Red Meat, Dietary Heme Iron, and Risk of Type 2 Diabetes: The Involvement of Advanced Lipoxidation Endproducts[1,2]

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ABSTRACT

There is growing evidence of disordered iron homeostasis in the diabetic condition, with links proposed between dietary iron intakes and both the risk of disease and the risk of complications of advanced disease. In the United States, Britain, and Canada, the largest dietary contributors of iron are cereals and cereal products and meat and meat products. This review discusses the findings of cohort studies and meta-analyses of heme iron and red meat intakes and the risk of type 2 diabetes. These suggest that processed red meat is associated with increased risk, with high intakes of red meat possibly also associated with a small increased risk. Historically, humans have relied on large quantities of heme iron and red meat in their diets, and therefore it is paradoxical that iron from meat sources should be associated with the risk of type 2 diabetes. A reason for this association may be drawn from studies of dietary advanced glycation and lipoxidation endproducts present in processed food and the mechanisms by which insulin output by pancreatic islet cells might be influenced by the protein modifications present in processed red meat. *Adv. Nutr. 4: 403–411, 2013.*

Introduction

The global prevalence of type 2 diabetes is now 10% of adults aged 25 y of age and older (1) and accounts for 12% of global health care spending (2). Rates are set to continue increasing as obesity levels increase. The involvement of iron in the risk of type 2 diabetes has generated substantial interest over the past 15 y, initially sparked by an association with increased serum ferritin and the observation that diabetes frequently develops in those individuals with iron overload diseases.

Evidence of a link between heme iron and the risk of type 2 diabetes exists, as discussed in the following, and is an association that is stronger with processed meat than with red meat. However, a link between total iron and nonheme iron intake and diabetes has not been found (3–5); thus, it is the involvement of meat products that are of particular interest.

In the United Kingdom, which, in common with the United States and Canada, fortifies wheat and breakfast cereals with iron; the largest dietary contributors of iron are cereals and cereal products (44%–55%), and meat and meat products (13%–19%) (6), giving 85% to 100% nonheme iron (absorbed at 0.1%–35% efficiency), and 10% to 15% heme iron (absorbed at 20%–50% efficiency) (7,8). Historically, humans have evolved to have a plentiful supply of iron from diets rich in muscle tissue from meat and fish. Why then should heme iron intake be positively associated with the risk of type 2 diabetes? It seems unlikely to be due to elemental iron itself, considering the high amounts consumed in ancient diets and the body's ability to regulate dietary absorption of both heme and nonheme iron to match requirement (9). Although heme iron is more efficiently absorbed, high intakes do not lead to accumulating iron stores in healthy people. Although absorption of both types is influenced by iron status, the absorption of nonheme iron is more strongly influenced by physiological need (9).

A link via dietary glycoxidation and lipoxidation products between meat, animal fats, among diabetes has been proposed (10,11), which occur after reaction between carbonyl groups on sugars and amine groups on proteins, DNA, and lipoproteins. Dietary advanced glycation endproducts (AGEs)[3] and advanced lipoxidation endproducts (ALEs) are produced in large amounts in animal products high in protein and fat. These products are absorbed in proportion to the

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[3] Abbreviations used: AGE, advanced glycation endproduct; ALE, advanced lipoxidation endproduct; CEL, ε-N-(carboxyethyl)lysine; CML, ε-N-(carboxymethyl); CRP, C-reactive protein; INHIO, insulin resistance hepatic iron overload; iNOS, inducible nitric oxide synthase.

amounts consumed (12) and have known deleterious effects on the body (13).

This review considers the evidence of a link between physiological iron status and the risk of type 2 diabetes and of dietary heme iron and red meat iron intakes and the risk of diabetes. The historical role of red meat in the human diet is reviewed, and the contribution of AGEs and ALEs to the modern diet and as a potential risk factor for diabetes is discussed.

Current status of knowledge

Physiological iron status and risk of type 2 diabetes

Evidence of a link to the risk of diabetes and increased physiological iron status was first put forward in 1998 (14), when positive serum ferritin correlations with serum insulin and blood glucose were reported. Ferritin is an acute-phase reactant, however, and inflammation should be controlled for in these studies, often undertaken with C-reactive protein (CRP). Using CRP alone does not fully account for inflammation (15,16), and the results of studies thus controlled may still include inflammation as a factor in the level of risk seen. Three meta-analyses of studies of serum ferritin and the risk of type 2 diabetes were reported recently (17–19) (**Table 1**) Zhao et al. (17) included 6 prospective studies with a total of 14,870 participants, and 2336 cases. All studies controlled for age and BMI and inflammation with CRP, apart from Jehn et al. (20), who used an inflammation score, and Le et al. (21), who used no inflammation control. For diabetes in the highest compared with lowest categories at baseline, [pooled RR = 1.66 (95% CI = 1.15, 2.39) I^2 = 66.3% for heterogeneity], leading the authors to conclude that higher serum ferritin concentrations were associated with an increased risk of type 2 diabetes. Bao et al. (18) found an RR 1.63 [(95% CI = 1.03, 2.56) $P = 0.036$], which, combined with their findings for dietary heme iron and risk (Table1), led the authors to suggest that in countries where most of the population have sufficient intakes, it may be necessary to reconsider dietary reference values for iron.

Most recently, Kunutsor et al. (19) conducted a meta-analysis of 9 studies, with a total of 26,339 participants, and 3391 cases. The pooled RR for diabetes in the highest quintile for serum ferritin compared with the lowest was 1.73 [(95% CI = 1.35, 2.22) I^2 = 58%)]. The authors concluded that serum ferritin may be used to identify individuals at risk of type 2 diabetes.

The mean and median concentrations of ferritin in the highest category of status, on which these RRs are based, are 136 μg/L (18), and 222 ng/mL (19) and therefore are not excessive by normal concentrations [(males, 15–300 μg/L; females, 15–200 μg/L (22)]. Increased serum ferritin is seen in patients with the genetic iron overload disease hemochromatosis, a group who have an increased risk of secondary diabetes (23) due to impaired insulin secretion as a consequence of pancreatic-iron deposition (24). However, the presence of increased pancreatic iron has not been established in nonhemochromatosis type 2 diabetes.

Fernandez-Real et al. (25) found a protective effect of repeated venesection on the risk of diabetes in a small study of 21 healthy blood donors; however, other studies disagree (26). found no significant difference in risk between frequent donors (>8 donations per 2 y) and infrequent donors (1–2 per 2 y). The results of the largest study of this kind (27) do not support a link between blood donation and risk of type 2 diabetes, following 33,541 men for 12 y. The highest quintile

Table 1. Summary of published meta-analyses of studies of serum ferritin concentration, dietary heme iron, red meat, and processed meat intake, and risk of type 2 diabetes

Authors, year (reference) (included studies)	Participants	Cases	Exposure (typical, median or mean)		RR	95% CI	P-trend if given	I^2
			Lowest category	Highest category				
Serum ferritin concentration	*n*	*n*						%
Zhao et al., 2012 (17) (3–5,15,20,21,27,90–97)	14,870	2336	—	—	1.66	1.15, 2.39	—	66.3
Bao et al., 2012 (18) (4,14,15,20,21,96)	10,016	2198	34 μg/L	136 μg/L	1.63	1.03, 2.56	0.036	68.7
Kunutsor et al., 2013 (19) (4,15,20,21,90,96,99,100)	26,339	3391	0 μg/L	222 μg/L	1.73	1.35, 2.22	—	58
Dietary heme iron								
Zhao et al., 2012 (17) (3,5,27,62)	188,935	9246	—	—	1.31	1.21, 1.43	—	0
Bao et al., 2012 (18) (3,5,27,62,98)	197,488	9269	0.56 mg/d	2.39 mg/d	1.33	1.19, 1.48	<0.001	27.4
Kunutsor et al., 2013 (19) (3,5,27)	159,123	7688	—	—	1.28	1.16, 1.41	—	0
Dietary red meat (excluding processed red meat)								
Aune et al., 2009 (34) (5,10,62,101–107)	433,070	12,226	<100 g/wk	>600 g/wk	1.21	1.07, 1.38	—	58.5
Pan et al., 2011 (10,35) (62,101–104,106,109,110)	442,101	28,228	220.5 g/wk	1166.2 g/wk	1.34	1.26, 1.43	<0.001	—
Micha et al., 2010 (36) (10,101,102,104)	372,279	10,782	110 g/wk	830 g/wk	1.16[1]	0.92, 1.46	0.25	—
Feskens et al., 2013 (37) (38,62,103–105,110,112)	517,192	18,235	—	—	1.13[2]	1.03, 1.23	—	36
Dietary processed meat								
Aune et al., 2009 (34) (10,101–103,105,107,108)	380,606	9999	<50 g/wk	>250 g/wk	1.41	1.25, 1.60	—	53.2
Pan et al., 2011 (35) (62,101–104,106,109,110)	442,101	28,228	3.15 g/wk	583.1 g/wk	1.32	1.24, 1.40	<0.001	—
Micha et al., 2010 (36) (10,62,101,102,104,111)	372,279	10,782	20 g/wk	285 g/wk	1.19[3]	1.11, 1.27	<0.001	—
Feskens et al., 2013 (37) (38,110,112)	369,445	13,957	—	—	1.32[4]	1.19, 1.48	—	89

[1] RR of highest versus lowest category of status or intake, apart from per 100-g serving/day.
[2] RR of highest versus lowest category of status or intake, apart from per 100 g.
[3] RR of highest versus lowest category of status or intake, apart from per 50-g serving/day.
[4] RR of highest versus lowest category of status or intake, apart from per 50 g.

of donation (≥30 in 30 y) gave an RR of 1.12 [(95% CI = 0.78, 1.61) *P*-trend = 0.70)].

Insulin resistance hepatic iron overload (IRHIO) or dysmetabolic iron overload disease is seen in approximately one third of patients with nonalcoholic fatty liver disease and the metabolic syndrome (28). Hepatic iron loading, associated with overweight, dyslipidemia, hypertension, and glucose intolerance and separate from genetic iron-overload disease, was first identified by Moirand et al. (29). IRHIO is associated with increased serum ferritin independently of CRP and increased liver iron seen in periportal hepatocytes and less frequently in sinusoidal Kupffer cells (29). Although increased stored liver iron is thought to cause insulin resistance, the mechanisms by which it does are undefined (28). Iron depletion therapy has been shown to increase peripheral and hepatic insulin sensitivity, increase pancreatic insulin sensitivity, reduce hemoglobin A1c, improve liver function test results, and ameliorate low-grade inflammation in patients with IRHIO, shown by numerous studies (28,30).

In summary, increased iron status, as measured by serum ferritin, has a positive association with the risk of type 2 diabetes. This risk does not appear to be reduced by regular blood donation in people without IRHIO, and the adaptability of the gut to adjust iron absorption to physiological need may lead the body to respond to venesection by absorbing more iron.

Meta-analyses of heme iron intake and the risk of diabetes

Zhao et al. (17), Bao et al. (18), and Kunutsor et al. (19) also conducted meta-analyses of studies of heme iron intake and the risk of type 2 diabetes (Table 1). For heme iron, Bao et al. (18) found median intakes of 2.39 g/d versus 0.56 mg/d, with an RR of 1.33 [(95% CI = 1.19, 1.48) $P < 0.001$], RRs similar to those found by Zhao et al. (17) [1.31 95% CI = 1.21, 1.43)], and Kunutsor et al. (19) [1.28 (95% CI = 1.16–1.41)]. There was a low degree of heterogeneity between the studies considered by Bao et al. (18) ($I^2 = 27.4$). It should be noted that some large prospective studies included in these analyses (3,4) interpret red meat intake as being solely heme iron, but in fact it has a significant proportion of nonheme iron from ferritin and mitochondria. For example, in beef muscle meat, 64% of total iron is in the heme form (31). Other studies have used a factor of 0.6 (32) to calculate nonheme iron in meat. Incorporating this attributes greater weight to a link with heme iron. It is not clear from these studies whether it is heme iron from red meat or total heme iron (red meat, poultry, and fish) that increases the risk of diabetes. As total iron intakes are not similarly associated with risk, it is not the iron content per se that is influencing risk, but other factors related to red meat, poultry, and fish. One possibility may be saturated fat, but analysis included adjustment for saturated fat (4), animal fat (5), and polyunsaturated fat to saturated fat ratio (3).

A link was also suggested between heme iron intake and the risk of gestational diabetes (33) in a cohort study of 3158 pregnant women, in 158 of whom gestational diabetes developed. The authors found that intakes of >1.12 mg/d versus <0.48 mg/d had an RR of 2.15 [(95% CI = 1.09, 4.27) *P*-trend = 0.09].

Meta-analyses of red and processed meat intake and the risk of type 2 diabetes

Four meta-analyses of studies assessing red and processed meat intake and the risk of type 2 diabetes were conducted (34–37) (Table 1). These have some degree of overlap but between them cover 24 studies and follow >1,016,400 participants with 37,200 incident cases of diabetes. Included are the recent European Prospective Investigation into Cancer and Nutrition (EPIC)-InterAct results; 8 case-cohort studies nested within the European Prospective Investigation into Cancer and Nutrition (38). These meta-analyses find for red meat intakes in the highest intake group compared with the lowest, an RR of 1.21 [(95% CI = 1.07, 1.38) for >600 g/wk vs. <100 g/wk (34)] and 1.34 [(95% CI = 1.26, 1.43) median, 1166.2 g/wk vs. 220.5 g/wk (35)]. The RR per 100 g/d was 1.16 [(95% CI = 0.92, 1.46) $P = 0.25$ (36)] and an RR of 1.13 per 100 g [(95% CI = 1.3, 1.23) (37)] (Table 1).

For processed meat intake, a significant association was found by Pan et al. (35) for highest versus lowest intakes [RR = 1.32; (95% CI = 1.24, 1.40) *P*-trend < 0.001]. Significance was not reported by Aune et al. (34), who found an RR of 1.41 (95% CI = 1.25, 1.60) or by Feskens et al. (37), who found an RR of 1.32 per additional 50 g (95% CI = 1.19, 1.48). Micha et al. (36) found an RR of 1.19 per 50 g/d [(95% CI = 1.11, 1.27) $P < 0.001$].

Not included in these meta-analyses, but of relevance, are the results of Lajous et al. (39) for unprocessed and processed red meat intake and incidence of type 2 diabetes in a cohort of 66,118 healthy French women. The authors report an association with processed meat only [HR = 1.30 for a median intake of 336 g/wk vs. 35 g/wk (95% CI = 1.07,1.59)].

Mechanisms

Humans have historically consumed large amounts of heme iron. Evidence from fossil isotope and tooth enamel studies indicates large quantities of grazing animal meat in ancient diets, and comparison of gut physiology with other mammals also suggests that meat contributed a significant amount to the diet of early hominids, ~1.8 million years ago (40). Hunter-gatherer cultures today still have a high reliance on meat, fish, and other tissues, preferring to obtain at least half of their energy from animal foods when possible (41). In some cultures, protein intakes reach 86% of total energy intake. Fatty acid profiles have changed in developed countries, however, compared with 229 hunter-gatherer societies today (41), of the 55% to 65% of daily energy from animal foods (heme iron providers), half would be derived from aquatic animals and half from terrestrial animals (41). This would provide a fatty acid profile significantly different from that seen in the typical modern diet, with a saturated fat content of 7% energy compared with between 9% and 19% today (42), and an n3:n6 ratio of 1:1.5, compared with >1:15 today (43). In support of this, a review of cohort studies of

dietary fat, carbohydrate, and risk of diabetes (44) found that higher intakes of PUFAs and possibly n3 PUFAs could be beneficial, but there was no general consensus on proportions of total fat or carbohydrate as a risk factor for diabetes. Substituting a highly SFA acid diet for a highly monounsaturated fatty acid diet has been shown to improve insulin sensitivity in 162 healthy men and women over a 3-mo period (45); however, no benefit in fat type substitution for individuals with a high fat intake (>37% of total energy) or with the addition of n3 fatty acids. One review (46) also found consistently positive associations between saturated fat and hyperinsulinemia, although, again, n3 supplementation had no effect on insulin action. In a review of clinical trials (47), no changes in fasting glucose or insulin measurements were found with n3 fatty acid supplementation. Conversely, 2 epidemiological studies found an inverse relationship between fish intake and glucose tolerance and positive links between total fat and saturated fat and diabetes risk (48). The authors recommend that total fat intakes not exceed 30% and saturated fat not exceed 7%of the total energy intake as beneficial to diabetes risk. They did not include iron or meat intakes as part of their review.

Branched-chain amino acids

In consideration of other factors in meat associated with insulin resistance, Wang et al. (49) identified 5 branched-chain and aromatic amino acids that have highly significant associations with future diabetes, by serum amino acid profiling at baseline, in 2422 normoglycemic individuals followed for 12 y. Branch-chain amino acids have long been established as increased in obese compared with normal weight controls and correlate with insulin resistance (50). They are increased in insulin resistance after changes in amino acid catabolism (51), and their catabolism is enhanced by exercise (52). Postprandial concentrations of amino acids, particularly branched chain, interfere with insulin signaling in animals (53) and in humans (54) by inhibiting the early stages of postinsulin receptor activity, preventing phosphorylation of insulin receptor substrates and subsequent protein kinase C and other kinase subunits, and interfering with GLUT4 translocation to the cell membrane (55).

Amino acid–initiated insulin resistance would have benefited historic diets high in meat, because where low glucose intakes are the norm, a protein-rich meal will inhibit muscle glucose uptake, conserving available glucose for the brain and allowing peripheral cells to metabolize lipids and protein for energy (56). Branch-chain amino acids are an important contributor to total amino acids in muscle tissue (57); however, they cannot account fully for the increased risk of diabetes seen with heme iron because processed meat has a lower amino acid and a higher fat content per gram of meat and a greater risk of diabetes.

Free fatty acids

Free fatty acids, from the diet and adipocyte lipolysis, have a known capacity to produce insulin resistance in muscle and liver, by a number of postulated mechanisms (58–60). Girousse et al. (61) described improvement of insulin sensitivity by inhibition of adipose tissue lipolysis in mice fed a high-fat diet. Fatty acids are plentiful in processed foods and may present a link between processed meat and the risk of diabetes; however, 1 cohort study (62) of 37,309 women over 8 y found an RR of 1.38 for diabetes in those consuming processed meat $\geq$5 times per week in a multivariate analysis that included controlling for total and saturated fat intake. Pan et al. (35). also used a dietary score in their model that included a PUFA-to-SFA ratio; thus, fatty acids do not appear to explain the effect.

Nitrates and nitrites

Dietary nitrates and nitrites have been suggested as a possible reason for the increased risk associated with processed meats (36,37). Nitrites are used to preserve meats and are transformed in the gut by reaction with amines and amides to become the N-nitroso compounds nitrosamines and nitrosamides. Nitrites have been linked to the development of type 1 diabetes (63), although the mechanism involved is unclear, and nitrates are found in higher amounts in vegetables (64) and are beneficial in the form of NO (discussed in references 37 and 65). Regulation in 1978 led to strict control of nitrite use in meat processing, and amounts have subsequently decreased. There is little evidence of an influence on the risk of type 2 diabetes, and calls for clearer sighted discussions of the benefits and risks of nitrates and nitrites have been made (65,66).

Advanced glycation endproducts

The term advanced glycation endproduct refers to a heterogeneous group of compounds known to have pro-oxidant and proinflammatory effects in the body (13). AGEs occur after reaction between carbonyl groups on sugars and amine groups on proteins, DNA, and lipoproteins to form glycated proteins. This nonenzymatic glycation is the first stage of the Maillard reaction, also responsible for browning reactions between carbohydrates and amines in cooked food. Proteins can also be modified by lipid peroxidation, becoming ALEs. Within the dietary AGE literature, the term AGE is often used generically for any nonenzymatic protein modification, i.e., for reactions involving either carbohydrate or lipids. The label AGEs for these products is misleading because they refer to $^{\epsilon}$N-(carboxymethyl) (CML) and $^{\epsilon}$N-(carboxyethyl lysine) (CEL), downstream products of glycation that can occur between lipids and protein independently of the Amadori compound fructolysine (67). Consequently, the presence of glucose (or fructose) is not essential for their formation, and meats and cheese, for example, can have high amounts despite having very little or no intrinsic carbohydrate content. One common route of formation is from PUFAs, where oxidation of a double bond causes fatty acid cleavage and formation of a 4-hydroxy-2-nonenal moiety, which can then bind to a protein lysine residue, forming a protein carbonyl (68).

For the role of dietary AGEs in diabetes risk, support for earlier work (10) is put forward (11), which proposes that dietary glycoxidation products are the link between animal

fats, meat, and diabetes because the highest amounts of AGEs and ALEs are seen in animal products high in protein and fat, with industrially processed animal products such as hot dogs and bacon containing large amounts. Formation is increased by higher cooking temperatures and method of cooking, and meats cooked with a high dry heat such as grilling, frying, and roasting have the highest AGE values (13). Tables of AGE amounts in common foods are available (69).

The proposal of AGEs as the link between animal fats and meat and diabetes can be extended to include the positive association between heme iron intake and risk, with perhaps an involvement by N-nitroso compounds. It also raises the question of whether the formation of AGE products within these foods is enhanced by the presence of elemental iron, as shown to be the case in vitro with copper, LDL, and PUFA formation of CML (67) and suggested within the body (70), or whether some other factor(s) present in heme is influential, alongside the effects of heat during processing. The mechanical process of mincing meat, for example, breaks down tissue, exposing myoglobin and heme, and oxidation of the ferrous iron to ferric occurs when the reducing environment of the tissue surrounding the exposed myoglobin is exhausted. With storage, unsaturated fatty acids oxidize and produce free radicals that can oxidize the myoglobin (71). Protection against meat protein oxidation by dietary antioxidants is able to compensate for high amounts of PUFAs in pasture-fed compared with grain-fed lamb (72). The potential for heme iron and ferric iron from ferritin to catalyze reactions has received some investigation by the meat industry, and myoglobin is found to be a good predictive marker for protein carbonyl formation; however, relative contributions from different iron forms have not been determined (68). Two studies (73,74) compared the production of thiobarbituric acid reactive substances (a marker of lipid peroxidation) on stored raw and cooked muscle meats. Amounts were low in chicken and pork compared with beef, and all increased with cooking, with myoglobin content best explaining the difference (73), later agreed by Peiretti et al. (74). Again, no iron factor has been drawn by which the contribution of iron-to-lipid oxidation can be estimated.

Dietary AGEs in the body

Approximately 10% of dietary AGEs are absorbed, directly proportional to the amount consumed (12), and a growing body of evidence describes their deleterious effects on the body. For example, a single AGE drink led to a significant increase in serum AGEs and significantly decreased flow-mediated dilation of the brachial artery in both diabetic and healthy subjects, at 90 min post-administration (75). The authors suggest that elevated circulating AGEs may alter vascular endothelium response by reducing cellular NO production or inhibiting NO activity. AGE intake leads to increased oxidative stress and inflammation, and reductions in dietary AGEs result in improved flow-mediated vasodilation in diabetes patients (76). A high AGE meal compared with a low AGE meal results in a marked increase in circulating markers of endothelial function (vascular cell adhesion molecule 1 and E-selectin) in type 2 diabetes patients (77). Dietary AGE products have also been found to activate cell membrane AGE receptors, triggering mitogen-activated kinase activation of pathways for inflammation, cell proliferation, and tumor growth (78).

AGEs and insulin

Of direct relevance to the risk of diabetes, evidence that AGEs can cause changes that predispose to diabetes has come from a number of studies, using the insulin-resistant mouse model C57/BL/KsJ *db/db*. Dietary AGE restriction while maintaining other nutrient values (including kilocalories) improves insulin resistance, with mice fed a low-AGE diet demonstrating lower circulating AGE concentrations, improved insulin sensitivity, and a doubling of glucose uptake by abdominal tissue compared with those receiving a high AGE diet (79). Sandu et al. (80) found that high-fat and high-AGE diets led to increased visceral fat, plasma 8-isoprostane, plasma glucose, and plasma insulin; altered pancreatic islet structure, with fewer insulin- and glucagon-producing cells; and increased diabetes. Less adiponectin (the mediator for transcription factor peroxisome proliferator–activated receptor γ) was also apparent.

A positive association was demonstrated between serum AGE and insulin resistance in a cross-sectional study of 322 healthy adults. Tahara et al. (81) found mean $\pm$ SD serum AGE concentrations of 8.96 $\pm$ 2.57 U/mL, where 1 U AGE is equivalent to 1 μg of AGE–bovine serum albumin (BSA) standard. Serum AGE correlated with homeostasis model assessment of insulin resistance ($r = 0.281$, $P < 0.001$).

Impaired insulin secretion in type 2 diabetes is thought to be due to cell function impairment and cell loss by apoptosis (82). β-Cell apoptosis is thought to result from endoplasmic reticulum stress (83), which can be induced by high glucose and FFAs in type 2 diabetes, and inflammatory cytokines in type 1 diabetes (84) [although the effect on endoplasmic reticulum in type 2 has been proposed to be primarily lipotoxic rather than glucotoxic (82)]. Functionally, the cell-signaling pathways that result in insulin regulation in β cells are not fully elucidated, but are known to involve transcription factor pancreatic homeobox factor 1, with a possible negative feedback inhibitory action by protein kinase casein kinase 2 (85).

Zhao et al. (86) describe a link connecting AGEs to insulin resistance whereby AGEs inhibit ATP production in islet β cells, subsequently inhibiting insulin secretion. In C57BL/6J mice, glycated BSA [AGE (CML)-BSA; 50 g/L BSA incubated in 0.5 mol/L glucose, at 37°C, for 8 wk], administered intraperitoneally for 2 wk. Serum insulin, glucose tolerance, and insulin tolerance were all significantly impaired in a dose-dependent manner with AGE-BSA. Few morphological changes in islet structure were seen, but the isolated cells dose-dependently contained significantly less insulin. Fresh islets were isolated from healthy mice and treated with AGE-BSA for 48 h. Inducible NO synthase (iNOS) mRNA was induced in a dose-dependent manner, accompanied by NO release in parallel. NO is thought to regulate mitochondrial

oxygen consumption by inhibiting cytochrome c oxidase activity (87); therefore, the cells were treated with aminoguanidine, which selectively inhibits iNOS, restoring cytochrome c oxidase activity. Inhibition of iNOS also restored ATP production and insulin secretion, leading the authors to conclude that AGE inhibits insulin secretion via iNOS upregulation (via cell membrane AGE receptor signaling cascade and nuclear factor-$\kappa\beta$ activation) and NO upregulation, inhibiting cytochrome c oxidase–dependent ATP production and insulin secretion.

Other effects of circulating AGEs on insulin resistance cells have been reported (88), in which chronically elevated AGE ingestion in C57BL/6 mice, compared with a low-AGE diet, led to higher blood glucose and insulin after a glucose tolerance test ($P < 0.05$). Isolated insulin-sensitive cells showed suppression of insulin signaling targets tyr-phosphorylated insulin receptor, and insulin receptor substrates. Negative regulators of insulin signaling were enhanced.

A systematic review of dietary AGE restriction in humans for improvement of insulin resistance, oxidative stress, and endothelial dysfunction was recently completed (89). Twelve studies were included, with 289 participants in total. Some evidence was found of the reduction of oxidative stress, inflammation, and homeostasis model assessment of insulin resistance, but the quality of the evidence led the authors to conclude that there is currently insufficient evidence to recommend dietary AGE restriction for prediabetes, diabetes, and renal disease. They recommend that long-term high-quality randomized, controlled trials be conducted to better address these questions.

Conclusions

Many factors govern the risk of type 2 diabetes, including primarily obesity, age, physical inactivity, and genetic inheritance. Other factors of less importance offer potentially alterable contributors to risk, and understanding their pathological mechanisms may give insight to future therapies. Meta-analyses of body iron status as measured by serum ferritin demonstrate a positive relationship with the risk of type 2 diabetes, as do meta-analyses of dietary heme iron and risk. Heme iron intake is representative of meat in the diet; however, citing meat intake as accounting for this link is an oversimplification, and processed meat intake gives a higher profile of risk across the meta-analyses that differentiate between red and processed meat. Processed meat may increase the risk of type 2 diabetes potentially via AGE (specifically ALE), produced during food processing and cooking, with meat PUFA content, iron, and heat facilitating their composition. Mechanisms are described in the literature that outline pathophysiological links between dietary AGEs and insulin loss and insulin resistance. The level of contribution from iron to dietary protein oxidation and AGE development in processing is not known, but experimental laboratory testing of this should be carried out in meats with varying lipid contents and between red meat and other dietary AGEs.

Acknowledgments

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