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Oxidative Stress Genes, Antioxidants and Coronary Artery Disease in Type 2 Diabetes Mellitus

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Abstract: The worldwide increasing prevalence of obesity and sedentary lifestyle is the main cause of the rising incidence of T2DM. Due to chronic macrovascular and microvascular complications, T2DM represent a huge socioeconomic burden in the world. Oxidative stress is a key pathogenic mechanism implicated in diabetic coronary artery disease (CAD). Polymorphisms of oxidative stress genes are known to influence oxidative stress levels and are therefore thought to impact CAD pathogenesis. Identifying higher risk groups would be rational, since it would allow better sample selection and thus better results in antioxidant trials. In this review, we summarize the evidence of oxidative stress gene polymorphisms related to the pathogenesis of CAD. Moreover, we provide a review of antioxidants tested in subjects with CAD.

Keywords: Antioxidants, coronary artery disease, diabetes mellitus, insulin, obesity, oxidative stress.

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INTRODUCTION

Diabetes mellitus (DM) is a well-recognized heterogeneous group of metabolic disorders caused by both impaired insulin action and diminished insulin production [1]. Defining characteristics are fasting blood glucose of $\geq 7\text{mmol/l}$, random plasma glucose of $\geq 11.1\text{mmol/l}$, HbA1c $\geq 6.5\%$ or OGTT 2-hour glucose in venous plasma $\geq 11.1\text{mmol/l}$ [2]. Based on the etiology it is further divided in Type 1 Diabetes mellitus (T1DM) with predominant autoimmune destruction of pancreatic islet β -cells, Type 2 Diabetes mellitus (T2DM) with β -cell dysfunction in conjunction with impaired insulin sensitivity, and other rarer forms. T2DM makes up about 90% of all cases of diabetes [3].

The increasing prevalence of diabetes in Europe and worldwide has become a matter of major global concern. It is estimated that 9% of the world population has diabetes which was directly responsible for 1.5 million deaths in 2012 [4]. The economic burden associated with diabetes in the USA in 2012 was estimated to be more than \$322 billion, which was 48% more than in 2007 [5]. In Slovenia, with an estimate of 163,780 diabetics [6], the costs account for 5.2% of all health-related costs with an 3-5% increase of this tendency on an annual basis [7].

T2DM is usually an adult-onset form of diabetes with increasing thirst, frequent urination and persistent hunger as typical presenting symptoms. Obesity and sedentary lifestyle are the most important environmental factors which play a major contributing role in genetically susceptible individuals.

In contrast to T1DM, there are numerous studies which confirm a firm genetic background of T2DM as a multifactorial disorder [1].

Normally, glucose homeostasis is maintained in a tight range by a negative feedback loop between β -cells and insulin sensitive tissue. Insulin acts directly on target tissues causing cellular uptake of glucose, amino acids and fatty acids. These tissues, in turn, convey information about their catabolic need back to β -cells through a yet unknown mechanism [8]. A defect along this loop triggers increased insulin secretion and after the maximum output is achieved, plasma glucose rises [3, 8]. Apart from hyperglycemia low-grade inflammation and oxidative stress are implicated in the pathogenesis of T2DM [9-11].

Long-term hyperglycemia-induced tissue damage ranges from micro- to macrovascular, resulting in diabetic retinopathy, nephropathy, neuropathy, cardiac and vascular disease [9, 12]. The main mechanism for consequential tissue damage is the overproduction of reactive oxygen species (ROS) which, in turn, activates the polyol pathway, increases the production of advanced glycation end product (AGEs) precursors, increases the expression of the nuclear factor $\kappa\beta$ (NF $\kappa\beta$) through the activation of protein kinase C (PKC) and increases hexosamine pathway activity [9].

PATHOPHYSIOLOGY OF CORONARY ARTERY DISEASE IN T2DM

According to many studies [13-16], coronary artery disease (CAD) in diabetic population is 2-4 times more frequent than in non-diabetics and is more severe, more rapidly progressive, and commonly found as multi-vessel disease. The presence of other risk factors, such as hyperlipidemia, arterial hypertension, smoking and obesity, further aggravates CAD severity. Cardiac involvement in

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T2DM is mainly a consequence of accelerated atherosclerosis [10, 13] of coronary vessels with a wide range of clinical presentations, including asymptomatic patients, patients with angina, heart failure, myocardial infarction or sudden cardiac death. The presentation can also be nonvascular, seen as myocardial (diabetic cardiomyopathy) or nervous intracardial (conduction aberrancies) dysfunction [13].

NITRIC OXIDE (NO) AND ATHEROSCLEROSIS

Accelerated atherogenesis is the net effect of endothelial dysfunction, prothrombotic state and vascular inflammation [13] with intertwined pathologic pathways resulting in plaque formation. Endothelial dysfunction is in general regarded as a hindered expression or activity of endothelial nitric oxide synthase (eNOS) [17]. eNOS produces nitric oxide (NO) which exerts various antiatherogenic effects on smooth muscle cells and the endothelium itself, and is stimulated by both biochemical (acetylcholine, bradykinin) and mechanical pathways (shear stress sensing) [18, 19]. NO functions as a paracrine hormone eliciting relaxation of vascular smooth muscle cells (vasodilatation), it inhibits smooth muscle cell proliferation, thrombocyte aggregation, endothelial apoptosis and proliferation, transcription of endothelial adhesion molecules (ICAM, VCAM), thus decreasing leukocyte infiltration of vessel walls and the resulting inflammation [13, 19, 20]. In physiological conditions, insulin stimulates NO (antiatherogenic) production through the phosphatidylinositol-3 kinase (PI3-K)/Akt transduction pathway and endothelin (ET)-1 (proatherogenic) production through the ERK/MAPK pathway. The quantities of both NO and ET-1 are well balanced. In T2DM, eNOS and NO functions are impaired, and therefore the balance is shifted towards the proatherogenic pathway [20].

OXIDATIVE STRESS AND ATHEROSCLEROSIS IN SUBJECTS WITH T2DM

It is now widely accepted that, in T2DM, oxidative stress embodies the pivotal role as a joint mechanism by means of which all diabetic complications, including atherosclerosis, occur [21]. In contrast to microvascular complications in T2DM, the key pathogenic mechanism in macrovascular involvement is not only hyperglycemia but, more importantly, increased free fatty acids (FFA) flux [9]. FFA flux is a direct consequence of impaired insulin action on adipocyte cells, where there is no inhibitory effect of insulin on lipolysis. In endothelial cells, FFA enter the tricarboxylic acid cycle where they are oxidized, reducing NAD^+ to NADH. NADH enters oxidative phosphorylation on the electron transport chain which over increases the proton gradient across the mitochondrial membrane. The proton gradient increase causes the uncoupling of electrons and the generation of reactive oxygen species (ROS).

ROS are roughly defined as reactive substances arising from incomplete oxygen reduction [20, 22]. The most commonly produced is the superoxide radical (O_2^-). Other ROS include hydrogen peroxide (H_2O_2), hydroxyl ($\text{OH}^\bullet$), peroxy ($\text{RO}^\bullet$) and hydroperoxy ($\text{HRO}^\bullet$) radicals. In the pathogenesis of CAD in T2DM, reactive nitrogen species (RNS), especially peroxynitrite (ONOO^-), are also involved. In the physiological state, around 5% of electrons end up

producing ROS [18] which, together with RNS, are essential for normal processes, such as the maintenance of the vascular tone, cell adhesion, immune responses and cellular growth [23]. Except for the electron transport chain, ROS and RNS (RS) are produced by enzymatic systems (xanthine oxidase and lipoxygenase), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and uncoupled eNOS [18]. Normally, RS are quickly removed by antioxidants either endogenous (superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), bilirubin, urate) or exogenous (carotenoids, vitamin C, E, flavonoids) [20].

When RS production exceeds the elimination capacity of the antioxidant system, RS trigger reversible or irreversible modifications of lipids, proteins and nucleic acids [13, 20] which, in turn, engage in negative or positive feedback loops. Membrane lipid peroxidation causes the induction of reactive aldehydes that uncouple mitochondria through uncoupling proteins thus decreasing ROS production [22]. Low density lipoprotein (LDL) oxidation implicated in the pathogenesis of atherosclerosis is thought to be catalyzed by RS [24]. Through protein modification, RS cause a change in the activity of signal transduction pathways, increasing transcription factor concentrations, especially $\text{TNF}\alpha$ and $\text{NF-}\kappa\text{B}$. $\text{TNF}\alpha$ and $\text{NF-}\kappa\text{B}$ increase mitochondrial Ca^{2+} concentration promoting ROS production [20, 22]. ROS directly affect insulin signaling PI3-K/Akt pathway on different levels [20], finally decreasing NO creation and mediating insulin resistance through insulin receptor substrate (IRS) degradation [25]. Reduced NO bioavailability by RS is directly achieved by two means: direct reaction of NO with O_2^- radical forming ONOO^- , and by inhibition of eNOS activity by ONOO^- -dependent tetrahydrobiopterin (BH_4) depletion (eNOS cofactor) [13, 18, 26].

CAD in T2DM patients arise from increased flux through the polyol pathway, production of advanced glycation end product (AGE) precursors, protein kinase C (PKC) activation and increased hexosamine pathway activity. A joint mechanism by means of which all the above mentioned pathways ensue is thought to be FFA flux-driven ROS production [21]. ROS, specifically O_2^- , brakes DNA strands, activating the poly(ADP-ribose) polymerase (PARP), a DNA repair enzyme. Activated PARP not only repairs damaged DNA strands, but also forms polymers of poly(ADP-ribose) which modify glyceraldehyde-3 phosphate dehydrogenase (GAPDH), a key downstream glycolytic enzyme, and reduce its activity [9]. Lesser activity of GAPDH tends to increase concentrations of upstream intermediates, namely glyceraldehyde-3 phosphate (GAP), fructose-6 phosphate (F6P) and glucose itself.

Excess GAP is converted to diacylglycerol, an activator of PKC, triggering vascular smooth muscle cell proliferation, angiogenesis, vascular permeability, activation of $\text{NF-}\kappa\text{B}$ (proinflammatory protein), decreasing eNOS and increasing NADPH oxidase expression [9, 13].

F6P is shunted through the hexosamine pathway, forming UDP (uridine diphosphate) N-acetyl glucosamine which glycosylates transcription factors like Sp-1 which, in turn, overexpresses proinflammatory cytokines [9]. It has also been suggested that overactivity of hexosamine pathway inhibits eNOS activity [27].

Intracellular hyperglycemia itself causes increased flux through the polyol pathway where sorbitol (osmotic agent) is formed in a reaction consuming NADPH as a cofactor, thus decreasing its levels. Since NADPH is also utilized as a cofactor in glutathione regeneration, there is a decrease in cellular antioxidant activity and the levels of oxidative stress rise again [28]. High intra- and extracellular glucose glycates proteins in non-enzymatic reactions forming AGE precursors. In respect to CAD, ONOO⁻ cross-links AGE proteins, which are then deposited in the arterial wall, making it less elastic; furthermore, AGE bind to receptors called RAGE which activate PKC, increasing inflammation [29].

With the correction of hyperglycemia, the dangers of CAD development remain high for a prolonged period, implicating the so-called metabolic memory phenomenon. Metabolic memory is a result of DNA methylation, post-translational histone modifications, and microRNA- plus long-non-coding-RNA-based mechanisms, all consequences of the altered activity of signal transduction pathways mentioned above [30].

ANTIOXIDANTS

ROS act through various mechanisms, instigating perivascular inflammation, endothelial dysfunction and prothrombotic state key pathogenic processes of CAD in T2DM. Antioxidants deplete ROS, thus preventing their function. Endogenous antioxidants, such as bilirubin, uric acid, superoxide dismutases, catalase, and glutathione peroxidase, act in hand with exogenous substances [20] (vitamin C, vitamin E, vitamin A, β -carotene, flavonoids, selenium, zinc, N-acetylcysteine (NAC), coenzyme Q10, L-carnitine, allopurinol, edaravone, nicorandil and more); therefore, various studies have been and are being carried out with efforts to balance the oxidative stress scale towards the antioxidative state, most of them by exogenous antioxidant supplementation. Numerous in-vitro and animal studies showed an effective inhibition of the above mentioned ROS pathologic pathways, decreasing oxidative stress [31, 32] and insulin resistance, but were mainly focused on one or a couple of arms of oxidative stress pathways.

OBSERVATIONAL STUDIES AND ANTIOXIDANTS

Observational studies that followed, chiefly supported the alleged positive effects of antioxidants. One of the first studies was carried out in the US between 1964 and 1978, and revealed a significant reduction in cardiovascular (CV) mortality with greater vegetable and fruit (rich in vitamin C) consumption [33]. The study [34] from 1989 used pooled data from 8 European populations and discovered that plasma levels of vitamin E and A were each inversely related to ischemic heart disease mortality. Another two major studies reported a lower risk of CAD in more than 87,000 US female nurses [35] and almost 40,000 male health professionals [36] with at least 100 IE of daily vitamin E supplementation and also with β -carotene intake. Beneficial effects on the lowering of CV mortality with an intake of vitamin E from food was also suggested for postmenopausal women, whereas by contrast, the intake of vitamins A and C was not associated with lower risks of dying from coronary disease [37]. Mixed results were similarly shown in a

smaller, Finnish 14-year follow-up study on >5000 men and women [38]. Coronary mortality with dietary vitamin E intake was inversely related to vitamin E consumption, whereas dietary intake of vitamin C and β -carotene showed an inverse relation only in women. Contradictorily, the Scottish Heart Health Study [39] involving around 11,500 women and men who were observed for 9 years, displayed a weak but significant reduction in CAD with vitamin C and β -carotene in men, but not in women; furthermore, there were no reductions in risk of CAD with increased vitamin E ingestion in either sex. A large study regarding vitamin C was conducted by Enstrom *et al.* on a sample of >11,000 individuals and reported a significantly lower general mortality, even lower compared to CV causes [40]. Other observational vitamin C studies exhibited inconsistent results, either with suggested beneficial effects on CAD risk, MI risk or CV mortality [41-43], or showed no favorable effect [35, 36, 44].

VITAMIN C

Vitamin C, or ascorbic acid, is a water soluble antioxidant found primarily in fruit, vegetables, fortified drinks and cereals. The human body lacks synthetic activity and vitamin C is therefore regarded as an essential nutrient. It functions as an important cofactor in the synthesis of collagen, carnitine and catecholamines [45]; intracellularly, it acts as a potent antioxidant by regulating intracellular glutathione recovery, scavenging free radicals [46], and is necessary as a co-antioxidant for vitamin E function [47]. There is evidence that vitamin C reverses defects caused by smoking, including oxidative stress [48, 49] and increased monocyte adhesion to endothelium [50]. Not only by scavenging free radicals, vitamin C moreover downregulates NADPH oxidase, suppresses NF- κ B activation and prevents oxidation of tetrahydrobiopterin – a cofactor of NO synthase [47].

Even with maximum orally tolerated supplementation doses, the plasma concentration of vitamin C is always <250 μ mol/L and reaches 25-30 mmol/L with safe intravenous injections [47]. For vitamin C to be effective in O₂⁻ scavenging 10 mmol/L concentrations are necessary, otherwise O₂⁻ reacts with NO since the rate of reaction with NO is 10⁵ fold greater [51]. For that reason, intravenous supplementation is thought to be preferred. On the other hand, intracellular levels of vitamin C do not necessarily reflect intracellular concentrations, since there are at least two types of active membrane transporters, one of them specifically involved in vitamin C uptake [47, 52].

There are some randomized controlled trials regarding the beneficial effects of vitamin C in CAD and MI, but most of them are small, one-centered. Only one large study was conducted concerning the primary prevention of CAD. Physicians Health Study II followed more than 14,500 physicians without CAD for 8 years and found no effect on major adverse cardiac events or all-cause mortality with treatment of 500 mg of vitamin C daily [53].

On the other hand, a few large studies were done regarding secondary prevention of CAD. The Heart Protection Study randomized >20,000 patients with CAD, T2DM or vascular disease to 5 years of either mixed supplementation of vitamin C, E and β -carotene, or a

placebo with no effect on MI or CV mortality [54]. The Women's Antioxidant Cardiovascular Study assessed vitamin C, E or β -carotene intake in almost 8,200 women and found no effects after a mean of 9.4 years [55]. Contradictorily, The Women's Angiographic Vitamin and Estrogen study observed a higher mortality in the vitamin supplement group [56] - the study randomized 423 postmenopausal women with CAD to therapy with vitamin C and E, or placebo.

Some smaller studies investigated antioxidative protection with vitamin supplementation in acute MI. A double-blind placebo controlled multicenter trial tested clinical outcomes of 800 patients with acute MI after vitamin C infusion followed by vitamin C and E oral supplementation. In-hospital cardiac mortality, non-fatal new myocardial infarction, shock, and nonviable rhythms occurred less frequently with antioxidant supplementation [57]; moreover, 30-day mortality was significantly reduced in treated DM patients, but not in non-diabetics [58]. Three smaller studies analyzed the influence of either a combination of vitamin C and E [59, 60] or vitamins A, C, E and β -carotene [61], or placebo, and reported a reduction in mean infarct size, less ECG alterations and a decrease in QTd in treated patients.

VITAMIN E

Vitamin E is a lipid soluble vitamin, mainly in the form of α -tocopherol. It acts as the major peroxyl radical scavenger in lipid phases, such as membranes and LDL, and thus inhibits lipid peroxidation through its own conversion into the α -tocopheroxyl radical, which can further react with lipids and conversely promotes the formation of lipid radicals [47]. Consequently for its antioxidant effect it necessities coantioxidant such as vitamin C, or other reducing agents. Additionally, its antioxidant effect is exerted not only by ROS scavenging but also through stimulation of glutathione peroxidase activity and downregulation of NADPH oxidase [47]. It has been reported that vitamin E also reverses endothelial dysfunction in patients with variant angina [62], increases arterial compliance [63], inhibits platelet aggregation [64], decreases monocyte-endothelial cell adhesion [65], and has inhibitory effects on smooth muscle proliferation [66], all theoretically resulting in lower CAD risk.

Randomized controlled trials found no benefit of supplementation with vitamin E for the primary prevention of CAD. The Finnish Alpha Tocopherol Beta-Carotene Cancer Prevention Study followed more than 27,000 male smokers for six years and reported no significant effect on the incidence of MI or cardiac death with vitamin E supplementation [67]. The Primary Prevention Project monitored almost 4,500 people with risk factors for CAD for 3.6 years, ones taking daily vitamin E supplementation had the same MACE as the placebo group [68]. The Women's Health study investigated the benefits of vitamin E intake for 10 years on 40,000 apparently healthy women. Supplementation had no significant effect on all-cause mortality and on the first major cardiovascular event as the primary endpoint [69]. The above mentioned Physicians Health Study II revealed no effect of vitamin E treatment on neither MACE or all-cause mortality [53].

Large clinical trials studied the correlation of vitamin E treatment regarding secondary prevention of CAD. A meta-analysis [70] of 7 of those trials pooled data from 81,788 patients and observed no significant change in CV death. Similar results were reported from each of those trials separately.

β -CAROTENE

β -carotene is a lipid soluble pro-vitamin A with similar antioxidant action as vitamin E because of its lipophilic structure. It scavenges the peroxyl radical with the help of coantioxidants needed for its regeneration, whereas in excessive doses, it exhibits prooxidant behavior [71]. As with vitamin C and E, trials investigating the effects on primary and secondary prevention have found no benefit. A meta-analysis of 8 randomized controlled trials involving 138,113 patients actually reported a small, but significant increase in CV mortality with β -carotene intake [70].

OTHER ANTIOXIDANTS

Other antioxidants investigated in clinical studies included edaravone, allopurinol, nicorandil, N-acetylcysteine, deferoxamine, atorvastatin. Edaravone and N-acetylcysteine act as free radical scavengers; allopurinol inhibits the ROS generating xanthine oxidase; nicorandil opens the mitochondrial K_{ATP} channels, causing mitochondrial depolarization, which decreases ROS formation; deferoxamine binds ferric iron, decreasing its availability for ROS generation, and atorvastatin [72] decreases the expression of essential NADPH oxidase subunits [73]. A significant reduction of oxidative stress parameters after acute MI was found in trials with edaravone [74], allopurinol [75], nicorandil [76], N-acetylcysteine [77], and deferoxamine [78]. The cardiac function after acute MI was improved with edaravone [74], allopurinol [75], nicorandil [76] and N-acetylcysteine [77], whereas the cumulative cardiac event-free rate was significantly higher with edaravone [74], while there were significant decrease of intrahospital cardiac events and rehospitalization rate with nicorandil [76].

THE EFFECTIVENESS OF ANTIOXIDANTS

Based on the results of randomized controlled trials, the effect of antioxidants has not been found to have a major impact on the prognosis of patients with CAD. A few issues, however, need to be taken into account. Firstly, most trials used safe, widely available antioxidants in their cheapest synthetic form that is not necessarily the same as in dietary compounds; natural vitamin E, for instance, is composed of 8 different isoforms [79] which may affect its effect. Secondly, supplemental antioxidants also tend to distribute to different phases depending on their hydrophily or lipophily. Vitamin E is mostly active in lipid phases, whereas vitamin C, for instance, in hydro phases, so consequently there is probably no single antioxidant which would act sufficiently in preventing atherosclerosis in both phases. If oxidative stress is a unifying mechanism in its pathogenesis, an effective antioxidant would need to prevent oxidative reactions in lipid (*i.e.* LDL particles) and in non-lipid phases (*i.e.* glutathione recovery); therefore, newer antioxidants are needed. Another potential explanation may

be that we do not yet fully understand ROS function and with the usage of one or a couple of specific antioxidants there are still other intact pathogenic mechanisms than those affected. Furthermore, most ROS are generated intracellularly and react promptly, thus antioxidants must be present at the location of radical formation and readily available in sufficient concentrations. Vitamin C is transported intracellularly against the concentration gradient by specific and nonspecific transporters, but for a satisfactory concentration to be achieved it has to be given intravenously in high doses [51]. To conduct large-scale prospective trials it is not feasible to administer daily intravenous infusions or boluses for that matter, since oral administration does not allow for high doses needed to reach desirable concentrations without reaching the upper toxic dose or the emergence of non-tolerable side effects. β -carotene and vitamin E studies [70, 80] suggested that supplementation in high doses increase all-cause mortality. One of the potential reasons is that antioxidants in high concentrations conversely tend to transform to the prooxidative form which promotes oxidative stress if there is no coantioxidant present to recycle it, hence the optimal dose remains controversial. Last but not the least, atherosclerosis is a continuous process with the onset probably sometimes around birth. Clinical studies mostly investigate antioxidant effect later in life, after several decades of oxidative stress already took their toll on the vascular system. Therefore, it is irrational to presume that a couple of years of antioxidant treatment would reverse it sufficiently. Numerous trials reported a significant reduction of oxidative stress parameters, but not many observed significant effects on clinical outcomes, such as MACE, CV or all-cause mortality, potential reasons may be the length of treatment or the length of the follow-up. But the duration of treatment/follow-up is not the only thing that needs to be taken into account, as correct timing—start of supplementation—is another important aspect that we have yet to determine. It would also be rational to identify higher risk groups, since primary or secondary interventions on those risk groups would be more cost-effective and would likewise yield better results.

To summarize, it can be safely concluded that antioxidants may still be effective, but large, well designed randomized controlled trials with a long-lasting follow-up using appropriate antioxidants in appropriate doses and on high risk population should be carried out. A good example of a well-designed prospective study is the randomized prospective interventional study “PREvencio’n con Dieta MEDiterranea” [81]. In this study, positive effects of nuts on DM prevention and CAD prevention were reported. Nuts are nutrient-dense foods with complex matrices rich in unsaturated fatty acids and other bioactive compounds, such as L-arginine, fibre, healthful minerals, vitamin E, phytosterols, polyphenols, and antioxidants. By virtue of their unique composition, nuts are likely to beneficially affect cardiovascular health [81]. There is increasing evidence that nut consumption has a beneficial effect on oxidative stress, inflammation and vascular reactivity. Moreover, blood pressure, visceral adiposity and the metabolic syndrome also appear to be positively influenced by nut consumption [81].

METHODOLOGY AND SEARCH STRATEGY FOR GENES OF OXIDATIVE STRESS

The search was performed in two electronic databases: PubMed and ScienceDirect. Article selection was performed in July 2015 and no date limit was applied to the selected articles. We limited our search to articles in English and to those on humans. Search terms were combined using Boolean operators and some of the terms were defined by the MeSH thesaurus. The search phrase included terms: "Diabetes mellitus", "diabetic", "Diabetes Mellitus, Type 2"[Mesh], "Polymorphism", "Polymorphism, Genetic"[Mesh], "Oxidative Stress", "Oxidative Stress"[Mesh], "Myocardial Infarction", "Coronary Artery Disease", "Coronary Heart Disease", "Myocardial Infarction"[Mesh], "Coronary Disease"[Mesh]. Initially, articles were screened manually according to titles, obvious non-significant articles and duplicates were omitted. Then, articles were screened by abstracts and data was collected through their full texts.

The studies included were cohort, cross-sectional or case control studies of T2DM population, and looked at the prevalence or incidence of CAD, myocardial infarction (MI), major adverse cardiac events (MACE), or death from CV causes depending on the distribution of gene polymorphisms implicated in oxidative stress. The exclusion criteria were non-human studies, editorials and systematic reviews. No ethnic origin distinctions were applied. Out of 25 studies matching the above criteria, the following data were extracted and pooled: year of publication, population type, sample size, observed polymorphism, risk genotype/allele, odds ratio, p-value and disease type. The main conclusions were summarized. The studies were published between 2000 and 2015, and included a total of 23,382 participants.

OXIDATIVE STRESS CANDIDATE GENES FOR CAD IN T2DM

Several oxidative stress candidate genes have so far been implicated in the pathogenesis of CAD in subjects with type 2 diabetes. Oxidative stress levels are principally dependent on the body's ability to produce ROS and its capacity to eliminate them. Therefore, candidate genes in this review will be split based on whether they influence ROS production or the antioxidant system (Table 1).

GENE POLYMORPHISMS OF THE ROS PRODUCTION SYSTEM

With increased ROS production, oxidative stress increases as well. So far, polymorphisms of three enzymes of this system have been reported to be involved in the pathogenesis of CAD in T2DM subjects [82-85].

NADPH OXIDASE P22Phox (CYBA) POLYMORPHISMS

NADPH oxidase is one of the chief sources of O_2^- in vascular cells, monocytes and neutrophils [83, 86]. The P22phox subunit is its main catalytic subunit [86] with two polymorphisms implicated in CAD pathogenesis, namely C242T (rs4673) and A640G. The published studies of both polymorphisms in patients with CAD provide contradictory results [87-90]. Only rs4673 polymorphism association

Table 1. Oxidative stress systems and genes implicated in THE pathogenesis of CAD in T2DM.

System	Gene		Gene Symbol
ROS production system	NADPH ¹ oxidase p22phox		CYBA
	Myeloperoxidase		MPO
	Poly (ADP-ribose) polymerase-1		PARP-1
Antioxidant system	Endothelial nitric oxide synthase		NOS3
	Glutathione system	Glutamate-cysteine ligase modifier subunit	GCLM
		Glutathione peroxidase 1	GPx1
		Glutathione S-transferase	GSTM1, GSTT1, GSTP1
	Heme system	Haptoglobine	Hp
		Heme oxygenase 1	HMOX1
	Methylenetetrahydrofolate Reductase (NAD(P)H ¹)		MTHFR
	NAD(P)H ¹ : quinone oxidoreductase		NQO1
	Paraoxonase 1		PON1
	Superoxide scavenger system	Superoxide dismutase 1	SOD1
		Superoxide dismutase 2	SOD2
		Catalase	CAT
		Thioredoxin reductase 2	TXNRD2
	Uncoupling protein 2		UCP2

¹nicotinamide adenine dinucleotide phosphate.

studies with CAD in T2DM (Table 2) were done in two different Asian subsets of patients, and 3 studies [83-85] were conducted on a similar pool of patients by the same author. The results were again contradictory, however, the largest study [85] demonstrated no association.

MYELOPEROXIDASE (MPO) POLYMORPHISMS

MPO is a member of the heme peroxidase superfamily which produces strong oxidant hypochlorous acid HOCl and is positioned in lysosomes of monocytes and neutrophil cells [83, 91]. A large study [92] conducted on a mixed population examined rs2107545, Val717Ile and rs2071409 polymorphism association with CAD, confirming rs2107545 and rs2071409 association with with CAD prevalence. No analyses of such polymorphisms were done with regard to CAD in T2DM. The promoter polymorphism -463 G/A (rs2333227) GG genotype was associated with higher MPO activity and was suggested to be a risk factor for T2DM [91]. A few studies have so far tested a possible association of the MPO rs2333227 polymorphism with CAD in T2DM (Table 2) [83-85]. The studies were done on a similar large cohort by the same author who found no association with CAD.

POLY (ADP-RIBOSE) POLYMERASE-1 (PARP-1) POLYMORPHISMS

PARP-1 is a DNA repair enzyme and is not directly implicated in ROS production. Overexpression of PARP-1

triggers more severe ROS-induced damage on the account of over activation of glycolysis upstream pathways (polyol pathway, production of AGE precursors, PKC, hexosamine pathway) [9, 93] whereas the downregulation of PARP-1 limits oxidative stress injury [94]. A lower enzymatic activity was shown in the PARP-1 Val762Ala (rs1136410) polymorphism with the Ala allele [95]. Among several reported studies analyzing the association of PARP-1 polymorphisms with CAD in T2DM, an association of PARP-1 polymorphisms with the prevalence with CAD in T2DM has so far been reported in only one study [82], whereas there was no association with MI (Table 2). Further studies are warranted.

GENE POLYMORPHISMS OF ANTIOXIDANT SYSTEM

Extra- and intracellular levels of ROS are dependent on the activity of antioxidant system. Many analyses of antioxidant system polymorphisms have been conducted so far, mainly focused on the glutathione system, the superoxide dismutase system and paraoxonase-1 genes.

POLYMORPHISMS OF GLUTATHIONE SYSTEM GENES

Glutathione is a ubiquitous intracellular antioxidant present in variable but abundant concentrations [96]. In addition to reducing ROS, it functions as an important cofactor for many enzymes, such as glutathione peroxidase 1 (GPx1) and glutathione S-transferase (GST) [96].

Table 2. Reported studies of ROS production system genes and CAD in subjects with T2DM.

Population	Year	Subjects with T2DM (n)	Polymorphism	Risk Genotype/allele	OR (P value)	Studied Association with	Refs.
Asian	2012	283 (CAD, MI vs. no CAD)	CYBA ¹ C242T (rs4673)	T	0.56 (0.002) CAD, 0.8 (0.39) MI	CAD, MI	[82]
Japanese	2014	1977 (CAD, MI vs. no CAD)	CYBA C242T	No association	1.27 (0.401) CAD, 1.06 (0.753) MI	CAD, MI	[83]
Japanese	2009	2561 (MI vs. no MI)	CYBA C242T	No association	N/A ²	MI	[84]
Japanese	2010	3819 (MI vs. no MI)	CYBA C242T	No association	1.22 (>0.05)	MI	[85]
Japanese	2014	1977 (CAD, MI vs. no CAD)	MPO ³ -463G/A (rs2333227)	No association	1.15 (0.605) CAD, 0.93 (0.644) MI	CAD, MI	[83]
Japanese	2009	2561 (MI vs. no MI)	MPO -463G/A	No association	N/A	MI	[84]
Japanese	2010	3819 (MI vs. no MI)	MPO -463G/A	No association	1.18 (>0.05)	MI	[85]
Asian	2012	283 (CAD, MI vs. no CAD)	PARP-1 ⁴ Val762Ala (rs1136410)	Ala	0.6 (0.02) CAD, 0.74 (0.35) MI	CAD, MI	[82]

¹NADPH oxidase p22phox; ²not available; ³Myeloperoxidase; ⁴Poly (ADP-ribose) polymerase-1.

Table 3. Reported studies of glutathione system genes and CAD in subjects with T2DM.

Population	Year	Subjects with T2DM (n)	Polymorphism	Risk Genotype/allele	OR (P value)	Studied Association with	Refs.
Japanese	2014	1977 (CAD, MI vs. no CAD)	GCLM ¹ -588C/T	No association	1.36 (0.086) CAD, 1.09 (0.506) MI	CAD, MI	[83]
Japanese	2009	2561 (MI vs. no MI)	GCLM -588C/T	No association	N/A ²	MI	[84]
Japanese	2010	3819 (MI vs. no MI)	GCLM -588C/T	No association	1.14 (>0.05)	MI	[85]
South Indian	2012	539 (CAD vs. no CAD)	GPx1 ³ C198T	No association	1.341 (0.340)	CAD	[114]
Japanese	2004	184 (CAD vs. no CAD)	GPx1 Pro198Leu (rs1050450); GPx1 -602A/G	Pro/Leu; no association	4.07 (0.0068); N/A (0.083)	CAD	[97]
Caucasian - Italian	2009	231 (CAD vs. no CAD)	polymorphic deletions of GSTM1 ⁴ GSTT1 ⁴	GSTT1-0	N/A (0.003)	CAD	[115]
Caucasian - Slovenian	2012	463 (MI vs. No CAD)	polymorphic deletions of GSTM1 GSTT1; GSTP1 ⁴ Ile105Val	GSTM1-0/GSTT1-0; no association	3.22 (0.03); 0.78 (0.71)	MI	[98]
South Indian	2011	512 (CAD vs. no CAD)	polymorphic deletions of GSTM1 GSTT1; GSTP1 Ile105Val	GSTT1-0; no association	1.981 (0.014); 0.997 (0.992)	CAD	[99]

¹Glutamate-cysteine ligase modifier subunit; ²not available; ³Glutathione peroxidase 1; ⁴Glutathione S-transferase (different classes).

Glutathione Peroxidase 1

GPx1 is a soluble selenoprotein which reduces H₂O₂ to water. Its few polymorphisms implicated in enzymatic and transcriptional activity [97] have been studied with regard to CAD, with a positive association reported in a large study for the leucine allele at codon 198 (rs1050450) [92]. The Rs1050450 polymorphism with the Pro/Leu genotype was strongly associated with CAD prevalence in T2DM subjects

[97] (Table 3). Other tested polymorphism (-602A/G) revealed no association with CAD or other types of macrovascular disease [97] in T2DM.

Glutathione S-transferases

GST are a highly polymorphic family of detoxifying enzymes that catalyze the conjugation of glutathione to a wide range of substances, thus reducing the oxidative stress

level [98, 99]. Deletions of GSTM1 and GSTT1 along with the GSTP1 Ile105Val polymorphism are the most studied polymorphisms of the GST group, resulting in a complete lack of enzymes in GSTM1-0 and GSTT1-0 and a diminished activity in GSTP1 105Val [100]. A firm association has been established between these polymorphisms and risk for T2DM development [99, 101-106], however, contradictory results have been produced regarding diabetic complications [107-110] and regarding ischemic vascular disease in non-T2DM-only population [111, 112]. Reported studies on CAD in T2DM subjects (Table 3) mostly agree on the deleterious effects of GSTM1-0 and GSTT1-0 polymorphisms and on the absence of association with GSTP1 105Val.

Glutamate-cysteine Ligase Modifier Subunit

Glutamate-cysteine ligase is a rate-limiting enzyme in glutathione synthesis. The modifier subunit (GCLM) increases the activity of the catalytic subunit, whereby the -588T allele of the -588C/T polymorphism decreases ROS-dependent upregulation of GCLM, thus increasing oxidative stress [83]. The association of -588T with increased intima-media thickness and MI has been reported [84, 113]. Up to now, studies have revealed no association of the mentioned polymorphism with CAD prevalence in T2DM subjects [83-85] (Table 3).

POLYMORPHISMS OF HEME SYSTEM GENES

Heme Oxygenase 1 (HMOX1)

HMOX1 is a rate-limiting enzyme in the heme catabolism that minimizes oxidative damage done by the heme molecule [116]. The HMOX1 isoform is highly inducible as a result of ROS. Its activity plays an important role in oxidative stress level in heart vasculature [117] and the promoter microsatellite (GT)_n repeat polymorphism was shown to influence it [116]. Several studies have been investigating the association between either (GT)_n repeats or various polymorphisms (rs9607267, rs2071749 and rs2071746) and CAD or MI. The analyses yielded no association or protective haplotype, with a low number of (GT)_n repeats [92, 116-120]. One study, however reported an

association of the promoter repeat polymorphism with CAD in T2DM subjects, deducing a positive association with more than 32 (GT) repeats [116] (Table 4).

Haptoglobine (Hp)

Hp is a serum α_2 -glycoprotein, an acute phase reactant synthesized mainly in the liver. Free heme is bound by the Hp stabilizing iron within, and consequently prevents oxidative stress damage [121]. In humans, there are two alleles of Hp, Hp1 and Hp2 [122]. Hp1 exerts greater antioxidant activity than Hp2, with various studies confirming the association with higher oxidative stress and diabetic complications [123]. All reported studies similarly confirmed the association with prevalence of CAD, MI or MACE in T2DM [121, 122, 124, 125] (Table 4).

POLYMORPHISMS OF SUPEROXIDE SCAVENGER SYSTEM GENES

Superoxide dismutases are a class of enzymes that catalyze the dismutation of O₂⁻ to H₂O₂ [92]. H₂O₂ is then further reduced by cytoplasmic catalase (CAT) to water [126], or by the mitochondrial thioredoxin system. Superoxide dismutases consist of cytoplasmic SOD1, mitochondrial SOD2 (also called manganese superoxide dismutase) and extracellular SOD3 [127].

Superoxide Dismutase 1 (SOD1)

SOD1 detoxifies most of O₂⁻ in human cells and expresses high activity in the kidney and vascular wall [127]; therefore, it is safe to assume it is implicated in the pathogenesis of T2DM and CAD. A study [92] investigating the rs1041740 polymorphism found no association with CAD, while a study [128] of the A35C polymorphism found an association of the C allele with macrovascular disease in T1DM or T2DM subjects. Only one reported study [127] looking into SOD1 polymorphisms in connection with CAD or MI in T2DM observed no association, whereas the incidence of death from CV causes was higher in rs9974610, rs2173962, rs10432782 and rs1041740 polymorphisms (Table 5).

Table 4. Reported studies of heme system genes and CAD in subjects with T2DM.

Population	Year	Subjects with T2DM (n)	Polymorphism	Risk Genotype/allele	OR (P value)	Studied Association with	Refs.
Chinese	2002	214 (CAD vs. no CAD)	HMOX1 ¹ microsatellite (GT) repeats	L ²	4.7 (0.001)	CAD	[116]
American Indians	2002	412 (CAD, MI vs. no CAD)	Hp1 ³ Hp2 ³	Hp2-2	4.96 (0.002)	CAD, MI	[124]
Egyptian	2014	160 (CAD vs. no CAD)	Hp1 Hp2	Hp2-2	N/A ⁴ (<0.01)	CAD	[121]
Tunisian	2014	209 (CAD vs. no CAD)	Hp1 Hp2	Hp2-2	1.9 (0.018)	CAD	[122]
Israel	2003	224 (MACE ⁵ after MI vs. no. MACE)	Hp1 Hp2	Hp2	4.9 (0.007)	MACE after MI	[125]

¹Heme oxygenase 1; ²L allele represents >32 GT repeats; ³Haptoglobine; ⁴not available; ⁵Major adverse cardiac events (composite endpoint combining MI, all-cause mortality, coronary revascularization).

Table 5. Reported studies of superoxide scavenger system genes and CAD in subjects with T2DM.

Population	Year	Subjects with T2DM (n)	Polymorphism	Risk Genotype/allele	OR (P value)	Studied Association with	Refs.
Caucasian	2012	3744 (MI, stroke, CV death ¹ vs. no MI, no stroke, no CV death)	SOD1 ² rs9974610; SOD1 rs2173962; SOD1 rs10432782; SOD1 rs2070424; SOD1 rs1041740/rs17880196; SOD1 rs17880135; SOD1 rs202449	rs9974610; rs2173962; rs10432782; rs1041740	0.64 (0.005) CV death; 1.80 (0.03) CV death; 1.71 (0.007) CV death; 1.78 (0.02) CV death; No association with MI (all polymorphisms)	MI, CV death	[127]
Caucasian - Slovenian	2012	463 (MI vs. No CAD)	SOD2 ³ Val16Ala (rs4880)	No association	1.62 (0.56)	MI	[98]
Japanese	2014	1977 (CAD, MI vs. no CAD)	SOD2 Val16Ala	No association	1.01 (0.981) CAD, 1.11 (0.534) MI	CAD, MI	[83]
Caucasian	2010	776 (CAD, MI vs. no CAD)	SOD2 Val16Ala	TT in females	2.22 (0.01)	CAD, MI	[126]
Japanese	2010	3819 (MI vs. no MI)	SOD2 Val16Ala	No association	1.10 (>0.05)	MI	[85]
Caucasian - Brazilians	2006	520 (CAD vs. no CAD)	CAT ⁴ -262C/T	No association	N/A ⁵	CAD	[134]
Caucasian - Slovenian	2015	972 (MI vs. no CAD)	TXNRD2 ⁶ rs1548357; TXNRD2 rs4485648; TXNRD2 rs5748469	rs1548357 (CC+CT); no association; no association	0.589 (0.027); 0.939 (0.804); 0.887 (0.611)	MI	[135]

¹Deaths from cardiovascular causes; ²Superoxide dismutase 1; ³Manganese superoxide dismutase; ⁴Catalase; ⁵not available; ⁶Thioredoxin reductase 2.

Superoxide Dismutase 2 (SOD2)

SOD2 is in cytosol and is posttranscriptionally transported to the mitochondria by a specific mitochondrial targeting sequence [98]. The Val16Ala polymorphism (rs4880) located in the mitochondrial targeting sequence hampers translocation and results in an up to 40% lower activity [129]. Some studies demonstrated a positive association of the 16Val polymorphism with T2DM or T2DM complications [109, 128, 130, 131], while one study [132] yielded contradictory results, associating 16Ala with diabetic retinopathy, whereas another study found no association with diabetic nephropathy [133]. Most studies [83, 85, 98] investigating the association of Val16Ala with CAD or MI in T2DM patients reported no association, whereas in one of them [126], an association between the TT genotype and CAD in females was demonstrated (Table 5).

Catalase (CAT)

Two promoter polymorphisms of the CAT gene have been investigated (-21A/T and -262C/T) in regard to the association with diabetic complications [128, 134] and only -262C/T [134] in regard to CAD in T2DM. None of the conducted studies found any association (Table 5).

Thioredoxin Reductase 2 (TXNRD2)

H₂O₂ in the mitochondria is reduced by thioredoxin which is then further reduced by TXNRD2 defending cells from H₂O₂-induced oxidative stress [135]. So far, polymorphisms in the TXNRD2 gene have been associated with various

cancers [135], one reported study [135] testing rs1548357, rs4485648 and rs5748469 polymorphisms in relationship to MI in T2DM subjects proposed a positive association of CC and CT genotypes (rs1548357) (Table 5). More studies are needed to determine the role of TXNRD2 in the pathogenesis of CAD in T2DM.

POLYMORPHISMS OF OTHER ANTIOXIDANT SYSTEM GENES

Methylenetetrahydrofolate Reductase (MTHFR)

Methylenetetrahydrofolate reductase (MTHFR) is indirectly involved in antioxidation. It is an important enzyme involved in the metabolism of folate and methionine. The lack of MTHFR activity leads to hyperhomocysteinemia through inhibition of methionine formation [136]. Hyperhomocysteinemia is reported to induce the generation of ROS, upregulate NADPH oxidase and downregulate thioredoxin in endothelial cells [137]. The T allele in the C677T (rs1801133) polymorphism yields MTHFR thermolabile and decreases its activity [136]. In one reported study [136], the T allele was positively associated with CAD in T2DM (Table 6).

Endothelial Nitric Oxide Synthase (NOS3)

NOS3, or eNOS, catalyzes the synthesis of NO from L-arginine and is constitutively expressed in the vascular endothelium [85, 138]. Its effects on oxidative stress are summarized in the Pathophysiology section of this review. As most studied, the G894T polymorphism (rs1799983)

Table 6. Reported studies of other antioxidant system genes and CAD in subjects with T2DM.

Population	Year	Subjects with T2DM (n)	Polymorphism	Risk Genotype/allele	OR (P value)	Studied Association with	Refs.
Chinese	2005	228 (CAD, MI vs. no CAD)	MTHFR ¹ C677T (rs1801133)	T	2.54 (0.001)	CAD	[136]
South Indian	2013	283 (CAD, MI vs. no CAD)	NOS3 ² -786T/C (rs2070744); NOS3 G894T (rs1799983); NOS3 4a/b	T; no association; no association	1.84 (0.004) CAD, 1.53 (0.11) MI; 1.64 (0.08) CAD; 1.22 (0.6) MI; 0.83 (0.48) CAD; 0.98 (0.96) MI	CAD, MI	[138]
Japanese	2014	1977 (CAD, MI vs. no CAD)	NOS3 G894T	No association	1.05 (0.861) CAD, 1.04 (0.840) MI	CAD, MI	[83]
Japanese	2010	3819 (MI vs. no MI)	NOS3 G894T	No association	1.30 (>0.05)	MI	[85]
South Indian	2012	539 (CAD vs. no CAD)	NQO1 ³ C609T (rs1800566)	TT	1.637 (0.049)	CAD	[114]
Japanese	2009	2561 (MI vs. no MI)	PON1 ⁴ Gln192Arg (rs662)	No association	N/A ⁵	MI	[84]
Egyptian	2012	93 (CAD vs. no CAD)	PON1 Gln192Arg	Arg	4.62 (<0.001)	CAD	[143]
Mixed	2012	589 (CAD vs. no CAD)	PON1 Gln192Arg; PON1 L55M (rs854560)	No association; no association	N/A; N/A	CAD	[144]
Caucasian - Swiss	2000	434 (CAD vs. no CAD)	PON1 Gln192Arg; PON1 -107C/T (rs705379)	(GlnArg+ArgArg); TT	1.92 (0.03); 2.12 (0.01)	CAD	[145]
North-West Indian Punjabis	2012	550 (CAD vs. no CAD)	PON1 Gln192Arg; PON1 L55M; PON1 -909G/C; PON1 -162A/G; PON1 -108C/T (rs705379)	No association; no association; no association; no association; T	1.2 (0.09); 0.7 (0.06); 1.1 (0.32); 1.2 (0.05); 1.7 (0.0001)	CAD	[146]
Caucasian	2008	3122 (CAD, MI vs. no CAD)	UCP2 ⁶ -866G>A	A in males	0.88 (0.006)	CAD, MI	[147]

¹Methylenetetrahydrofolate Reductase (NAD(P)H); ²Endothelial nitric oxide synthase; ³NAD(P)H: quinone oxidoreductase; ⁴Paraoxonase 1; ⁵not available; ⁶Uncoupling protein 2.

predisposes NOS3 to the proteolytic cleavage, thereby reducing its activity [138]. In the context of a higher prevalence of CAD, a positive association with the TT+GT genotype of the G298T polymorphism was reported in one study [139], whereas the analysis of G894T, rs3918188 and rs1808593 polymorphisms reported no association [92, 140]. A higher incidence of diabetic nephropathy was described with the G894T polymorphism [109, 141], diabetic retinopathy seems not to be connected with NOS3 polymorphisms [11, 131]. Analyses of CAD or MI in the T2DM population (Table 6) reported no association with classically investigated NOS3 polymorphisms [83, 85, 138], but implicated an association with the T allele in the promoter -786T/C polymorphism, which decreases NOS3 expression by 50% [138].

NAD(P)H: Quinone Oxidoreductase (NQO1)

NQO1 detoxifies quinines and their derivatives, it serves as an antioxidant by maintaining ubiquinone and vitamin E in their antioxidant form, and is also thought to be an

inducible O₂⁻ scavenger [142]. The C609T (rs1800566) polymorphism in the homozygous T allele form completely abolishes NQO1 activity, whereas in the heterozygous form, the enzymatic activity is weakened [114, 142]. The T allele was stated to be associated with carotid artery plaques in T2DM [142], whereas the study [114] also confirmed its involvement in CAD in T2DM subjects (Table 6).

Paraoxonase 1 (PON1)

PON1 is an enzyme found in high-density lipoproteins (HDL), with its exact function still in debate. PON1 is thought to play a major role in preventing or minimizing LDL oxidation and therefore ROS-driven atherosclerosis [145-148]. Many polymorphisms of PON1 were reported, all diminishing its expression or activity to some degree [148]. A recent meta-analysis [148] of 35 studies showed no conclusive relationship of PON1 polymorphisms with either CAD or MI. Studies looking specifically at CAD or MI in T2DM subjects [84, 143-146] yielded the same arguable conclusions (Table 6).

Uncoupling Protein 2 (UCP2)

UCP2 is a member of the superfamily of uncoupling proteins positioned on the inner mitochondrial membrane. By decreasing electrical potential across that membrane, they uncouple ATP synthesis and decrease O_2^- production by complex I of the electron transport chain [149]. UCP2 is mainly found in endothelial and smooth muscle cells of the vasculature and in macrophages [147], thus its diminished activity increases oxidative stress in those tissues. Common promoter polymorphism of UCP2 -866 G/A was reported to be associated with obesity, hyperinsulinemia [150] and dyslipidemia [147]. In a large study [147], the A allele in this polymorphism was reported to be more prevalent in T2DM males with CAD or MI (Table 6). More studies are needed.

GENE POLYMORPHISMS OF OTHER OXIDATIVE STRESS GENES IMPLICATED IN OTHER DIABETIC COMPLICATIONS OR IN CAD IN NON-T2DM SUBJECTS

Tetrahydrobiopterin (BH4) depletion caused by polymorphisms in GTP cyclohydrolase 1 (GCH1), the main enzyme involved in BH4 biosynthesis, increases oxidative stress and is thought to be implicated in diabetic macrovascular disease [151, 152]. To our knowledge, no studies have investigated its sole connection with CAD.

Another DNA-repair enzyme involved in oxidative damage stress control is 8-Oxoguanine DNA Glycosylase (OGG1). A few studies with contrary results have been published so far regarding its polymorphism's involvement in T2DM [105, 153], while the connection with CAD was also suggested [154].

Recently, the reactive oxygen species modulator 1 (ROMO1) which increases ROS levels was found to be associated with diabetic retinopathy for the rs6060566 polymorphism [155].

Studies investigating folate hydrolase 1 (FOLH1), 5-methyltetrahydrofolate-homocysteine methyltransferase (MTR) and serine hydroxymethyltransferase 1 (SHMT1), all involved in methionine and folate metabolism, reported an association with CAD with FOLH1 C1561T (rs202676) and SHMT1 C1420T (rs1979277) polymorphisms [156], whereas no association with MTR A2756G (rs1805087) was found [157].

ROS production and the consequent response is dependent also on the transcription of mitochondrial DNA (mtDNA). G10398A (more ROS), T16189C (impaired response to ROS) variants of mtDNA were suggested as independent risk factors in developing T2DM [158], and T16189C was also associated with CAD [159].

CONCLUSION

The worldwide increasing prevalence of obesity and sedentary lifestyle is the main cause of the rising incidence of T2DM. Due to chronic macrovascular and microvascular complications, T2DM represent a huge socioeconomic burden in the world. T2DM and CAD are multifactorial disorders, and both environmental and genetic factors are involved in their pathogenesis. The paramount mechanism

for tissue damage in CAD in T2DM is the overproduction of reactive oxygen species (ROS) which, in turn, activates the polyol pathway, increases the production of AGE precursors, activates PKC and increases hexosamine pathway activity. ROS levels primarily depend on the amount of ROS produced and the body's ability to eliminate them. Polymorphisms of genes implicated in either of the systems represent alleles/genotypes that are individually relatively common among the population, but significantly contribute to the disease burden when they are present simultaneously and/or together with environmental factors, such as obesity, smoking, hypertension or physical inactivity. Identifying higher risk groups would be rational, since primary or secondary interventions in those risk groups would be more cost-effective and would likewise yield better results with potential antioxidant therapy.

Genetic biomarkers (*i.e.* gene polymorphisms) may be especially helpful in risk prediction, prognosis, or prediction of the response of patients with CAD with T2DM to antioxidants. Moreover, the impact of nutritional factors is still insufficiently understood in patients with CAD and well-designed prospective randomized clinical trials are needed to properly address the role of antioxidants. Finally, personalized medicine will most probably have an important part in managing subjects at increased risk for CAD according to clinical and genetic information, providing that genetic tests (*i.e.* cost) become more widely available and that the genetic markers will be confirmed in prospective studies.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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