VIEWPOINT

Post-challenge hyperglycaemia, nitric oxide production and endothelial dysfunction: The putative role of asymmetric dimethylarginine (ADMA)

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Abstract
The endothelium is a thin layer of cells at the internal surface of blood vessels in continuous contact with the circulating fluids. The endothelial cells represent the primary barrier for the transport of glucose from the vascular conduits into the interstitial space. Insulin and nitric oxide have an important role in the regulation of glucose transport and metabolism.

Hyperglycaemia is the main criteria for the diagnosis of diabetes and is responsible for the micro- and macro-vascular pathology seen in diabetic patients. Recent evidence suggests that post-challenge hyperglycaemia is a better predictor of cardiovascular risk than fasting glucose. Acute glucose elevations have been associated with a reduced endothelial-dependent flow mediated dilation indicating a decrease in nitric oxide production. Post-prandial hyperglycaemic peaks have been directly associated with increased intima media thickness in type 2 diabetic patients indicative of an increased atherosclerotic risk.

The increase in intra-cellular glucose concentrations in the endothelial cells induces a hyper-generation of reactive oxygen species via the activation of different pathways (polyol-sorbitol, hexosamine, advanced glycated end products, activation of PKC, asymmetric dimethylarginine (ADMA)). These mechanisms influence the expression of genes and release of signalling and structural molecules involved in several functions (inflammation, angiogenesis, coagulation, vascular tone and permeability, cellular migration, nutrient metabolism).

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Introduction

The patho-physiology of type 2 diabetes (T2D) is characterised by an impairment of insulin action and by the consequent development of hyperglycaemia which, in the long term, determines an increased risk of fatal and non-fatal cardiovascular events [1–3]. The risk is linked to the damaging effects of extracellular and intra-cellular glucose accumulation on metabolic, immune and vascular functions (glucotoxicity) [4,5]. Normally glucose concentrations are finely regulated and maintained within a narrow range by a counter-regulatory feedback system involving insulin as a glucose-lowering and anabolic hormone and glucagon and the sympathetic system (adrenalin, noradrenalin) as glucose-producing and catabolic hormones [6]. The production of these hormones responds concertedly to glucose fluctuations in order to re-establish euglycaemia but a malfunction, in excess or in defect, in any of these systems will result in abnormal glucose levels [6].

Type 2 diabetes is an example of a dysfunctional homeostatic system not able to maintain physiological glucose concentrations and the progressive deterioration from normoglycaemia to T2D is well described by the disposition index (DI) [7]. The DI represents the reciprocal, curvilinear, dynamic relationship between systemic insulin sensitivity and pancreatic insulin secretion and it predicts the adjustment of β-cell insulin secretion induced by changes in insulin sensitivity [7]. For example, a decrease in insulin sensitivity in normal subjects elicits an increased insulin secretion in order to maintain glucose stability. The relationship progressively deteriorates in impaired glucose tolerance and T2D, which are characterised by a reduction in insulin sensitivity (or increased insulin resistance) not compensated by a greater insulin release [7]. The inability of the β-cells to counteract the higher insulin resistance leads to the development of hyperglycaemia and the onset of clinical diabetes coincides with a significant decline of the secretory response [8–10].

Hyperglycaemia and elevated glycated haemoglobin (HbA1c > 6.5%) are the only criteria used for the diagnosis of diabetes and their correction is the primary target of diabetes management [11]. The current guidelines indicate a diagnosis of T2D if fasting concentrations of plasma glucose are above 7.0 mmol/L and/or 2-h post-challenge glucose concentrations are above 11.1 mmol/L [11]. The latter tests the efficiency of the endocrine pancreatic system to dispose of a standardized oral dose (75 g) of glucose (oral glucose tolerance test (OGTT)). However, the current clinical guidelines do not take into account the magnitude of the elevation of glucose levels (hyperglycaemic spike) after the challenge or the time for the glycaemia to return to baseline levels to guide diabetes management. The influence of post-challenge glucose elevations on metabolic or cardiovascular risk have been reported in large cohorts such as the Whitehall II [12] and Diabetes Intervention Study [13]. Similarly, post-prandial glucose peaks were a more significant predictor of cardiovascular events than fasting glucose and glycated haemoglobin (HbA1c) levels in a clinical sample of type 2 diabetic subjects [14]. Other studies using more controlled research protocols (clamp studies) have confirmed the insulin-independent effects of post-challenge hyperglycaemia on endothelial function and also on biomarkers of cardiovascular risk, which are mediated by an increased production of reactive free radicals [15–19].

Notwithstanding the accumulating evidence of a superior sensitivity of post-challenge hyperglycaemia as an index of cardio-metabolic risk, its application for the clinical management of diabetes is still secondary to the assessment of fasting glucose and HbA1c [11]. This position could be a consequence of the diverse methodological approaches used in the different studies for the assessment of post-challenge hyperglycaemia which has hindered the gathering of consistent and comparable evidence.

Definition of post-challenge hyperglycaemia

The association of cardio-metabolic risk with glucose levels lies on a continuous scale but convenient cut-offs for fasting and 2 h-OGTT glucose levels have been introduced for the diagnosis of diabetes in clinical practice. Glucose cut-offs of 7.0 mmol/L and 11.1 mmol/L have been used for the diagnosis of diabetes using fasting and 2 h-OGTT glucose levels, respectively. However, pre-diabetic states have also been identified and categorized respectively as impaired fasting glycaemia (fasting glucose level between 6.1 and 7.0 mmol/L) and impaired glucose tolerance (2-h OGTT glucose level between 7.8 and 11.1 mmol/L) [11]. Glycated haemoglobin (HbA1c) is non-enzymatically formed when haemoglobin is exposed to high plasma levels of glucose and it is routinely used in clinical practice to monitor the long-term effectiveness of diabetic therapies with the aim of reducing HbA1c to less than 7.0% [11,20].

The Gonzaga Diabetes study found that 2 h post-challenge glucose was a better predictor of coronary heart disease and cardiovascular mortality than fasting glucose and HbA1c levels [14]. The superior sensitivity of the post-challenge glucose is particularly relevant in subjects with otherwise apparently good glycaemic control (HbA1c < 7% or fasting glucose < 7 mmol/L). These subjects may have a more pronounced response to the oral challenge with differences in the magnitude and slope of the hyperglycaemic peaks. The assessment of the profile of the glycaemic curve is clinically relevant because hyperglycaemic peaks have been shown to be independent predictors of atherosclerosis and cardiovascular diseases in patients with and without type 2 diabetes [21,22].

ADMA is considered as a biomarker of endothelial dysfunction and it has been associated with an increased risk of atherosclerosis and cardiovascular diseases. The increased generation of ADMA and reactive oxygen species in subjects with persistent hyperglycaemia could lead to an impairment of nitric oxide synthesis.

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The American Diabetes Association (ADA) has recently reviewed the evidence for the association between cardio-metabolic risk and post-prandial glucose and the most recent recommendations are for a 2-h glucose below 7.0 mmol/L [23]. Similarly, the International Diabetes Federation has published an official statement recommending a less rigorous cut-off of 7.8 mmol/L for the management of post-challenge hyperglycaemia [24]. However, the adoption of post-challenge hyperglycaemia for the assessment of cardio-metabolic risk in clinical practice is still under debate [25].

The focus of diabetes research should in our opinion be shifted to the re-evaluation of the methods for the assessment of post-challenge hyperglycaemia in order to standardize measurements across studies and provide comparable evidence based results. This consideration is derived from the use of different methodological approaches used to induce (oral vs IV, glucose vs meal) [16,26,27] and/or to assess hyperglycaemia (time of hyperglycaemic spike, glucose after 1 hr, glucose after 2 hr, area under the curve) [1,21,22,28]. These variables are important physiological features of the glucose response and additional information on the extent of the hyperglycaemic stress on cellular functions could be provided by the measurement of variables such as the rate of post-challenge glucose elevation (strength), the rate of post-hyperglycaemic peak decline (intensity) or the difference between fasting and 2-h glucose (quality). These parameters are briefly outlined in Fig. 1.

The association of post-challenge hyperglycaemia and cardio-metabolic health

Post-challenge glucose is a better predictor of fatal and non-fatal cardiovascular events than fasting glucose and HbA1c [22]. The Hoorn study reported a significant association of 2-h post-challenge glucose with risk of cardiovascular mortality after 8 years even in subjects with normal fasting glucose and that 2-h glucose was a better predictor of mortality than HbA1c [29]. In addition, the association between cardio-metabolic risk and post-challenge glucose was not influenced by the study design (epidemiological and clinical investigations) [30,31], the type of population (population and clinical samples) [12,32], socio-
demographic characteristics (age, ethnicity) [31,33] and metabolic status (healthy, type 2 diabetes) [34,35]. Two meta-analyses, each of several thousands of subjects (>25000), have confirmed the higher sensitivity of the 2-h post glucose for the assessment of cardiovascular risk [36,37].

The stratification of hyperglycaemia showed a direct association of the cardio-metabolic risk with post-challenge glucose values which was confirmed in analyses using both 1 hr and 2 hr glucose levels [38,39]. The diagnostic value of the OGTT has been questioned as the glucose response would only provide a measure of the efficacy of the risk (the isolated consumption of a glucose drink is unlikely in free living individuals) whereas a meal test could provide a better estimate of glycaemic control as more representative of free-living situations (effectiveness). However, the glucose response obtained during an OGTT was significantly correlated to the glucose curve obtained in a test-meal [40]. The OGTT has also the additional advantages of being more practical and simple to apply in different settings, which promotes the standardization of the measurements across studies.

Another open question in this area is whether hyperglycaemic peaks and glucose excursions are more important predictors of cardiovascular risk than 2-h glucose. One study showed that hyperglycaemic peaks at any time after a meal increased atherosclerotic risk in type 2 diabetics [21]. Continuous glucose monitoring can be used to assess glucose excursions in free living conditions and the level of glucose variability can be estimated by calculating different indexes such as the mean amplitude of glycaemic variability (MAGE). This approach was recently employed in type 1 and type 2 diabetic populations to investigate the relationship between hyperglycaemia and oxidative stress but with controversial results[18,41,42]. The main difference was the lack of association between MAGE and 8-isoprostaglandin -F2α, a marker of oxidative stress, in type 1 diabetic patients[41,42]and type 2 diabetes treated with insulin[42] despite being characterised by a higher glucose variability compared to type 2 diabetes treated with oral hypoglycaemic agents alone. In this group of diabetic patients a significant association was found between MAGE and oxidative stress [18,42]. The discrepant results could be related to the inhibitory effects of insulin on the activation of inflammatory and oxidative response [42] as well as to technical limitations of the glucose monitors in their ability to detect rapid changes in glucose excursions and to provide accurate measurements of glucose levels (lower interstitial glucose levels compared to plasma levels)[43].

The effective management of diabetes is based on the daily assessment and monitoring of glucose levels in free living conditions using portable glucometers given to patients. An acceptable measurement error (=10–15%) [44] has to be balanced against the importance of assessing glucose control in subjects exposed to a normal diet, habitual lifestyle and individual socio-emotional interactions. Two large Italian studies have incorporated this method in a research protocol to assess the impact of post-prandial hyperglycaemia on metabolic health. Bonora et al. [34] conducted a study to assess the prevalence of post-prandial hyperglycaemia in subjects with T2D and found that the 40% of the patients had glucose excursions greater than 1SD (≥2.22 mmol/l) and they were commonly observed in subjects with HbA1c <7% and fasting glucose ≤6.66 mmol/l. Esposito et al. [21] used home-glucose monitoring to assess the relationship between post-prandial incremental glucose peaks and intima media thickness (IMT) in T2D. The study found a progressive increase in Hb1Ac and IMT across the quintiles of incremental glucose peaks. The effect of post-challenge hyperglycaemia on atherosclerotic risk was observed in another non-diabetic population where it was found that 2 h post-prandial glucose was a significant predictor of IMT after adjustment for sex and age whereas the contribution of fasting glucose to the model was not significant [45]. It is suggested that post-challenge hyperglycaemia is associated with endothelial dysfunction, the formation of atherosclerotic plaques and the progression of macro-vascular lesions which are directly related to coronary, peripheral and cerebral arterial diseases [17,22,46–48].

Endothelial function, nitric oxide and hyperglycaemic oxidative stress

The endothelium is a thin layer of cells covering the internal surface of blood vessels (intima) and in direct contact with circulating fluids [49,50]. Endothelial cells (ECs) and pericytes form the intima layer; the former have mechanical and regulatory functions and the latter providing structural support to the ECs and being involved in vascular growth (angiogenesis) [49]. Endothelial cells are continuously exposed to the mechanical forces of blood flow (shear stress). The endothelium is not passive to the action of these forces and reacts by adjusting tone and resistance via mechanisms involving several molecules (nitric oxide, endothelin 1, bradikinin, prostacyclines and tromboxanes, angiotensin II, acetylcholine, cathecolamines) [51–53]. The endothelium is a permeable membrane as it allows the transport of molecules and cells from the lumen into the interstitial space. The main isoform of glucose transporters expressed on endothelial cells is the insulin-independent carrier GLUT-1 [54]. The activation of the insulin receptor on the endothelial cells instead induces a vasodilatory response via the activation of the phosphoinositol-3-phosphate – Akt pathway which increases NO production by the enzyme endothelial nitric oxide synthase (eNOS) [55]. The exact mechanisms responsible for the release of glucose into the interstitial space are not completely understood and a different transporter which may or may not be dependent on sodium ions may be utilised to transport the glucose molecule across the basal membrane and release it into the interstitial fluid [6]. The endothelial cells therefore play a critical role in the glucose metabolism system and are consequently exposed to the deleterious effects of a rapid entry of glucose molecules into the cytoplasm, causing intra-cellular hyperglycaemia. Several other physiological functions have been ascribed to the endothelial cells (angiogenesis, inflammation, coagulation, adhesion, permeability) and review articles have already been published on these topics [56,57].

The most important signalling molecule to regulate blood flow in humans is NO, which is tonically released by the endothelial cells. Nitric oxide (NO) is an endothelium derived vasoactive mediator involved in a variety of
regulatory mechanisms in the cardiovascular system [58]. It is important in regulating vascular tone via endothelium dependent vasodilation [59], vascular structure via inhibition of smooth muscle cell proliferation [60] and cell—cell interactions via inhibition of platelet adhesion and aggregation [61]. NO is synthesised from the amino acid precursor L-arginine by NO synthases (NOS), which include type 1 or neuronal (nNOS), type 2 or inducible (iNOS) and type 3 or endothelial (eNOS) [50].

There is now growing evidence to suggest that NO release and/or bioavailability is reduced with consequent endothelial dysfunction in insulin resistance and type 2 diabetes [62]. Brownlee has suggested four main molecular mechanisms as being important in glucose-mediated vascular damage via overproduction of superoxide by the mitochondrial transport chain: increased polyol pathway flux, increased intra-cellular formation of advanced glycation end products (AGEs), activation of protein kinase C and increased flux through the hexosamine pathway [5]. According to this hypothesis, the increased generation of reactive oxidative species is the key element of the cellular deregulation related to the hyperglycaemic stress. The superoxide anion induces an inflammatory response (NFkB, RAGE, NAPDHoxidase) [63,64] and increase the expression of adhesion molecules on the plasma membrane to recruit circulating immune cells (V-CAM, E-CAM, MCP-1, E-Selectin) [65], it activates coagulation and platelet aggregability (tissue factor, PAI-1, pro-thrombin, vWF, nitric oxide, tromboxanes and prostacyclins) [66], stimulates vascular permeability and angiogenesis (VEGF, sFlt-1) [67], influences protein methylation (asymmetric dimethylarginine, homocysteine) [68] and increases vascular tone (ET-1, ANG-II) [69] (Fig. 2).

Asymmetric dimethylarginine (ADMA) may also be a key regulator of NO biosynthesis [62,70] and a number of studies have identified elevated plasma ADMA concentrations in T2D patients and insulin resistance related disorders (obesity, polycystic ovary syndrome, hypertension) [71–73].

### Asymmetric dimethylarginine and nitric oxide production

NOS can be selectively inhibited by guanidino-substituted analogues of arginine, including endogenously produced ADMA which is a naturally occurring amino acid which acts as a competitive inhibitor of NOS [74] particularly nNOS and eNOS and, to a lesser extent, iNOS [75]. ADMA concentrations are ten-fold higher than the other endogenous inhibitor, N-monomethyl-L-arginine (L-NMMA) and ADMA is therefore considered the predominant species [70]. Arginine contains two amino groups that can be methylated with three possible conformations as a result of methylation [76]. Methylated arginines are synthesised when protein arginine methyltransferases (PRMTs) methylate arginine residues in proteins [77] with type 1 PMRTs catalysing production of asymmetrically methylated arginines and type 2 PMRTs catalysing production of symmetrically methylated arginines [76,78].

ADMA is eliminated by renal excretion (20%) and metabolic degradation (80%) [75]. It is partially excreted in urine and therefore accumulates in patients with renal failure [74,79] but is predominantly removed by catabolism via the enzyme dimethylarginine dimethylaminohydrolase (DDAH) [62,77,80] which catalyses one molecule of ADMA into one molecule of L-citrulline and one molecule of dimethylamine [75]. Two isoforms of DDAH exist, with DDAH-1 predominating in tissues expressing nNOS such as kidneys and liver, and DDAH-2 predominating in tissues expressing eNOS such as endothelial suggesting tissue specific regulation of ADMA [75,81].

Both the synthesis and degradation of ADMA appear to be highly regulated with dysregulation leading to increased levels which may contribute to endothelial dysfunction [82]. As ADMA can only be synthesised from protein methylation and not from free arginine, concentration is dependent on protein turnover, rate of arginine methylation, DDAH activity and extrusion from the cell [77]. In humans, ADMA reduces heart rate and cardiac output, increases systemic vascular...
Asymmetric dimethylarginine, nitric oxide and post-challenge hyperglycaemia

In both animal models and human endothelial cells, elevated glucose levels have been shown to impair DDAH activity leading to accumulation of ADMA suggesting an important link between hyperglycaemia and ADMA [88]. In studies of human umbilical vein and coronary artery endothelial cells TNFα decreases DDAH activity leading to ADMA accumulation. This effect can be inhibited in a dose dependent manner by insulin and adiponectin which suggests that multiple mechanisms are involved. It is thought that adiponectin counteracts the TNFα induced accumulation of ADMA through the DDAH pathway [89].

Increased levels of ADMA have been found in both type 1 [86] and type 2 [90] diabetes. A study of 18 non-diabetic and 16 T2D patients found that plasma concentrations of ADMA are significantly higher in T2D patients, suggesting that abnormal ADMA regulation may play a role in the endothelial dysfunction and accelerated CHD risk in T2D patients [90]. It is thought that ADMA may accumulate due to both increased production, as a result of redox-sensitive activation of protein arginine N-methyltransferases (PRMTs) which form ADMA [91], and decreased degradation as a result of redox-sensitive dimethylarginine dimethylamino-hydrolase (DDAH) inactivation, the enzyme which degrades ADMA [92]. It is therefore thought that oxidative stress results in elevated levels of ADMA that inhibit NOS activity [93]. The association between fasting glucose and ADMA levels has been tested by plotting average fasting glucose values reported in 66 manuscripts published in the medical literature which have shown the significant association of glycaemia with ADMA levels compared to BMI and systolic blood pressure (Fig. 3).

The evidence on the effect of post-challenge hyperglycaemia on changes in ADMA levels is scarce as only two studies has investigated this relationship [94,95]. The acute response of ADMA during a standard 75 g OGTT in subjects with normal glycaemia, impaired glucose tolerance and type diabetes was tested [94]. ADMA responded acutely to the increase in circulating glucose and after 2 h ADMA levels were increased by 33% in healthy subjects, 30% in subjects with impaired fasting glycaemia and 45% in type 2 diabetics [94]. Changes in ADMA after a 2-h OGTT were not reported in another study comparing lean subjects to obese and older aged subjects [95]. However, ADMA levels were directly correlated with 2-h glucose and inversely correlated with glucose infusion during a hyperinsulinaemic euglycaemic clamp [95]. ADMA significantly increased after 5 h in patients with type 2 diabetes consuming a high fat meal while glucose levels remained elevated (7.5 mmol/L) but constant during the entire duration of the test [96]. On the contrary, in healthy subjects high insulin levels during a hyperinsulinaemic normo-glycaemic clamp determined a small but significant decrease (12%) in ADMA levels compared to saline infusion [97]. Further research is therefore warranted to understand the effects of acute post-prandial glycaemia on changes in ADMA levels and NO production.

The detrimental effects of ADMA are thought to be primarily due to reduction of NO via concentration-dependent competitive inhibition of NOS [78]. However, elevated ADMA levels are also thought to lead to increased generation of the superoxide anion radical (O2·) which is produced by NOS when its substrate (l-arginine) or cofactor (tetrahydrobiopterin) are depleted, in an effect called ‘uncoupling’ [78,98]. ADMA levels may lead to decreased NO as ADMA, L-NMMA and SDMA all compete with cellular uptake of l-arginine by plasma membrane cationic amino acid transporter (y+1) and can therefore lead to decreased intracellular concentrations [78,98]. Finally it is suggested that ADMA may help regulate angiogenesis as increased ADMA in mice with DDAH-1 over-expression is associated with enhanced angiogenesis [78]. These mechanisms are thought to attenuate the vascular regulatory effects of NO leading to a pro-inflammatory state that promotes atherosclerosis [78]. ADMA may also be able to alter β-cell function as nNOS which is present in β-cells exerts a tonic inhibitory effect on insulin secretion and nNOS inhibition leads to amplified
insulin secretion and suppression of the biphasic pattern of normal insulin response [99]. ADMA concentrations can be increased by increased PMRT activity while PMRT inhibition reduces ADMA levels. It is also known that shear stress, oxidised LDL (ox-LDL) and LDL-cholesterol increase PMRT activity and ADMA synthesis [81] and while increased free fatty acids (FFA) do not acutely increase ADMA concentrations, prolonged exposure to FFA leads to increased ADMA secretion in vitro which suggests chronic elevation of FFA may also increase ADMA concentrations [100].

The mechanisms tested in these studies are summarised in Fig. 4. The emphasis is on the hyper-generation of superoxide anion which is linked to: 1) the reduction in NO production by direct quenching and formation of peroxynitrite (ONOO⁻) and 2) the increase in intra-cellular concentrations of ADMA capable of down-regulating eNOS and cause a further increase in the generation of O₂⁻ by uncoupling eNOS.

Research needs and potential therapeutic targets

The relationship between post-challenge hyperglycaemia and increased generation of reactive oxygen species and ADMA is still largely unexplored and experimental investigations are needed to determine the causality and direction of the association. The studies should also aim at determining the effects of acute versus chronic hyperglycaemia on changes in levels of ADMA, NO and their effects on endothelial function. Supplementation of arginine or antioxidants could potentially improve endothelial function by reducing the intra-cellular ADMA/arginine ratio and the production of oxygen species. Nitrate supplementation could also be used to increase the enzyme independent production of NO whereas supplementation of Nω-hydroxy-L-arginine (NOHA), the intermediate product of the
reaction between arginine and NO, may represent a viable therapeutic route to increase the production of NO by bypassing the inhibitory effects of ADMA on eNOS.

Conclusions

It is suggested that post-challenge glucose levels are better markers of vascular dysfunction and cardiovascular events than fasting glucose in diabetic and non-diabetic subjects. Post-challenge hyperglycaemia causes an increased generation of reactive free radicals which can impair endothelial function and nitric oxide synthesis via an increased generation of ADMA. Asymmetric dimethylarginine and post-challenge hyperglycaemia are potential biomarkers of cardio-metabolic health but more evidence needs to be gathered before they could be introduced in clinical practice for the assessment of cardiovascular and metabolic risk.

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