

Metabolic Syndrome and Microangiopathy

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In their article in this issue of *IMAJ*, Abdul-Ghani et al. report [1] a significant clinical association of three medical entities: type 2 diabetes mellitus, metabolic syndrome and microvascular disease. They emphasize that diabetic patients with criteria for the metabolic syndrome develop more microvascular complications as compared to diabetic patients without the syndrome.

The link between diabetes mellitus and microangiopathy has been well established. In the prospective Diabetes Control and Complications Trial [2] it was demonstrated that intensive glycemic control in patients with type 1 diabetes mellitus delayed the appearance of microvascular complications, especially when hemoglobin A1C was below 7%, and also slowed progression of established microangiopathy. In addition, the United Kingdom Prospective Diabetes Study [3-5] showed that intensive glycemic control in type 2 diabetic patients reduced microvascular complications, but this reduction was far more significant when hypertension was better controlled (a reduction of hypertension from 154/87 to 144/82 mmHg had greater impact on the appearance of microvascular complications than a reduction of HgA1c from 7.9% to 7%).

On the other hand, although the link between metabolic syndrome, diabetes mellitus and cardiovascular disease is well known, the association between the former and microangiopathy is less obvious. There is, however, emerging data that support this association and the results obtained by Abdul-Ghani and his team [1].

First, there is evidence that each individual criterion of the metabolic syndrome, either defined by the World Health Organization [6], or the NCEP-III (National Cholesterol Education Program) [7], is significantly associated with an increased incidence of microangiopathy in diabetic patients (who were not defined as having the metabolic syndrome), independently of hyperglycemia and hypertension (known risk factors for microangiopathy in diabetic patients). For example, renal microangiopathy has been linked to low density lipoprotein-cholesterol levels and size in patients with type 1 diabetes mellitus [8,9]; in type 2 diabetic patients, renal nephropathy was associated with high total cholesterol levels, low high density lipoprotein levels, high LDL levels, and hypertriglyceridemia [10]; diabetic retinopathy has been linked to higher waist-hip ratio [11]; and distal symmetric diabetic neuropathy in patients with type 1 diabetes mellitus was found to be related to cardiovascular risk factors such as dyslipidemia, elevated body mass index and smoking [12]. It is important to note that microangiopathies

may interact together, as evidenced by reports of increased urinary albumin excretion in type 2 diabetic patients associated with the development of retinopathy and neuropathy [10]. Last but not least is the discovery of the influence of elevated C-reactive protein levels, a strong marker of inflammation. Indeed, high CRP levels are associated with the occurrence and progression of microalbuminuria even in patients without diabetes mellitus [13], but are also higher in type 2 diabetic patients with the metabolic syndrome than in patients without (and therefore CRP is considered by some authors as an added criterion of the metabolic syndrome), and were statistically significantly associated with the development of diabetic nephropathy [14]. Thus, the fact that microangiopathy in diabetes mellitus is mediated by parameters that are components of the metabolic syndrome helps us to understand the association between microangiopathy and the metabolic syndrome. We could therefore anticipate that patients with the metabolic syndrome without diabetes are prone to develop microvascular disease, in addition to macroangiopathy. It seems, however, that both diseases together entail more microangiopathic complications together than each one individually.

The association of diabetes mellitus, microangiopathy and metabolic syndrome is related to their effect on endothelial function. Indeed, the first two risk factors for microangiopathy that were identified in diabetic patients were, as mentioned above, poorly controlled glycemic levels and hypertension [15], and both were found to lead to endothelial dysfunction. The former (i.e., hyperglycemic status) induces glucose toxicity by several possible different molecular mechanisms (the polyol pathway, advanced glycation end-products pathway, the reactive oxygen intermediate pathway, the protein kinase C pathway), which induce oxidative stress and also lead to endothelial dysfunction and damage, characterized by abnormal angiogenesis, blood flow and/or contractility [16]. The latter (i.e., hypertension) leads to elevated soluble adhesion molecules [17], and impaired nitric oxide availability [18]. It seems logical that the same pathophysiologic mechanisms lead to microangiopathy in patients with the metabolic syndrome. Indeed, it was found that other components of the metabolic syndrome are also involved in endothelial dysfunction [15]. Dyslipidemia participates in endothelial dysfunction as triacylglycerol-rich lipoproteins increase oxidative stress (and is therefore associated with the development of nephropathy), and obesity might also lead to endothelial dysfunction via modulation of the secretion of mediators

LDL = low density lipoprotein

CRP = C-reactive protein

by adipocytes, such as fatty acids, tumor necrosis factor-alpha and adiponectin. Moreover, endothelial dysfunction in diabetes mellitus type 1 and 2 is worsened by increased microalbuminuria (higher plasma levels of von Willebrand factor and soluble E-selectin) and is associated with a chronic low grade inflammation (CRP has a pro-atherogenic effect via decreased expression of nitric oxide and prostacyclin and increased expression of endothelin-1, cell adhesion molecules monocyte chemoattractant protein-1, interleukin-8, plasminogen activator inhibitor-1).

This inflammatory state might be the source of the insulin-resistance state that is common to type 2 diabetes mellitus and the metabolic syndrome [19]. It was recently shown that insulin suppresses the expression of pro-inflammatory genes such as nuclear factor-kappa B, Egr-1, and activating protein-1. Insulin was also found to have an antioxidant effect by decreasing reactive oxygen species and expression of p47^{phox}. However, inflammatory mediators were found to counterbalance all the anti-inflammatory effects of insulin; for example, tumor necrosis factor-alpha induces serine-phosphorylation of the insulin receptor and interferes with insulin signal transduction. Many other key proteins, such as SOCS3, TRB3 and Akt2, which might be expressed in the inflammatory state, interfere with the insulin receptor by different mechanisms and thereby interfere with the insulin signal transduction, leading to an insulin-resistant state, which in turn increases the expression of pro-inflammatory factors (as we have seen, insulin acts as an anti-inflammatory agent), and consequently increases endothelial dysfunction.

In conclusion, there is accumulating evidence that the association between diabetes mellitus and the metabolic syndrome is a potent mediator of elevated inflammatory markers, the insulin resistance state and endothelial dysfunction. Micro and macroangiopathies share similar risk factors. In patients with metabolic syndrome but without diabetes, impaired fasting glucose is mainly associated with a significant risk for microvascular complications, whereas impaired glucose tolerance is primarily associated with the development of macrovascular complications [20]. How might different patterns of glucose disorder influence the development of vascular complications? There is no clear answer for this at the moment but genetic factors may play a role. The pathophysiology of microangiopathy and macroangiopathy in patients with diabetes and/or metabolic syndrome appears still to be very complex. Finally, therapeutic options should focus on the prevention of vascular complications by reduction of the inflammatory and the insulin-resistant states. Some options include a low caloric diet, exercise, administration of statins, metformine, agonist to peroxysome proliferator-activated receptor-gamma, and perhaps in the future, drugs against transcription of pro-inflammatory cytokines.

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