Oxidative stress in diabetes - circulating advanced glycation end products (AGEs), lipid oxidation and vascular disease

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Individuals with both type 1 and type 2 diabetes show vascular complications that may remain undetected for many years until the disease is at an advanced stage. Clinical trials to date have been unsuccessful in identifying a therapeutic approach that addresses the underlying problem in diabetes, poor glycaemic control while also reducing incidence of microvascular disease (1). Oxidative stress; an imbalance of oxidants and antioxidants in the favour of oxidants has been considered to play a central part in protein glycation and complications in diabetes (2-4). Neutralisation of oxidants by increased antioxidant availability has been considered as one possible way to mitigate oxidative stress. Indeed, several human intervention studies have been undertaken to determine whether dietary antioxidants can exert any beneficial effects for T2DM patients (5, 6).

Chronically elevated levels of glucose increase the frequency of non-enzymatic glucose-adduction with proteins, lipids and DNA to form advanced glycated end products (AGEs). One of the major plasma proteins that can undergo secondary modification by glucose or oxidised lipids in diabetes is the cholesterol carrying low density lipoprotein (LDL). In Type 2 diabetic patients, LDL are more glycated and more susceptible to oxidation (7) increasing their clearance by macrophages in a non-regulated manner and increasing foam cell formation.

Complications such as microalbuminuria, are associated with renal protein oxidation, which is in turn preceded by LDL fatty acid oxidation. The initiator is H_2O_2 produced from an auto-oxidation of homocysteine and increased metabolism of arachidonic acid towards its pro-inflammatory eicosanoids. The backdrop of increased oxidative stress state promotes a state of diffused vasculopathy (8).

In both type 1 and type 2 diabetes patients, there is an increased risk of cognitive impairment in later life. In the glucose control intervention study, cognitive function was an independent predictor of glycaemic control, and the risk of cognitive decline or dementia is not decreased by improving blood glucose levels (9). The presence of AGEs and carbonylation of LDL, which is indicative of oxidative stress and glycation are shared common risk factors for both diabetes and cognitive impairment (10, 11).

Free radicals, AGEs and biomarkers

The generation of free radicals physiologically is a common phenomenon (12). Where there is an imbalance between radical production and scavenging, their detrimental effects on macromolecules are observed (11, 13). Owing to their high rates of reaction with biological macromolecules they cannot be easily monitored directly unless trapped for example by a biological molecule or through reacting with biomolecules to form stable end-products of radical attack.

Accumulating evidence suggests that AGEs are involved in a vicious cycle of generating free radicals (14, 15). AGEs increase the expression and activity of NADPH (nicotinamide adenine dinucleotide phosphate) oxidase in human endothelial cells, an important source of vascular oxidative stress in type 2 diabetes (16). Increased NADPH oxidase activity results in formation of free radicals, depletion of

cellular antioxidants such as glutathione, glutathione peroxidase, superoxide dismutase and catalase. Free radical mediated lipid peroxidation of polyunsaturated fatty acids gives rise to formation of several reactive α-, β-unsaturated aldehydes such as 4-hydroxy-trans-2-nonenal (HNE), 4-oxotrans-2-nonenal (4-ONE), acrolein and 4-oxo-trans-2-hexanal, all of which are aldehydes like glucose, have the potential to be considered as biomarkers of glycaemic status but can also form advanced lipid peroxidation end products (ALE). The detection of 4-HNE and malondialdehyde (MDA) adducts, and oxLDLs within the atherosclerotic plaque is an hallmark in atherosclerosis (17). Similarly, the radical oxidised lipid, MDA has been shown to generate ALE and together with AGEs these cause secondary damage to proteins (15). 8-iso-$PGF_{2\alpha}$, is widely used as a biomarker of lipid oxidation. It is measured in plasma or urine by mass spectrometry techniques or enzyme-linked immunosorbent assay (ELISA). However, discrepancies between the specificity of these methods means care must be taken when interpreting findings between different studies (18). Nevertheless, it is widely adopted as a marker for measuring *in vivo* lipid oxidation and a recent meta-analysis considered F_2-isoprostanes, considered the evidence for its association with coronary artery disease, stroke and peripheral artery disease. These authors considered the differences in sample handling/storage and assays as key contributors to the variation between studies. Nevertheless, high levels of F_2-isoprostanes in urine or blood did appear to be a non-specific indicator of CVD and should be explored in prospective studies (19).

Given the rapidly increasing incidence of type 1 diabetes and obesity-associated type 2 diabetes in mid-life which contributes to increased risk for dementia, recently termed type 3 diabetes, there is an urgent need to understand how systemic changes in metabolism may predispose to dementia in order to develop early risk biomarkers which can be applied for monitoring health outcomes. With sufficient care taken in sample collection coupled with analytical precision, F_2-isoprostanes may prove to be very useful and offer improved bio-monitoring opportunities to support the implementation of strategies to minimise vascular complications.

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