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GLOBAL RISK REDUCTION OF REACTIVE OXYGEN SPECIES IN METABOLIC SYNDROME, TYPE 2 DIABETES MELLITUS, AND ATHEROSCLEROPATHY

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REVIEW

ABSTRACT. METABOLIC SYNDROME (MS), prediabetes (PD), type 2 diabetes mellitus (T2DM), and accelerated atherosclerosis (atherosclerosis) are associated with multiple metabolic toxicities. These toxicities are associated with an excessive production of reactive oxygen species (ROS), which cause damage to proteins, lipids, and nucleic acids, resulting in structural damage to the vessel wall and the development of vasculopathy consisting of both macro- and micro-vessel diseases. In addition, a multitude of other serious medical conditions, including atherosclerosis, cardiomyopathy, endotheliopathy, intimopathy, isletopathy, neuropathy, nephropathy, and/or retinopathy, may be developed as complications. In order to have a favorable outcome in the treatment of these horrific diseases and their associated complications, it is suggested that the primary care clinician should consider taking a global risk reduction approach in preventing the progressive nature of these diseases as well as their morbid mortal complications. This global risk reduction approach may be utilized more frequently if it can be made into a simplified identification and treatment process. To this end, two acronyms that may be of assistance for the team approach to global risk reduction are discussed in this paper. The A-FLIGHT toxicity acronym for identification and the RAAS acronym for treatment regimens are discussed in detail in order to concentrate on the at-risk population.

The understanding and use of these two acronyms will assist the clinician in restoring endothelial cell function – endothelial nitric oxide synthase enzyme reactions and return to the endothelial cell its health maintenance function to delay and prevent macro and micro vessel complications in MS, PD, and overt T2DM.

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1. INTRODUCTION

There are multiple metabolic toxicities associated with metabolic syndrome (MS), prediabetes (PD), type 2 diabetes mellitus (T2DM) and their companion, the accelerated atherosclerosis (atherosclerosis) [1-3]. These multiple metabolic toxicities can be conveniently grouped in an acronym termed the A-FLIGHT toxicities (TABLE 1). Each of these toxicity substrates results in excessive production of reactive oxygen species (ROS) responsible for the damaging effects of reduction and oxidation (redox stress) to proteins, lipids, and nucleic acids (TABLE 2). Each of these A-FLIGHT toxicities may be viewed individually as an independent risk factor and is known to have a synergistic effect when acting in concert.

As can be noted from TABLES 1 and 2, many of the damaging effects of ROS occur prior to the diagnosis of overt T2DM and the associated glucotoxicity. Redox stress and ROS in turn may accelerate and contribute to the transition (in certain individuals) from MS to PD to overt T2DM while promoting accelerated atherosclerosis (atherosclerosis) resulting in increased cardiovascular events [4,5].

MS, PD, and T2DM can now be identified according to accepted definitions and guidelines set forth by the National Cholesterol Education Program Adult Treatment Panel III and the American Diabetes Association (TABLE 3) [6,7]. This trio is rooted in a polygenic origin and the interaction with current environmental stressors of over nutrition, under exercise, and smoking with the association of insulin resistance and beta cell dysfunction. Concurrently, this trio runs parallel to atherosclerosis and plays additional and important roles in today's overfed, sedentary, and super-sized society. By utilizing a global risk reduction approach, we may be able to slow or halt the progressive natural history of T2DM (TABLE 4) and atherosclerosis with a reduction in diabetic complications and cardiovascular events [2,8].

2. METABOLIC SYNDROME AND INSULIN RESISTANCE

Reaven [9] first described the MS in 1988 (initially termed Syndrome X) and over time we have come to know that insulin resistance is central to the development of coronary heart disease (CHD) and overt T2DM. This unique clustering of clinical syndromes and metabolic derangements has obviously gained in its acceptance by the clinical community due to its multiple renaming terms. The accepted term for this clustering phenomenon is now termed the metabolic syndrome by the World Health Organization in 1999 and will be the preferred term throughout this discussion [10]. Elevations in insulin levels (endogenous hyperinsulinemia) have been shown to be a marker and are also independently associated with the increased risk of CHD and cardiovascular disease (CVD) (TABLE 5) [11,12].

Insulin and amylin are co-synthesized, co-packaged, and co-secreted by the pancreatic beta cell's insulin secretory granule. Recently, amylin has been proposed as being a definite contributor to the accelerated atherosclerosis (atherosclerosis) associated with the insulin resistant state and the compensatory hyperinsulinemia [2-4,13]. The roles of the compensatory hyperinsulinemia, hyperproinsulinemia, and hyperamylinemia not only individually but also synergistically, merit a closer observation as the compensatory over expression of these beta cell-derived islet hormones and their associated activities contribute to the progressive nature of T2DM [4], atherosclerosis, acute coronary syndromes, and cardiovascular events.

3. REACTIVE OXYGEN SPECIES (ROS)

ROS consist primarily of various oxygen free radicals (superoxide [$O_2^{\cdot-}$], hydroxyl radical [$-OH^{\cdot-}$], and peroxynitrite [$ONOO^{\cdot-}$]), as well as the potent oxidizing agents of the non-radical family (peroxide [H_2O_2] and hypochlorous acid [HCLO]) (TABLE 2).

Both intracellular and extracellular antioxidants play important roles in neutralizing these toxic oxygen molecules. The endogenous antioxidant enzyme family consists primarily of superoxide dismutase (SOD), catalase, glutathione peroxidase and the tripeptide (gamma-L-glutamyl-L-cysteintyl-glycine) glutathione or (GSH), and free circulating thiols containing the sulfhydryl group (-SH) (TABLE 6). These are found to be systemically depleted in the clinical setting of T2DM and there is evidence

TABLE 1. THE A-FLIGHT ACRONYM

A	Angiotensin II (also induces PKC-β isoform)	ROS
	Amylin (hyperamylinemia) / amyloid toxicity	ROS
	AGEs/AFEs (advanced glycosylation/fructosylation endproducts)	ROS
	Apolipoprotein B	ROS
	Antioxidant reserve compromised	ROS
	Absence of antioxidant network	ROS
	Ageing	ROS
F	Free fatty acid toxicity	ROS
L	Lipotoxicity	ROS
I	Insulin toxicity (endogenous hyperinsulinemia-hyperproinsulinemia)	ROS
	Inflammation toxicity	ROS
G	Glucotoxicity (compounds peripheral insulin resistance) reductive stress	ROS
	Sorbitol/polyol pathway	PKC-β1 isoform
	Pseudohypoxia (increased NADH/NAD ratio)	ROS
H	Hypertension toxicity	ROS
	Homocysteine toxicity	ROS
T	Triglyceride toxicity	ROS

for the depletion in atheromatous lesions locally [2,8].

The islet beta cell is unique in that it is less well equipped to handle oxidative stress compared to other cells. This is why the oxidants alloxan and streptozotocin have a damaging effect on the beta cell before damaging renal or hepatic cells in the diabetes induced models currently utilized to develop diabetic animal models.

The delicate balance between the processes of reduction–oxidation is referred to as redox homeostasis. The redox imbalance will be referred too as oxidative and redox stress [2,8].

4. THE ENDOTHELIUM AND THE PROTECTIVE ROLE OF ENDOTHELIAL-DERIVED NITRIC OXIDE AND ITS ENZYME ENDOTHELIAL NITRIC OXIDE SYNTHASE

It is presently known that the endothelium is considered to be an organ that is actively engaged in the dynamic role of the health and structural maintenance of the arterial vessel wall and capillary beds. The endothelium is responsible for promoting a state of vasodilation vs. vasoconstriction, it is anti-inflammatory, antithrombotic, and possesses anti-oxidant properties largely due to the synthesis of endothelial nitric oxide (eNO) via the endothelial nitric oxide synthase (eNOS) enzyme reaction.

Endothelial-derived nitric oxide (eNO) is a wonderous gas and was awarded the distinction of being the molecule of the year in 1992 by Science Magazine [14]. The physicians who discovered that eNO was the elusive endothelial-derived relaxing factor and its fascinating properties of being a signaling molecule in the cardiovascular system were awarded the Nobel Prize in Medicine and Physiology in 1998 (R. F. Furchgott, L. J. Ignarro, and F. Murad).

Three statements need to be made before proceeding with this section:

(1) eNO is a natural occurring, endogenous, chain-breaking antioxidant synthesized by the vascular endothelial cell.

(2) The healthy endothelium is a net producer of endothelial nitric oxide [eNO].

(3) The activated or dysfunctional endothelium is a net producer of superoxide [$O_2^{\cdot-}$], associated with T2DM and atherosclerosis [2,3,7].

TABLE 2. ORIGIN, ENZYMATIC PATHWAYS OF REACTIVE OXYGEN SPECIES, AND THEIR OXIDIZED PRODUCTS.

[ORIGIN AND LOCATION] ENZYMATIC PATHWAYS:	[ROS] POTENT OXIDANTS:	[PRODUCTS] OXIDIZED LIPIDS AND PROTEINS:
Mitochondrial Respiratory Chain	$O_2^{\cdot}$ $-OH^{\cdot}$	Oxidized lipids, proteins, nucleic acids, and autooxidation byproducts
Inflammatory Macrophage Membranous NAD(P)H Oxidase	$O_2^{\cdot}$ $-OH^{\cdot}$ H_2O_2	Advanced lipoxidation endproducts (ALE) *ortho* o-tyrosine *meta* m-tyrosine
Granular Myeloperoxidase (MPO)	Hypochlorous acid HOCL Tyr (Tyrosine) NO_2	3-Chlorotyrosine di-Tyrosine NO_2^- Tyrosine (Nitrotyrosine)
MACROPHAGE		
Nitric Oxide Synthase (NOS) Inducible (iNOS) Large bursts - uncontrolled	$ONOO^{\cdot}$	NO_2^- Tyrosine (Nitrotyrosine)
ENDOTHELIAL CELL		
Nitric Oxide Synthase (NOS) Constitutive (cNOS) eNOS → NO nNOS → NO Small bursts - controlled	$NO + O_2^{\cdot} \rightarrow ONOO^{\cdot}$ $ONOO^{\cdot}$	 NO_2^- Tyrosine (Nitrotyrosine) NO_2^- Tyrosine (Nitrotyrosine)
eNOS-derived NO	NO The GOOD [46]	Natural-occurring, local-occurring, chain-breaking, antioxidant
Superoxide	$O_2^{\cdot}$ The BAD [46]	Toxic effects of ROS on proteins, lipid, nucleic acids
Peroxynitrite	$ONOO^{\cdot}$ The UGLY [46]	Toxic effects of ROS on proteins, lipid, nucleic acids
Hypochlorous Acid	HCLO The UGLY [46]	Toxic effects of ROS on proteins, lipid, nucleic acids
Restoration of eNO Via the eNOS Reaction	Antioxidant Antioxidant	Prevention of the toxic effects of ROS

eNO is the quintessential regulator of vascular homeostasis responsible for the modulation of vascular tone; platelet aggregation, leukocyte adhesion, intimal and smooth muscle cell proliferation, and plays an important role in providing vascular redox homeostasis. A summary of the positive/protective (health maintenance) role of eNOS and eNO can be summarized in (TABLE 7).

The arterial vessel wall in T2DM atherosclerosis and non-diabetic atherosclerosis becomes a net producer of superoxide with all of its damaging properties. In order to reverse this damaging effect, we need to restore endothelial health and recouple – restore the eNOS reaction so it can once again be a net producer of the wonderous, positive, protective gas eNO. This can be accomplished by utilizing current treatment modalities and current treatment guidelines in treating these patients to recognized goals through global risk reduction.

5. ABSENCE OF ANTIOXIDANT ENZYMES

Recently we have been made aware of a new mouse model, which has the complete absence of the eNOS enzyme. This model is referred to as the eNOS knockout or null mouse model. It is very interesting that this eNOS knockout mouse model

TABLE 3. CRITERIA FOR THE DIAGNOSIS OF THE METABOLIC SYNDROME

METABOLIC SYNDROME (any 3 of the following 5 parameters):
ABDOMINAL OBESITY:
WAIST SIZE: Men: > 102 cm (> 40 inches). Women: > 88 cm (> 35 inches).
BLOOD PRESSURE: ≥130/85. JNC VII ≥130/80
HDL-CHOLESTEROL: ≤40 in males. ≤50 in females.
TRIGLYCERIDES: (new cut point) ≥150 mg/dl
FASTING GLUCOSE: ≥110 mg/dl (new ADA ≥100 mg/dl)*
GLUCOSE CONCERNS:
PREDIABETES: DIAGNOSTIC CRITERIA: See IGT and IFG below.
IMPAIRED GLUCOSE TOLERANCE (IGT): stage III 140–199 mg/dl
IMPAIRED FASTING GLUCOSE (IFG): stage IV 100–125 mg/dl (new)
OVERT T2DM: T2DM IS THE EPITOME OF THE METABOLIC SYNDROME AND CONSIDERED A CHD RISK EQUIVALENT
FASTING: ≥126 mg/dl
RANDOM: ≥200 mg/dl
2 HOUR 75 GRAM ORAL GLUCOSE TOLERANCE TESTING: ≥200 mg/dl
NCEP ATP III. JAMA [2001] 285: 2486-2497.

develops a syndrome, which mimics the human MS. This model develops hypertension, insulin resistance, hyperlipidemia, and was just recently found to have hyperuricemia, elevated fibrinogen levels, and impaired glucose tolerance when stressed by feeding a high fat diet. This story in the mouse model is quite similar to what has happened in human medicine (gene abnormalities interacting with environmental alterations of over nutrition and under exercise) [15,16]. It is quite interesting that a single gene alteration can reproduce the metabolic syndrome.

In humans, the gene alteration would not have to be a complete knockout as there are conditions now known as gene polymorphisms (GP), which result in a misspelling of the amino acid sequence of transcribed proteins.

To have an effect on T2DM and atherosclerosis there would not have to be a complete knockout of the gene but just one or two changes (misspellings) in the 1203 amino acid sequence of eNOS. We now know if there is a misspelling (GP) resulting in the transcription of just one amino acid, such as the known Glu298→Asp GP of the eNOS enzyme, we find associated cardiovascular and metabolic abnormalities. These misspellings may not result in any disease state unless; the involved protein enzyme is stressed by its environment (such as over nutrition and under exercise). Currently, it is felt that human MS, T2DM, and atherosclerosis are polygenic in origin. It will be interesting to observe the gene polymorphism (Glu298→Asp), as it may become a major player in the polygenic cause of MS, T2DM, and atherosclerosis.

The Glu298→Asp GP is responsible for a statistically significant increased frequency of hypertension and spastic angina [17]. Interestingly, in a different set of patients the occurrence of increased abnormal coronary angiographic findings of atherosclerosis and an increased association of cardiovascular events did occur [18-20]. The Glu298→Asp GP is responsible for a decrease in basal NO production in healthy subjects according to the publication by Veldman BA et al. [21]. We now have a Japanese population, a UK population, and an Italian population that correlates Glu298→Asp GP to atherosclerosis and CAD events [19-21].

TABLE 4. THE FIVE STAGES OF T2DM: THE NATURAL PROGRESSIVE HISTORY

I	LATENT STAGE [EARLY]: Insulin Resistance: Genetic Component Environmental component. Modifiable: obesity/sedentary life style. Non-modifiable: ageing Beta Cell Defect: (Dysfunction) Genetic Component: Abnormal processing, storage or secretion. Intracellular/extracellular oligomers of Islet amyloid toxicity to the beta cell. Abnormal processing, storage or secretion Islet Amyloid: A diffusion barrier. A secretory defect. An intra islet absorptive defect.
II	TRANSITION STAGE [MIDDLE]: Persistent hyperinsulinemia, hyperproinsulinemia → accelerated atherosclerosis. Persistent hyperamylanemia → accelerated atherosclerosis Continued remodeling of the endocrine pancreas (islet amyloid). Beta cell displacement, dysfunction, mass reduction due to the toxic effect of IAPP oligomers and the progressive developing diffusion barrier.
III	IMPAIRED GLUCOSE TOLERANCE (IGT) STAGE [LATE]: "Pre-diabetes" Human Health Services (HHS) and American Diabetes Association (ADA) term. [Start treatment at this time] Diagnose earlier: rejuvenation of the 2 hour glucose tolerance blood sugar 140-199 mg/dl Increased insulin resistance → Glucotoxicity → Insulin resistance → Glucotoxicity: Creating a vicious cycle. Islet amyloid. Increasing beta cell defect. Loss of beta cell mass with displacement. (Remodeling of islet architecture including extracellular matrix). Beta cell loss centrally.
IV	Impaired Fasting Glucose (IFG) STAGE [LATER]: "Pre-diabetes" Human Health Services (HHS) and American Diabetes Association (ADA) term. Blood sugar ranging [110-125 mg/dl] *ADA new cut point IFG Nov 2003: [100 –125 mg/dl] Impaired hepatic glucose production: Increasing global insulin resistance (hepatic) with subsequent gluconeogenesis. Feeding forward in the vicious cycle to accelerate insulin resistance globally.
V	OVERT STAGE: [TOO LATE] FBG 126 or greater: Random or 2 hour OGTT ≥200. [50% loss of beta cell function at the time of clinical diagnosis] Use medications that do not increase endogenous insulin or amylin. Use combination therapy. Start treatment at stage III-IV (IGT-IFG). Paradigm Shift. Diagnose early. Start treatment early at the Stage III: IGT.

These findings indicate that the eNOS gene is important to the development of accelerated atherosclerosis and atheroscleropathy. Furthermore, these three distinct patient populations indicate that this gene polymorphism is widely distributed throughout diverse patient populations and according to Veldman is present in approximately 10% of patient populations [21].

Recently, Noiri E and colleagues have shown that there is a significant association of the Glu298→Asp GP and end stage renal disease in

TABLE 5. DELETERIOUS EFFECTS OF HYPERINSULINEMIA

• Insulin, proinsulin, and amylin synergistically activate the RAAS with subsequent increase in Ang II, renin, and aldosterone.
• Na^+ and H_2O retention, which increases blood volume and pressure.
• Activation of the sympathetic nervous system.
• Increases membrane cation-transport increasing intracellular Ca^{++}, which increases tone and pressure.
• Stimulates vSMC proliferation and migration and remodeling.
• Increases the number of AT-1 receptors.
• Creates cross talk between the insulin receptor and AT-1 receptor, resulting in a more profound Ang II effect.
• PI3 kinase Akt-MAP kinase Shunt. Impairing the metabolic (PI3kinase AKT) pathway while promoting the MAPkinase remodeling pathway.
• Ang II promotes the MAP kinase pathway and remodeling.
• Ang II most potent stimulus for production of NAD(P)H oxidase with superoxide production.
• Ang II promotes endothelin pathway MAP kinase.
• Potent stimulator for PAI-1 production.
• Endogenous hyperinsulinemia, hyperproinsulinemia and an increased proinsulin/insulin ratio were found to be associated with increased risk for development of T2DM in the Women Health Study. Insulin does not come without its fraternal twin (AMYLIN), whereas exogenous insulin is not associated with amylin or proinsulin.

T2DM, which once again points to the importance of the endothelial cell and the eNOS reaction [22].

The exciting finding by Monti LD et al. revealed a significant association between an eNOS GP and type 2 diabetes, and furthermore, suggested a new genetic susceptibility factor for hyperinsulinemia, insulin resistance, and T2DM [23].

Since eNOS contains 1203 amino acids there exists the possibility of other gene polymorphisms within the eNOS enzyme that have not been identified at this time. Additionally, these gene polymorphisms could interact with other gene polymorphisms of other endogenous antioxidant enzymes in the T2DM patient, as we know their antioxidant reserve is compromised.

Single nucleotide polymorphisms are being searched at an alarming pace to identify new susceptibility genes for insulin resistance and T2DM. We have focused on just one susceptibility gene, that being eNOS, while there are others too numerous too mention. Thus, as the human genome unfolds there may be multiple related and unrelated important gene polymorphisms identified.

6. THE VULNERABLE eNOS ENZYME REACTION

The following eNOS reaction demonstrates the location of the vulnerable three arms of the eNOS reaction responsible for the generation of eNO.

$$\text{(1) L-Arginine} \xrightarrow[\text{(3) } BH_4]{\substack{O_2 \\ \text{NAD(P)H / NAD(P)H Oxidase} \\ \text{(2) eNOS}}} \text{NO} + \text{L-Citrulline} + NAD(P)^+$$

If the eNOS reaction is uncoupled the reaction is as follows:

$$NAD(P)H \xrightarrow[\text{NAD(P)H Oxidase}]{O_2} NAD(P)^+ + O_2^{\cdot -}$$

L-Arginine is uncoupled and not converted to NO and L-citrulline.

TABLE 6. ANTIOXIDANTS: ENZYMATIC – NONENZYMATIC INACTIVATION OF FREE RADICALS.

ENZYMATIC ANTIOXIDANTS
SUPER OXIDE DISMUTASE (SOD) Reactions catalyzed: [O_2^- + SOD → H_2O_2 + O_2] Various isoforms: ecSOD (extracellular); Mn-SOD (mitochondrial); Cu/Zn-SOD (intracellular)
CATALASE – Location: peroxisome. Reaction catalyzed: [2 H_2O_2 + catalase → 2 H_2O + O_2]
GLUTATHIONE PEROXIDASE – Location: mitochondrion, cytosol, and systemic circulation. Glutathione (GSH or glutamyl-cysteinyl-glycine tripeptide): the reduced –SH of GSH is oxidized to disulfide GSSG. Glutathione peroxidase-catalyzed reation: [GSH + 2 H_2O_2 → GSSG + H_2O + O_2] Glutathione reductase-catalyzed reaction: [GSSG → GSH] at the expense of [NADH → NAD^+] and/or [NAD(P)H → $NAD(P)^+$]
NITRIC OXIDE SYNTHASE (NOS) – Location: membrane. Isoforms: eNOS (endothelial): good nNOS (neuronal): good iNOS (inducible-inflammatory): bad
O_2^- and nitric oxide (NO) are consumed in this process with the creation of reactive nitrogen species (RNS). O_2^- +NO → ONOO- (peroxynitrite) + tyrosine → nitrotyrosine. Nitrotyrosine reflects redox stress and leaves a measurable footprint. NO the good; $O_2^{\cdot}$ the bad; $ONOO^-$ the ugly [46]
NONENZYMATIC ANTIOXIDANTS
Uric acid Vitamins (A, C, and E) Thiols: Sulfhydryl (-SH)-containing molecules. Albumin: Is an antioxidant because of it is a thiol-containing macromolecule. Apoproteins: Ceruloplasmin and transferrin. Bind copper and iron in forms which cannot participate in the Fenton reaction.

NUMBER 1: THE SUBSTRATE L-ARGININE ARM. L-arginine is the essential amino acid substrate for the eNOS reaction. There is usually no problem with its supply, but there are factors (endogenous competitors) that create a relative deficiency of this necessary substrate. One such endogenous competitor is asymmetrical dimethyl arginine (ADMA), a naturally occurring endogenous competitive inhibitor of L-arginine.

ADMA accumulates by either a process of increased synthesis by the protein arginine N-methyltransferases (PRMTs) or decreased elimination by the enzyme dimethylarginine dimethylaminohydrolose (DDAH) [24-27].

DDAH selectively hydrolyzes ADMA to L-citrulline and dimethylamine, such that, the higher the DDAH activity, the lower the ADMA levels. Importantly, inhibition of DDAH activity results in increased ADMA levels. Both native and oxidized LDL-cholesterol has been shown to up-regulate PRMT while causing a decrease in the activity of DDAH [28]. This results in an elevation of ADMA levels contributing to endothelial cell dysfunction and increased oxidative stress to the intima with subsequent accelerated atherosclerosis.

There are multiple causes for the elevation in ADMA levels. Each of these toxicities relate to the A-FLIGHT acronym responsible for the production

TABLE 7. THE POSITIVE EFFECTS OF eNOS AND eNO

• Promotes vasodilatation of vascular smooth muscle.
• Counteracts smooth muscle cell proliferation.
• Decreases platelet adhesiveness.
• Decreases adhesiveness of the endothelial layer to monocytic WBCs (the "teflon effect").
• Anti-inflammatory effect.
• Anti-oxidant effect. It scavenges reactive oxygen species locally, and acts as a chain-breaking antioxidant to scavenge ROS.
• Anti-fibrotic effect. When NO is normal or elevated, MMPs are quiescent; conversely if NO is low, MMPs are elevated and active. MMPs are redox sensitive.
• NO has diverse anti-atherosclerotic actions on the arterial vessel wall including antioxidant effects by direct scavenging of ROS - RNS acting as chain-breaking antioxidants and it also has anti-inflammatory effects.

of ROS. Recently, Faldetta CM et al. [29] were able to demonstrate in both normal human subjects and T2DM human patients that acute L-arginine infusion decreased plasma total homocysteine concentrations, counteract oxidative stress, and increased the availability of nitric oxide.

In summary, the relative deficiency of L-arginine due to elevation of ADMA levels contribute to oxidative stress and result in the atheroscleropathy associated with insulin resistance, MS, PD, and overt T2DM.

NUMBER 2: THE eNOS ENZYME ARM. As already discussed previously the eNOS arm is susceptible to dysfunction due to the complete knockout of this gene in animal models. Additionally gene polymorphisms have been described such as the Glu298→Asp GP, which interferes with the normal function of the eNOS reaction to produce eNO. Since the eNOS enzyme is a 1203 amino acid protein enzyme there may be other gene polymorphisms affecting this enzyme that have not been identified at this time.

NUMBER 3: THE BH_4 COFACTOR. Tetrahydro-biopterin (BH_4) is the necessary cofactor for coupling L-arginine to the NAD(P)H oxidase enzyme in order for L-arginine to be oxidized to NO and L-citrulline. The importance of this essential cofactor and its mechanism is just starting to emerge.

If this cofactor is not functioning properly or deficient the entire eNOS reaction uncouples and the endothelium becomes a net producer of superoxide [$O_2^{\cdot -}$], through the uncoupled NAD(P)H oxidase reaction. In addition to BH_4 being the necessary cofactor it also serves as a naturally occurring antioxidant capable of scavenging ROS such as superoxide and peroxynitrite [$ONOO^{\cdot -}$]. If BH_4 is deficient in supply or function the eNOS reaction not only is capable of uncoupling with subsequent superoxide and peroxynitrite production but also is at a disadvantage, in that, there would be less BH_4 to scavenge the local occurring ROS being produced in excess amounts [30].

It is important to note that a direct effect of folic acid is to keep this important cofactor BH_4 intact so that it can maintain coupling of the eNOS reaction. The lowering of homocysteine (Hcy) is an indirect effect of folic acid aiding in the decreased production of ADMA due to the effect of Hcy on DDAH. Folic acid given to patients with T2DM has an immediate improvement of endothelial relaxation before Hcy has time to be lowered [31-32]. Folic acid is not only a methyl donor but also an electron and hydrogen donor being capable of converting oxidized BH_4 (BH_2-BH_3) back to the requisite BH_4 to run the eNOS reaction via a folate shuttle mechanism and once again produce eNO [1,33].

When you examine the three arms of importance of the eNOS reaction there are two possible changes in the treatment paradigm. First, we need to take a global risk reduction approach (by treating each risk factor – metabolic substrate in the A-FLIGHT toxicities acronym in order to decrease the clinical substrates of lipids, hypertension, and glucotoxicity without elevating endogenous insulin or amylin) in order to decrease redox stress and ROS, as well as,

TABLE 8. THE RAAS ACRONYM - GLOBAL RISK REDUCTION

R	Reductase inhibitors (HMG-CoA). Decreasing modified LDL-cholesterol, i.e., oxidized, acetylated LDL-cholesterol. Decreasing triglycerides and increasing HDL-cholesterol. Improving endothelial cell dysfunction. Restoring the abnormal lipoprotein fractions. Thus, decreasing the redox and oxidative stress to the arterial vessel wall and myocardium.
A	AngII inhibition or receptor blockade: ACEi-prils. ARBS-sartans. Both inhibiting the effect of angiotensin-II locally as well as systemically. Affecting hemodynamic stress through their antihypertensive effect as well as the deleterious effects of angiotensin II on cells at the local level - injurious stimuli -decreasing the stimulus for O_2^- production. Decreasing the A-FLIGHT toxicities. The positive effects on microalbuminuia and delaying the progression to end stage renal disease. Plus the direct-indirect antioxidant effect within the arterial vessel wall and capillary. Antioxidant effects. Aspirin antiplatelet, anti-inflammatory effect on the diabetic hyperactive platelet. Adrenergic (non-selective blockade) in addition to its blockade of prorenin → renin conversion. Amlodipine - Felodipine with calcium channel blocking antihypertensive effect, in addition to their direct antioxidant effects.
A	Aggressive control of diabetes to HbA1c of less than 7. This usually requires combination therapy with the use of insulin secretagogues, insulin sensitizers (PPAR-γ agonists), biguanides, α-glucosidase inhibitors, and ultimately exogenous insulin. Decreasing modified LDL cholesterol, i.e., glycated-glycoxidated LDL cholesterol. Improving endothelial cell dysfunction. Also decreasing glucotoxicity and the oxidative-redox stress to the intima and pancreatic islet. Aggressive control of blood pressure, which usually requires combination therapy, including thiazide diuretics to attain JNC 7 guidelines. Aggressive control of homocysteine with folic acid with its associated additional positive effect on re-coupling the eNOS enzyme reaction by restoring the activity of the BH_4 cofactor to run the eNOS reaction via a folate shuttle mechanism and once again produce eNO.
S	Statins. Improving plaque stability (pleiotropic effects) independent of cholesterol lowering. Improving endothelial cell dysfunction. Moreover, the direct/indirect antioxidant anti-inflammatory effects within the islet and the arterial vessel wall promoting stabilization of the unstable, vulnerable islet and the arterial vessel wall. Style. Lifestyle modification (weight loss, exercise, and change eating habits). Stop Smoking.

slowing the progressive natural history of cardiovascular disease and T2DM. Second, we should now include in the treatment paradigm the use of folic acid and possibly arginine supplementation. T2DM is now considered to be a coronary risk equivalent and therefore all patients with T2DM should consider folate supplementation, as well as, the non-diabetic atherosclerotic patient [33].

Those patients with persistent endothelial cell dysfunction after the standard goals have been reached should consider arginine supplementation and possibly should be considered even sooner in the treatment paradigm if there is a history or evidence of symptomatic peripheral arterial disease (PAD), congestive heart failure (CHF) and diastolic dysfunction [27,33-35].

Recently, there have been numerous articles published (in excess of 11,000 articles regarding C-reactive protein in Pub Med alone, making them too numerous to cite in this article) regarding the important role of low-grade inflammation not only regarding MS, PD, and overt T2DM but also in atheroscleropathy.

Upstream from the chronic inflammatory cycle exists the driving force of redox stress and ROS activating the redox sensitive nuclear transcription factor (NF-kappa B). This activation of NF-kappa B in turn affects the family of cytokines, chemokines,

and endothelial cellular adhesion molecules. In turn, these promote a further increase in oxidative and redox stress causing a chronic viscous inflammatory cycle [33].

Inflammation begets inflammation and ROS begets ROS, in that, redox stress is a redox signaling mechanism to certain nuclear genes (NF-kappa B) and promotes the inflammatory cycle [1-3,8,33-35]. Redox and oxidative stress - ROS are at the very core of this inflammatory cycle.

If the vulnerable eNOS reaction is functioning properly by being a net producer of eNO, we can then realize its chain-breaking antioxidant, inflammatory cycle-breaking, and oxidation cycle breaking properties. In contrast, it can be noted that if the endothelium becomes dysfunctional and/or uncoupled, it then becomes a net producer of superoxide and an accelerant to the inflammatory cycle [33].

7. GLOBAL RISK REDUCTION

Lowering the substrates responsible for the production of ROS will result in a decrease in the production of ROS. By reducing these substrates we may allow the endothelium to regain a more normal function, through recoupling and once again resume its protective health maintenance role to the surrounding tissues in the capillary bed and the arterial vessel wall by becoming a net producer of eNO. A simple acronym can aid in this drug treatment family paradigm once the "at risk" patients are identified. It is termed the RAAS acronym and if placed on the front of patient's charts or entered into a computerized electronic chart it can serve to alert the entire health care team involved in patient care.

Global risk reduction has an equally important effect on the affected diabetic target organs such as the heart, kidneys, neuronal unit, and the retina [36]. If we are to have a positive effect on this multifactorial disease process, it will require a multifaceted "team" approach.

8. THE RAAS ACRONYM

We have been familiar with the RAAS acronym as an abbreviation for the renin-angiotensin-aldosterone system over the past two decades. This has been due to the important roles of the angiotensin converting enzyme inhibitors (ACEi) in the treatment of hypertension and cardiovascular disease. Let us now turn to the specific RAAS acronym (TABLE 8):

R: stands for reductase inhibitors (3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors or statins). This represents the pure effects of this class of medications on the lipoprotein toxicities. The reductase inhibitors result in the lowering of LDL-cholesterol, VLDL, triglycerides, or the Apolipoprotein B fractions. Additionally, these medications result in an increase of the antioxidant, anti-inflammatory, protective HDL-cholesterol. This has a direct effect on lipotoxicity (L) in the A-FLIGHT toxicities acronym (TABLE 1). Also, by decreasing VLDL-cholesterol and triglycerides it affects triglyceride toxicity (T) and free fatty acid toxicity (F).

A: The first A stands for ACEi and/or angiotensin receptor blockers (ARBs). These two classes of medications represent their protective effect against the elevation of angiotensin II (Ang II) both at the systemic and local tissue levels. In addition to their antihypertensive effects they also serve as antioxidants in that they prevent the oxidative and redox effects of Ang II. Ang II is the most potent inducer of the membranous NAD(P)H oxidase and subsequent superoxide. ACEi and ARBs have a direct effect on hypertension toxicity (H) and (A) AngII toxicity (TABLE 1). Indirectly they have an important effect on insulin toxicity (I) and amylin toxicity (A) by blocking the effect of the metabolic mediator Ang II. A: also stands for aspirin and its antiplatelet effect associated with the hyperactive platelet abnormalities in this clustering phenomenon. A: also stands for adrenergic blockade, which has been shown to be so important in the treatment of cardiovascular disease. The use of the non-selective adrenergic beta-blockers has been especially important in their use with associated T2DM [36,37].

A: The second A in this acronym stands for the aggressive control of diabetes, which usually requires combination therapy with the use of insulin secretagogues, insulin sensitizers (thiazolidine-diones and additionally, rosiglitazone increases NO

[37]), biguanides, alpha-glucosidase inhibitors, and ultimately exogenous insulin [38-39]. This has a major effect on glucotoxicity (G) (TABLE 1), which, in turn, has an effect on the modification, i.e., glycation and glycoxidation of the lipoprotein particles.

A: aggressive control of blood pressure to therapeutic guidelines, which has a major effect on hypertension toxicity (H) (TABLE 1). A: aggressive control of hyperhomocysteinemia with folic acid supplementation. Folic acid not only has a lowering effect on homocysteine toxicity (H) (TABLE 1), but also has an additional positive effect of being an antioxidant through its role in restoring the eNOS reaction to produce eNO. Folic acid restores the oxidized BH_4 cofactor from BH_2, BH_3 to the requisite cofactor BH_4 to run the eNOS reaction via a folate shuttle [33]. Just as we have become familiar with the pleiotropic effects of statins, we need to be aware of the pleiotropic effects of folic acid [33].

S: stands for statins and their pleiotropic effects. Statins have a wonderful effect on the endothelium and up regulate the eNOS enzyme with subsequent increased eNO. In doing this the endothelium can once again be a net producer of eNO and improve atheromatous plaque stability. Recently, we have come to learn of the direct and indirect anti-inflammatory and antioxidant properties of this group of medications due to decreased isoprenylation with a decrease in the G-proteins Rac and Rho. S: stands for style: specifically the lifestyle modification of weight loss and increasing exercise and changing eating habits. S: also stands for stop smoking. These lifestyle modifications point to the gene-environment interaction discussed earlier.

The National Institutes of Health (NIH)–National Diabetes Education Program and American Diabetes Association use the abbreviation ABCs of diabetes care to aid the patient in proper risk reduction [40-43].

A: A1C < 7
B: BLOOD PRESSURE < 130/80
C: LDL-CHOLESTEROL < 100 MG/DL

The RAAS acronym is somewhat more detailed and identifies the additional importance of certain drug classes and is primarily for clinicians: Reductase inhibitors (HMG-CoA reductase inhibitors), ACEi and or ARBs, Adrenergic blockade, Aspirin, Aggressive control of diabetes, hypertension, and homocysteine with folic acid supplementation, and Statins for their pleiotropic effects on endothelial cell function. The entire RAAS acronym emphasizes redox stress reduction, in addition to global risk reduction.

9. CONCLUSIONS

How are we doing? Can we do better? McFarlane et al. [43] recently published data on a study of 1,372 active clinic patients with diabetes and hypertension, 1,247 (90.9%) had T2DM, and 26.7% met the target blood pressure of 130/85 mmHg. A total of 35.5% met the goal LDL cholesterol level of <100 mg/dl, 26.7% had a HbA1c <7%, and 45.6% were on antiplatelet therapy. Only 3.2% of patients met the combined ADA goal for BP, LDL cholesterol, and HbA1c [44].

While this is just one study, it definitely points to the problems of attaining goals of global risk reduction. Most of us feel we are doing better than the above study indicates, however, when a dedicated chart review is done we may find that we are not doing as well as we think.

The recently published Steno-2 study by Gaede et al. [44] revealed a significant reduction in cardiovascular and microvascular events of nearly 50%. Their intensified intervention and global risk reduction against multiple risk factors in patients with type 2 diabetes and microalbuminuria was very impressive and points to the possible outcomes associated with global risk reduction in this patient population [45-46].

It is important to note that the American Diabetes Association has just changed the cut point of impaired fasting glucose from levels of 110–125 mg/dl to a new cut point of 100–125 mg/dl [47]. This will identify an increased number of patients in the impaired fasting glucose (IFG) Stage IV section in the transition from latent T2DM to overt T2DM (TABLE 4).

The troublesome-terrible-triad of MS, T2DM, and CVD are rooted in chronic inflammation and oxidative stress [48]. Upstream from chronic inflammation is oxidative–redox stress, which

activates the chronic inflammatory cycle through the activation of nuclear factor kappa-B [33]. This triad is constantly interacting and leads to the acute cardiovascular events associated with accelerated atherosclerosis (atherosclerosis) and remodeling of the end organ diabetic complications and diabetic opathies. This unifying hypothesis of redox and oxidative stress with resulting ROS seems to be the binding tie underlying the MS, insulin resistance, prediabetes, overt T2DM, atherosclerosis, and CVD [1,2,8,33,48].

An increased awareness to global risk reduction in this patient population will require each of us to examine "the whole patient" with each of their individual clustering of multiple metabolic toxicities and multiple risks and clinical syndromes associated with the MS. This will require identification of the multiple metabolic toxicities (A-FLIGHT acronym) in each patient and a health care team approach will be the most efficient way to get these "at risk" patients to goal with the use of the RAAS acronym. It will require more time and effort, but the rewards will be of a large magnitude and well worth the time, effort, and energy. Treat the clustering phenomenon before it is too late. Identify and treat these high-risk patients early and often.

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ABBREVIATIONS USED:

Atherosclerosis: accelerated atherosclerosis in metabolic syndrome, prediabetes, and type 2 diabetes mellitus;

ACEi: angiotensin converting enzyme inhibitor;

ARB: angiotensin receptor blocker;

HbA1c: hemoglobin A1c;

T2DM: type 2 diabetes mellitus;

NO: nitric oxide;

eNO: endothelial nitric oxide;

NOS: nitric oxide synthase;

nNOS: neural NOS-1;

iNOS: inducible NOS-2;

eNOS: endothelial NOS-3;

$O_2^{\cdot -}$: superoxide;

BH_4: tetrahydrobiopterin;

ADMA: asymmetrical dimethylarginine;

DDAH: dimethylarginine dimethylaminohydrolose;

LDL: low-density lipoprotein;

PRMTs: protein arginine N-methyltransferases;

NAD(P)H: nicotinamide dinucleotide phosphate reduced;

Glu298→Asp GP: glutamic 298 → aspartyl gene polymorphism;

$ONOO^{\cdot -}$: perioxynitrite;

CAD: coronary artery disease;

CHL: coronary heart disease;

CVD: cardiovascular disease;

HMG-CoA: 3-hydroxy-3-methylglutaryl-CoA;

IR: insulin resistance;

MS: metabolic syndrome;

PD: prediabetes;

Hcy: homocysteine;

HHcy: hyperhomocysteinemia;

RAAS: renin-angiotensin-aldosterone-system;

A-FLGIHT acronym: referring to the multiple metabolic toxicities of IR, MR, PD, and T2DM producing reactive oxygen species;

ROS: reactive oxygen species;

5MTHF: 5-methyl tetrahydrofolate or folic acid;

GLUT 4: glucose transporter 4;

-/-: Gene knockout;

SOD: superoxide dismutase;

-SH: sulfhydryl group;

GSH: glutathione;

GP: gene polymorphism.

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