMA-IR index) compared to a western-type diet (typically high in animal products). Further, worsening of insulin resistance with ageing was only present in subjects on the western diet whereas the HOMA-IR value in vegetarians remained at approximately 1 in all age decades [55]. The relationship of animal versus plant protein intake and insulin resistance (HOMA-IR) was investigated in a cross-sectional analysis of the Adventist Health Study-2. Animal protein intake was associated with insulin resistance while plant protein was not in multiple linear regression models. At the same amount of protein consumption, insulin resistance is higher with animal protein than with total protein intake [72]. Three interventional studies reveal that animal protein intake aggravates insulin resistance compared to plant-based diets in healthy persons, overweight individuals, and obese subjects [41,59,73]. In a crossover study, nondiabetic persons were fed in random order two weight-maintaining diets, a plant-based diet and a diet rich in animal products (western diet). Insulin resistance assessed at the end of each diet period (oral glucose tolerance test) was higher on the western diet compared to the plant-based diet [59]. In a randomized controlled trial, overweight adults were assigned to two isoenergetic diets, a high-cereal-fiber diet and a high animal protein diet. Insulin sensitivity, evaluated by the M value during a euglycemic hyperinsulinemic clamp, was higher on the plant-based diet compared to the animal protein diet [41]. Similar results were obtained in obese subjects who completed a randomized controlled trial with either a high animal protein diet or a diet rich in cereal and fiber. Insulin resistance (evaluated by the M value) worsened in the subjects fed a high animal protein diet [73].

2.4. Effect of dietary patterns on insulin resistance in nondiabetic subjects

Investigations conducted on dietary patterns confirm an association between dietary habits high in animal products and low in vegetable food and insulin resistance, independently of BMI [42,74–78]. Dietary patterns characterized by elevated amounts of fruits, vegetables, legumes and whole grains are independently associated with lower risk of insulin resistance compared to western-type dietary patterns, high in meat and refined grains, in several population groups, including the general population from South Ireland, South Asians, and Tehrani females [42,74,75]. Clinical features of insulin resistance are also improved by dietary patterns low in animal products and high in vegetable food items in the Health Professionals Follow-up Study (HPFS) [76], the EPIC-Potsdam Study [77], and the Multiethnic Cohort study [78]. Diets characterized by high consumption of animal products and low intake of whole grains and other vegetable items have been independently associated with hyperinsulinemia, low HDLc, hypertriglyceridemia, and the metabolic syndrome, across different ethnic groups [75–78].

2.5. Insulin resistance worsens in population groups that change dietary habits toward an increase in animal dietary protein

Population groups that undergo a change in their dietary routine from traditional diets typically high in plant-based foods to western-type dietary habits experience a striking rise in the rate of T2D simultaneously with the westernization of their diets. This phenomenon has been consistently documented in different population groups, including Pima Indians and other Native Americans [79,80], Native Canadian communities [81], migrant Japanese populations [82–84], African population groups [85,86], Australian Aborigines [87], Pacific Ocean region population groups (Micronesians from Nauru island, Polynesians from Western Samoa and Wallis Island) [88,89], and Asian populations such as South Korea [90–92], China [93–95], and India [96]. Mexican and US Pima Indians share identical genetic background. However, unlike US Pimas, Mexican Pimas have maintained traditional dietary habits, with high intake of vegetable protein and reduced consumption of animal products. Despite their genetic homogeneity, the degree of insulin resistance (HOMA-IR index) is greater in US Pimas compared to Mexican Pimas, after controlling for confounders, including BMI and waist circumference [80]. The rate of T2D among US Pima Indians underwent a remarkable increase during the 20th century, coinciding with westernization of their diets. The role of insulin resistance in the development of T2D among the Pimas of Arizona was evaluated in a prospective study. Hyperinsulinemic euglycemic clamps were performed in nondiabetic US Pimas who were followed for an average of 5.3 years. Baseline insulin resistance was a major risk factor for the development of T2D, independently of BMI and other variables [79]. In 1979, the prevalence of diabetes was higher in Japanese migrants on the island of Hawaii and their offspring compared to Japanese living in Hiroshima, Japan. A nutritional survey revealed that Japanese migrants changed their dietary routine increasing markedly the consumption of animal products compared to their traditional Japanese diet. Despite identical genetic background between the two population groups, a change in the diet composition upon arrival on Hawaii promoted insulin resistance and T2D in the migrant group compared to their Hiroshima counterparts [82]. In a prospective study with 5-year follow-up, diet composition of Japanese American men was assessed at baseline and insulin resistance (impaired glucose tolerance) was ascertained at follow-up. Higher intake of animal products at baseline was associated with insulin resistance at follow-up, suggesting that intake of animal products has long-range detrimental effects on glucose tolerance [83]. The prevalence of impaired glucose tolerance in second-generation Japanese Americans living in Seattle, Washington is 36% in men and 40% in women. Among third-generation Japanese American youth, the prevalence of impaired glucose tolerance is 19% in men and 29% in women, suggesting that many second-generation and third-generation Japanese Americans are at risk of future T2D [84].

3. Differential effect of animal versus vegetable food items on insulin resistance in patients with diabetes

In patients with diabetes, animal protein intake intensifies insulin resistance and contributes to worsen the metabolic control of the disease while vegetarian diets enhance insulin sensitivity.

3.1. Type 1 diabetes

In patients with T1D, animal protein intake increases insulin requirement and postprandial glycemia compared with protein-restricted diets, suggesting that animal protein worsens insulin resistance [28,97]. Patients with T1D fed a high animal protein diet show increased hepatic insulin resistance. Animal protein increases gluconeogenesis and hepatic glucose output compared to normal protein intake. Further, the ability of insulin to suppress hepatic glucose output is impaired in patients with T1D on high animal protein diet compared to those on a normal protein diet. A remarkable parallelism between insulin-resistant hepatic glucose production and glucagon secretion is observed, indicating that glucagon contributes to insulin resistance associated to animal protein ingestion [27]. Consistently, the increase in plasma glucagon resulting from animal protein intake is accompanied by an increase in plasma glucose despite a constant infusion of insulin, suggesting that animal protein ingestion contributes to the postprandial hyperglycemia through an increase in glucagon secretion in patients with diabetes [98].

3.2. Type 2 diabetes

In patients with T2D, vegetarian diets enhance insulin sensitivity compared to conventional diets containing animal products [99–103]. In a randomized open parallel study, insulin sensitivity (evaluated by the hyperinsulinemic euglycemic clamp) improved to a greater degree in T2D patients on a vegetarian diet compared to control T2D patients on a conventional diet. More T2D patients fed a vegetarian diet reduced diabetes medication compared to the control group (43% versus 5%). Body weight, waist circumference, and body fat decreased more in the experimental group (vegetarian diet) than in the control group. The addition of exercise training further augmented the improved outcomes obtained with the vegetarian diet compared to the conventional diet. A vegetarian diet improved insulin sensitivity and reduced visceral fat more than a conventional diet with similar caloric restriction in T2D patients [99]. In obese patients with T2D who received a plant-based diet, insulin sensitivity (assessed by the hyperinsulinemic euglycemic clamp) improved compared to patients fed an isocaloric high animal protein diet [100]. Consistently, plant-based diets reduce insulin requirement or the need for hypoglycemic agents compared with conventional diets, suggesting that vegetarian diets reduce insulin resistance in patients with T2D [101–103]. Accordingly, fasting insulinemia decreases in patients with T2D after a diet with elevated content of vegetable food items compared to a conventional diet, regardless of weight [48,104].

Randomized clinical trials show that vegan diets improve glycemic control in patients with T2D to a greater degree than conventional diets following guidelines of the American Diabetes Association. The acceptability of vegetarian and vegan diets is comparable to other dietary plans [104–106]. The beneficial effect of a vegan diet on glycemic control in patients with T2D is apparent with no recommendations regarding exercise or other lifestyle changes [107]. A systematic review and meta-analysis of controlled clinical trials confirms that vegetarian diets are associated with improved glycemic control in patients with diabetes. A vegetarian dietary pattern reduced HbA1c by 0.4 percentage point. Furthermore, glycemic control improves following switch from omnivorous diet to a vegetarian diet [108]. The effect of replacing animal protein with plant protein on glycemic control in patients with diabetes was assessed in a systematic review and meta-analysis of randomized controlled clinical trials. Diets emphasizing a replacement of animal with plant protein lowered fasting insulin, fasting glucose, and HbA1c compared with control diets [109]. The effect of legumes intake (chickpeas, beans, peas, and lentils) on glucose metabolism was investigated in a systematic review and meta-analysis of 41 randomized controlled trials in subjects with and without diabetes. Pooled analyses demonstrated that legume intake improves glycemic control, supporting the consumption of legumes to optimize diabetes control [110].

Randomized controlled trials show that vegan diets and substitution of red meat with legumes improve lipid control in patients with T2D to a greater degree than conventional diabetes diets following the American Diabetes Association guidelines [104–106]. Similarly, randomized controlled trials show that vegan diets or soy-based meal replacement plans are associated with reduction in body weight and body fat to a greater extent than conventional diets in patients with T2D. The beneficial effect of vegan diets on weight loss is evident even in the absence of advice for exercise [103,107].

3.3. Gestational diabetes

Pregnancy is physiologically associated with maternal insulin resistance. Pre-pregnancy dietary patterns influence markedly the risk of developing gestational diabetes. The intake of unprocessed and processed meat before pregnancy is strongly associated with a higher risk of gestational diabetes, after adjustment for confounders, including BMI. In contrast, higher intake of vegetable protein is independently associated with a lower risk of gestational diabetes. Further, the substitution of red meat or processed meat with healthy protein sources such as nuts or legumes is associated with lower risk of gestational diabetes. On the contrary, substituting 5% of energy from vegetable protein with animal protein is associated with a 29% greater risk of gestational diabetes [111,112].

4. Effect of dietary components on cardiovascular risk

Diet composition has a prominent effect on cardiovascular risk. Consumption of animal products increases whereas intake of plant-based foods reduces the risk of cardiovascular disease [3–8]. Insulin resistance by itself is a major cardiovascular risk factor in the general population and patients with diabetes [9–11]. Diet-induced insulin resistance may contribute to explain the increased cardiovascular risk associated with western-type dietary profiles.

4.1. Intake of animal products increases cardiovascular risk

Prospective studies, such as the California Seventh-day Adventists, the NIH Diet and Health Study cohort, the NHS and the HPFS show a positive association between the intake of animal protein and mortality from cardiovascular disease. Both unprocessed and processed red meat are associated with an increased risk of cardiovascular mortality in fully adjusted models. Higher consumption of red meat is associated with an increased risk of coronary heart disease and stroke independent of established dietary and non-dietary cardiovascular risk factors [3–7]. Meat consumption is associated with higher incidence of coronary heart disease in a meta-analysis and systematic review of the literature [8].

4.2. Intake of healthy vegetable food reduces cardiovascular risk

A number of studies show an inverse association between consumption of vegetable food and cardiovascular mortality independently of BMI and other cardiovascular risk factors.

Large prospective cohort studies of Seventh-day Adventists show that the risk of coronary heart disease in nonvegetarians is greater than the risk in vegetarians of comparable age, suggesting that a vegetarian diet protects from cardiovascular disease. The lifetime risk of ischemic heart disease is reduced by 37% in vegetarians compared with nonvegetarians. Multivariate analyses show a negative association between nut consumption and ischemic heart disease [113,114]. The Puerto Rico Heart Health Program study investigated the prospective association of baseline nutrient intakes and subsequent six-year coronary heart disease in Puerto Rican men. Multivariate analysis demonstrated an independent inverse relation of complex carbohydrate intake (such as legumes) and incidence of coronary heart disease. Subjects who developed coronary heart disease had lower complex carbohydrate consumption [115]. In the NHS at 12-year follow-up, there was an inverse association between whole grain intake and risk of ischemic stroke after adjustment for cardiovascular disease risk factors. Higher intake of whole grain foods was associated with a lower risk of ischemic stroke independently of cardiovascular disease risk factors [116]. The Multi-Ethnic Study of Atherosclerosis is a prospective cohort study of Black, Hispanic, Chinese, and White adults aged 45–84 years. Incident cardiovascular events were identified over a median of 4.6 years of surveillance. Elevated intake of whole grains, nuts and seeds, fruit and vegetables was associated with a lower risk of cardiovascular disease after adjustment for confounders. This association remained strong after adjustment for waist circumference, blood pressure and lipids. High intake of whole grains, nuts, fruit and vegetables was associated with a lower relative risk of incident cardiovascular disease [117]. In the EPIC cohorts, consumption of fruit and vegetables was inversely associated with all-cause mortality. This association was driven mainly by cardiovascular mortality. Fruit and vegetable consumption is associated with a lower risk of death, particularly cardiovascular mortality [118].

In a randomized controlled trial, patients with coronary heart disease who underwent lifestyle modifications including a vegetarian diet showed regression of coronary atherosclerosis while patients who received usual care experienced progression of coronary artery lesions. Lifestyle modifications including a plant-based diet led to regression of even severe coronary atherosclerosis at 1-year and 5-year follow-up [58,119].

In a meta-analysis including 5 prospective studies that compared the death rates from cardiovascular disease of vegetarians with those of nonvegetarians with similar lifestyles, mortality from ischemic heart disease was 24% lower in vegetarians than in nonvegetarians after a mean follow-up of 10.6 years [63].

In a systematic review aimed to assess the effects of varying protein intake in healthy adults, the evidence is assessed as suggestive for an inverse relation of vegetable protein intake and cardiovascular mortality [57].

4.3. Differential effect of animal and vegetable protein on cardiovascular risk

Investigations that compare the effect of animal versus vegetable protein on cardiovascular risk find that the intake animal products increase cardiovascular risk whereas vegetable foods have the opposite effect [5–7,120–123]. In postmenopausal women, a prospective study with 15-year follow-up shows that animal protein has adverse effects on coronary heart disease mortality compared with vegetable protein. Red meat and dairy products were associated with increased coronary heart disease mortality. Further, coronary heart disease mortality decreased by 30% from an isoenergetic substitution of vegetable for animal protein [120]. In the NHS and the HPFS cohorts, a diet based on animal sources was associated with higher all-cause mortality and cardiovascular mortality whereas a vegetable-based diet was associated with lower all-cause mortality and cardiovascular mortality [121]. In the NHS during 26 years of follow-up, one serving per day of nuts is associated with a 30% lower risk of coronary heart disease compared with 1 serving per day of red meat. The elevated risk of coronary heart disease mediated by high intake of red meat may be reduced by shifting the source of protein to vegetable protein [5]. In the NHS and the HPFS cohorts, the substitution of vegetable protein sources for red meat is associated with lower risk of stroke and cardiovascular mortality [6,7]. In a study aimed to investigate the association of nutrient intakes with the extent of raised atherosclerotic lesions in coronary arteries measured at autopsy, intake of animal protein and fat was associated with greater coronary atherosclerosis. In contrast, intakes of protein of vegetal origin, total carbohydrate, starch, and crude fiber were associated with less coronary atherosclerosis [122]. When the association of foods rather than nutrients was examined, the intake of beef and milk was associated with greater coronary atheromatosis. In contrast, intake of legumes and grains was related to lesser raised coronary lesions measured at autopsy [123].

5. Summary

Diet composition has a striking effect on the risk of developing T2D and cardiovascular disease. The effect of dietary elements on insulin sensitivity may contribute to explain the marked influence of eating habits on these disorders. Animal protein intake intensifies insulin resistance while vegetable protein enhances insulin sensitivity in healthy subjects and patients with diabetes. Insulin resistance predispose to T2D in healthy subjects. In patients with diabetes, insulin resistance deteriorates the metabolic control of the disease. In diabetic and nondiabetic individuals, insulin resistance by itself is a well-established cardiovascular risk factor. Replacing sources of animal protein with plant protein enhances insulin sensitivity. Vegetarian diets enhance insulin sensitivity compared to diets that include animal products both in healthy individuals and in patients with diabetes, improving metabolic control and reducing cardiovascular risk. Population groups that change their dietary habits from traditional diets rich in vegetable protein to western-type dietary patterns with elevated content of animal products experience a marked increase in the rate of T2D and cardiovascular disease, probably mediated by intensification of insulin resistance. The association between animal protein consumption and insulin resistance is independent of BMI. Weight loss fails to enhance insulin sensitivity in the presence of a diet high in animal products. Diet composition has a definite impact on the risk of developing gestational diabetes, a condition characterized by maternal insulin resistance.

Pre-pregnancy intake of animal protein increases the risk of gestational diabetes, independently of BMI while vegetable food consumption decreases the risk. Dietary patterns that intensify insulin resistance predispose to cardiovascular disease and increase cardiovascular mortality.

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Conflict of interest

The authors declare that they have no conflict of interest.

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