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Reviews

A review of potential metabolic etiologies of the observed association between red meat consumption and development of type 2 diabetes mellitus

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ABSTRACT

Epidemiological studies suggest that red and processed meat consumption is related to an increased risk of type 2 diabetes. However, it is not clearly understood which components of red and processed meat contribute to this increased risk. This review examines potential mechanisms addressing the role of saturated fatty acid, sodium, advanced glycation end products (AGEs), nitrates/nitrites, heme iron, trimethylamine N-oxide (TMAO), branched amino acids (BCAAs) and endocrine disruptor chemicals (EDCs) in the development of type 2 diabetes based on data from published clinical trials and animal models. TMAO which is derived from dietary carnitine and choline by the action of bacterial enzymes followed by oxidation in the liver may be a strong candidate molecule mediating the risk of type 2 diabetes. BCAAs may induce insulin resistance via the mammalian target of rapamycin complex 1 (mTORC1) and ribosomal protein S6 kinase β 1 (S6k1)-associated pathways. The increased risk associated with processed meat compared with red meat suggests that there are interactions between the saturated fat, salt, and nitrates in processed meat and iron, AGEs and TMAO. Intervention studies are required to clarify potential mechanisms and explore interactions among components, in order to make firm recommendations on red and processed meat consumption.

Abbreviations: AGEs, advanced glycation end products; TMAO, trimethylamine N-oxide; BCAAs, branched amino acids; EDCs, endocrine disrupting chemicals; mTORC1, mammalian target of rapamycin complex 1; S6k1, ribosomal protein S6 kinase β 1; T2DM, type 2 diabetes mellitus; CVD, cardiovascular disease; HR, hazard ratio; 95% CI, 95% confidence interval; SFA, saturated fatty acid; BMI, body mass index; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; FSIGT, frequently sampled intravenous glucose tolerance test; IRS-1, insulin receptor substrate-1; PI3K, phosphatidylinositol 3-kinase; SF, saturated fat; RR, relative risk; OGTT, oral glucose tolerance test; HOMA, homeostatic model assessment; RAS, renin–angiotensin system; RAGE, receptor for AGE; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells;-; AAS, α-amino adipic semi-aldehyde; GGS, γ-glutamic semi-aldehyde; VCAM-1, vascular cell adhesion molecule 1; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1 beta; IL-6, interleukin 6; CRP, C-reactive protein; ROS, reactive oxygen species; AGE-BSA, advanced glycation end product of bovine serum albumin; NO, nitric oxide; ATP, adenosine triphosphate; ICAM-1, intercellular adhesion molecule 1; TBARS, thiobarbituric acid reactive substances; $ONOO^-$, peroxynitrite; LDL, low-density lipoprotein; NOx, nitric oxide metabolic pathway products; Fe^{3+}, ferric; O_2^-, superoxide; Fe^{2+}, ferrous; O_2, oxygen; H_2O_2, hydrogen peroxide; •OH, hydroxyl radicals, OH–, hydroxyl ion; GLUT4, glucose transporter type 4; FFA, free fatty acid; HOMA-IR, homeostasis model assessment of insulin resistance; CHD, coronary heart disease; TMA, trimethylamine; HbA1c, glycated hemoglobin; IRS-2, insulin receptor substrate 2; BPA, bisphenol A; DEHP, di-2-ethylhexyl phthalate; SML, specific migration limit; DBP, dibutyl phthalate; EFSA, the European Food Safety Authority; TDI, tolerable daily intake.

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1. Introduction

In 2011, an estimated 366 million people in the world had diabetes and this number is expected to increase to 552 million by 2030 [1]. Type 2 Diabetes Mellitus (T2DM) results in complications such as cardiovascular disease, retinopathy, nephropathy, neuropathy, leg ulcers and gangrene [2], which are very common, costly and shorten life expectancy [3]. In Australia, 65% of all cardiovascular disease (CVD) death occurs in those with T2DM and pre diabetes [4]. In the USA, people with diabetes on average, spent 2.5 times more on medical care than people without diabetes [5].

Individual characteristics including age, family history, ethnicity, obesity, smoking, sedentary lifestyle and hypertension are well-known risk factors for T2DM [3]. There is a strong focus on translating what has been learned from controlled trials into community action for the prevention of T2DM [6,7]. Although diet quality is associated with risk of T2DM exactly which components are important is not clear [8–10]. Over the last decade there have been a considerable number of prospective studies and meta-analyses of prospective studies that show that a diet rich in red and processed meat is associated with an increased risk of T2DM. Although many mechanisms for this association have been proposed there is no clear consensus on which may be the most likely candidates. This review aims to describe potential mechanisms and their interactions, and the implications for the prevention of T2DM.

2. Meta-analyses of Red and Processed Meat Intake

The association between red and processed meat intake and risk of T2DM has been investigated by four meta-analyses [11–14] (Table 1) with risk estimates of 1.13 to 1.19 per 100 g per day of total red meat and 1.19 to 1.51 per 50 g processed meat per day. The recent EPIC-Interact Study included 12,403 cases of newly diagnosed T2DM among 340,234 participants over 11.7 years of follow-up. In this study the hazard ratio (HR) was 1.08 per 50 g per day increase for total meat (95% confidence interval (CI) 1.05–1.12), 1.08 (95% CI 1.03–1.13) for fresh red meat and 1.12 (95% CI 1.05–1.19) for processed meat, after multivariate analyses [15]. A meta-analysis showed no interactions between dietary patterns and diabetes risk genetic loci on glucose and insulin levels [16], suggesting no individual genetic differences in susceptibility to the effect of diet on the risk of T2DM. However the association between red meat and diabetes may be confounded by other imperfectly measured or unmeasured lifestyle attributes.

3. Potential Mechanistic Pathways

A summary of all the possible mechanistic pathways is shown in Fig. 1.

4. Saturated Fatty Acids

Meat is a source of saturated fatty acids (SFA) and cholesterol that may increase insulin resistance [13]. In order to evaluate the potential impact of SFA intake on the risk of T2DM in this review, we approached evidence coming from i) association studies ii) interventional studies in model (i.e., animal) systems and iii) interventional studies in humans. A correlation between a higher SFA intake and decreased insulin sensitivity has been demonstrated in several cross-sectional studies [17]. Four of eight epidemiological studies showed a relationship between a high SFA intake and risk of T2DM independently of body mass index (BMI) [18–21]. In a 20-year follow-up study, 389 men with newly diagnosed diabetes were reported to have a higher intake of total, saturated, monounsaturated fatty acid (MUFA) and dietary cholesterol 20 years before diagnosis than men with no diabetes [18]. An association between total and saturated fat intake and fasting insulin concentrations was found in a non-diabetic community sample after adjustment for confounding factors such as age, sex, ethnicity, BMI, waist circumference, total energy intake and physical activity [19]. Similar results were found in a study of healthy female twins but there was no adjustment for obesity [22].

Three studies showed no significant association between total and saturated and insulin sensitivity, after adjustment for body fat [23] or BMI [24,25]. Five intervention studies all with a small sample size showed no effect of dietary

Table 1 – Meta-analyses of the association between red and processed meat intake and risk of T2DM.

Reference	Studies	RRs of red meat	RRs of processed meat
Aune et al. [11]	10 of 12 cohorts for red meat 9 of 12 cohorts for processed meat	1.21 for > 600 g/week vs <100 g/week (95% CI 1.07–1.38, I^2 = 58.5 %)	1.41 for > 250 g/week vs <50 g/week (95% CI 1.25–1.60, I^2 = 53.2 %)
Micha et al. [12]	7 cohorts (3 common to Aune's analysis)	1.16 for 100 g/day (95% CI 0.92–1.46, P = 0.25)	1.19 for 50 g/day (95% CI 1.11–1.27, P < 0.001)
Pan et al. [14]	79,570 women in NHS I 87,504 women in NHS II 37,083 men in HPFUS	1.19 for 100 g/day (95% CI 1.04–1.37) 1.34 for 1166.2 g/week vs 220.5 g/week (95% CI 1.26–1.43, P < 0.001)	1.51 for 50 g/day (95% CI 1.25–1.83) 1.32 for 583.1 g/week vs 3.15 g/week (95% CI 1.24–1.40, P < 0.001)
Feskens et al. [13]	14 cohorts for red meat 21 cohorts for processed meat	1.13 per 100 g (95% CI 1.03–1.23, I^2 = 36 %)	1.32 per 50 g (95% CI 1.19–1.48, I^2 = 89 %)

HPFUS, Health Professional Follow-Up Study; NHS I, Nurses' Health Study I; NHS II, Nurses' Health Study II; RR, relative risk; 95% CI, 95% confidence interval; I^2, Indicator of heterogeneity between studies.