Editorial

Diabetes, Obesity and Vascular Disease - An Update

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The increasing prevalence of diabetes mellitus (DM) [1, 2] and obesity [3, 4] inevitably leads to greater morbidity due to vascular disease [1, 2, 5]. As regards type 2 DM, the recent guidelines issued by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [6] are expected to promote more evidence-based and efficacious antidiabetic treatment [7]. However, unresolved issues remain. The present issue of the journal provides an update on DM, obesity and vascular disease.

Banach *et al.* [8] discuss the growing concern about new-onset diabetes after statin therapy. This class of agents is important for the reduction of cardiovascular (CV) morbidity [9, 10]. Nevertheless, a number of untoward effects in terms of insulin sensitivity and secretion, as well as adipokine production, associated with their use are now being recognised [8, 11, 12]. Data pertaining to their effect on other adipokines is contradictory [8]. In practice, the risk for new, statin-induced DM appears to be mainly dose-dependent, while older age and pre-existing borderline glucose elevation may also play a role [13]. At the same time, the beneficial reduction in CV events accomplished by statin treatment in such patients outweighs the potential risk of DM [13]. Thus, identification of those at high risk of DM and balancing the risk *vs* benefit in the individual patient is emerging as a therapeutic choice [8]. Further knowledge is urgently needed in this area.

Another drug-associated safety concern is the increased risk of bladder cancer following pioglitazone therapy, as discussed by Kostapanos *et al*. [14]. This thiazolidinedione has been on the market for more than 10 years and is a useful component of antidiabetic therapy [14]. It should not escape our notice that clinical data on bladder cancer among pioglitazone-treated subjects are mostly observational and rather contradictory [15-17]. A dose- and time-dependent relationship between pioglitazone treatment and bladder cancer has been noted and older age appeared to increase this risk [14]. PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) was the sole prospective trial providing data on cancer risk: it documented an insignificant increase of bladder cancer among pioglitazone-treated patients, but mean follow-up was only 34.5 months and the number of events was very small [18]. To increase complexity, DM and obesity are associated with increased cancer risk independently of antidiabetic treatment [19,20]. As regards bladder cancer specifically, smoking is also relevant [21]. Hence, the association between pioglitazone and bladder cancer needs to be viewed with caution and placed in the overall context of cancer risk factors [14]. Of relevance, experimental data suggest a protective effect of pioglitazone in other cancer sites, while corresponding clinical data are currently inadequate and contradictory [14]. Thus, the authors [14] conclude that future prospective clinical trials taking into account all implicated risk factors should re-address the issue of pioglitazone-induced bladder cancer. The opinion of the editors is that there is a need for re-enquiry into the relationship between antidiabetic agents and carcinogenesis. In this context, it is now being appreciated that metformin has a potential to protect from cancer [22].

A further relevant issue is serum uric acid (SUA) in DM (reviewed by Katsiki *et al*.) [23]. Hyperuricaemia is associated with the metabolic syndrome (MetS) [24] and vascular morbidity and mortality [25]. In pre-diabetes and early DM, relative hyperinsulinaemia enhances tubular re-absorption of uric acid in the kidney, resulting in elevated SUA concentration [26, 27]. However, as hyperglycaemia increases, glycosuria leads to diminished SUA levels [23, 24, 26, 27]. In this context, persistent elevation of SUA reflects hyperinsulinaemia and insulin resistance, and so it has been identified as a predictor of progression to overt type 2 DM [23]. In the latter state, hyperuricaemia is driven by obesity, MetS, impaired kidney function and certain drugs (e.g. thiazides, niacin and low-dose salicylic acid) [23]. Conversely, antidiabetic agents, statins, fenofibrate and other agents may reduce SUA levels [23]. Moreover, patients with diabetic neuropathy have been shown to have higher SUA levels compared with those without this complication [28, 29]. Similarly, elevated SUA has been noted in the presence of other diabetic microvascular [30-33] and macrovascular complications [34-36]. Of note, efficacious antidiabetic treatment may contribute to the diminution of SUA [23]. In the light of these considerations, it remains to be ascertained whether prospective SUA evaluation and its pharmaceutical reduction are of prognostic significance in DM.

Pharmacotherapy for obesity currently offers limited options, but new drugs are being developed, as reviewed by Gouni-Berthold *et al*. [37]. Anti-obesity drugs are used either as monotherapy or in combination [37]. Among several agents at various stages of development, *Qnexa*, *Contrave* and glucagon-like peptide-1 (GLP-1) analogues are the most promising [37]. *Qnexa* (FDA approval in 2012) is a combination of phentermine (an amphetamine derivative, adrenergic agonist and appetite suppressant) and topiramate (a neurostabilizer and anhydrase inhibitor) [38]. *Contrave* is a combination of the antidepressant bupropion and the opioid receptor antagonist naltrexone [39]. Liraglutide is a long-acting injectable synthetic analogue of GLP-1, which has been approved for the treatment of DM [40, 41]. Despite some favourable results, 2 major unsettled issues remain. First, more data on safety is required. Secondly, we need more experience with their long-term efficacy, given that management of obesity necessitates lifelong diet, exercise and/or treatment. Currently, this information is rather limited, and so caution in the interpretation of results is warranted [37].

In the context of targeting atherosclerosis, ghrelin, a peptide hormone produced mainly in the stomach, may prove useful (reviewed by Rizzo *et al*.) [42]. There is evidence that this hormone exerts a number of beneficial CV effects in humans, including reduction of blood pressure, increase of myocardial strength, and vasodilatation [42]. It also appears that ghrelin may exert an anti-inflammatory action [43]. However, there is also evidence of adverse metabolic actions of ghrelin, notably induction of lipolysis and insulin resistance [42, 44], along with suppression of pancreatic insulin secretion, impaired glucose tolerance and hyperglycaemia [41, 45]. To the best of current knowledge this apparent paradox in terms of beneficial and unfavourable actions of ghrelin may be explained by differences in ghrelin levels (supraphysi-

ologic *vs* physiologic concentrations) and clinical conditions (normal *vs* established atherosclerosis). There is a long way to go until therapeutic implementation of ghrelin can become a reality.

Lioudaki *et al*. [46] review the importance of microalbuminuria in non-diabetic subjects. The link with increased CV risk is largely attributable to the association of microalbuminuria with hypertension, atherosclerosis, endothelial dysfunction, insulin resistance, MetS, impaired kidney function and systemic inflammation [47, 48]. Better appreciation of the role of microalbuminuria is, therefore, advocated [46]. This interpretation may include a revised definition of microalbuminuria [49] and more aggressive therapeutic intervention.

Diabetic neuropathy is a major complication of DM and Várkonyi *et al*. [50] provide an update on its treatment. First, optimal glycaemic control is important, more so for type 1 than for type 2 DM [51]. Traditional CV risk factors (hyperlipidaemia, hypertension, smoking and obesity) should also be addressed [50]. Furthermore, there is a role for pathogenesis-oriented treatment, namely use of aldose reductase inhibitors, benfotiamine, alpha-lipoic acid and other less studied agents [50]. Alpha-lipoic acid is promising, as demonstrated in a recent 4-year trial [52]. Finally, symptomatic treatment mainly aims to alleviate neuropathic pain by use of modern anticonvulsants (pregabalin, gabapentin and others), antidepressants (duloxetine, traditional tricyclic agents), opiates, locally applied options (capsaicin, lidocaine) and non-pharmacological measures (e.g. physical exercise, phototherapy, transcutaneous electrical nerve stimulation or acupuncture) [50]. Combination therapy can be used [50], but further progress with this approach is eagerly awaited.

The diabetic foot is a grim complication that may lead to limb loss [53]. Edmonds [54] reviews the treatment of infection and ischaemia. Prompt initiation of aggressive antibiotic therapy, appropriate surgical debridement and revascularisation as necessary remain the main therapeutic principles [54]. Especially the need and the degree of urgency for revascularisation call upon the experience of the clinician to decide on a case-by-case basis [54]. Progress in revascularisation modalities, particularly endovascular treatment, has dramatically improved outcomes [55]. Not to be underestimated, all treatment should be offered in the setting of a multidisciplinary foot clinic [53, 54, 56-58].

The articles in the present special issue suggest that substantial progress has been achieved in the field of DM, obesity and vascular disease. However, several areas require further research to improve outcomes.

Comment on Relevant Topics not Covered in this Issue of the Journal:

Several topics are not covered in the present issue of the journal due to limitations of space. Among these is the thrombotic diathesis associated with DM. Furthermore, there is evidence that antiplatelet therapy is not as effective in patients with DM in comparison to those without DM. This subject is considered elsewhere [59-62]. The present issue of the journal also did not cover type 2 DM prevention in the general population. This topic deserves considerable attention and has been the subject of appropriately designed trials in the past and present [63-67]. Its importance is enhanced by the more recent recognition that microvascular complications may begin to develop even in the prediabetic phase [68]. Gestational DM is also a specific aspect of both DM prevention and management that requires greater recognition [69]. Moreover, diabetic retinopathy remains a common cause of blindness worldwide. There is no doubt that we need to improve screening programmes to provide appropriate treatment as early as possible [70-72]. However, we also need more research into the association of modifiable risk factors with retinopathy.

Pancreatic beta-cell transplantation may well become the future treatment for DM [73]. This option will be the subject of extensive research in the following years. Finally, hypoglycaemia and level of glycaemic control present another currently active debate regarding optimal antidiabetic treatment [74, 75].

Clearly, the treatment of DM is a vast topic that is constantly being updated [76]. We hope to return in the future with another issue of the journal dedicated to this theme.

CONFLICTS OF INTEREST

This editorial was written independently. No company or institution supported it financially. N Papanas has been an advisory board member of TrigoCare International, has participated in sponsored studies by Novo Nordisk and Novartis, has received honoraria as a speaker for Novo Nordisk and Pfizer and has attended conferences sponsored by TrigoCare International, Novo Nordisk, sanofi-aventis and Pfizer. N Katsiki has attended conferences sponsored by AstraZeneca, Pfizer and Merck Sharp & Dohme (MSD). Zsuzsanna Putz has had speaking engagements from Eli Lilly and Novo Nordirsk. DP Mikhailidis has been an advisory board member and speaker for MSD and has attended conferences sponsored by AstraZeneca, sanofi-aventis and MSD.

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