Editorial

(Postprandial) hyperglycemia is (cardio)vascular disease: are new concepts for diagnosis and treatment required?

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At present, there is a change of paradigm concerning the relationship between diabetes mellitus and cardiovascular disease[1]. Hyperglycemia is incrementally recognized to be not only a risk factor but an equivalent to coronary heart disease[2].

The combined incidence of diabetes and cardiovascular disease gives evidence for this association. About 80% of patients with diabetes die from cardiovascular disease. Looking to the other side of the coin, the incidence of diabetes and its subclinical pre-stage, impaired glucose tolerance, is considered to be about 20% in an unselected European population. However, there is a dramatic change, if addressing this very prevalence in patients with acute coronary syndrome, where it accounts to 85%[3]. The constituents are 20% known/treated diabetes, 25% newly diagnosed diabetes on the coronary care unit and, additionally, 40% with impaired glucose tolerance as diagnosed from an oral glucose tolerance test at the ward which corresponds to the accuracy by this test performed 3 months after discharge. In other words, from 5 patients with acute coronary syndrome, 4 had at least intermittent hyperglycemia, 3 of these had not yet been diagnosed, and 2 do not fulfill the present definition of diabetes mellitus[4]. Similarly, undiagnosed diabetes mellitus or impaired glucose tolerance with an incidence of about 40% has been observed in a study on the prevalence of diabetes mellitus in a 55-74-year-old German population and half of the total cases of diabetes were previously undiagnosed[5].

Indeed, there is a very close relation between loss of glycemic control and cardiovascular disease. A meta-regression analysis on 95 783 patients[6] has clearly shown that the risk for cardiovascular disease has a direct correlation not only with the fasting but in particular with the postprandial plasma glucose concentration; the latter contains significantly more risk than the fasting blood glucose value of the same individual patient would suggest – at least for the current definition of diabetes mellitus[4]. Still, there is inadequate awareness amongst cardiologists that reactive = postprandial hyperglycemia bears a more severe prognosis in acute coronary syndromes. As a consequence, hyperglycemia is often neglected and undertreated at the coronary care unit. However, cardiologists should perform screening glucose checks 2 hours after the first breakfast at the coronary care unit to establish early and aggressive treatment of hyperglycemia accordingly. If indicated, the diagnosis should be confirmed by an oral glucose tolerance test 4-5 days after admission by taking advantage from the diagnostic accuracy of the test at this early stage[3].

Biochemical/biophysiological investigations provided more insight into the complex mechanisms which link type 2 diabetes and its pre-stage impaired glucose tolerance and insulin resistance with the pathologic processes underlying arteriosclerosis (Fig. 1).

The basis for the intertwinement of hyperglycemia and cardiovascular damage is insulin resistance, which is associated with obesity, hyperlipidemia, endothelial dysfunction and hypertension, known as metabolic syndrome. It is worthwhile stating the

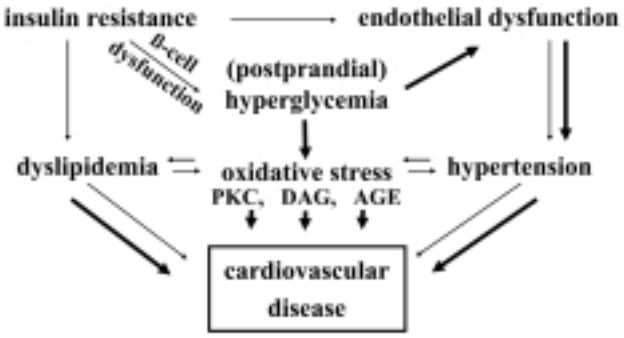

Figure 1. *Scheme of the intertwinement between hyperglycemia and cardiovascular damage.* Thin arrows *demonstrate the sequelae of the traditional cardiovascular risk factors,* thick arrows *demonstrate the sequelae of hyperglycemia. AGE = advanced glycation end products; DAG = diacylglycerol; PKC = protein kinase C.*

pivotal role of obesity and adipocytes with their proinflammatory cytokines in inducing insulin resistance and metabolic syndrome. Insulin resistance plus β-cell dysfunction leads primarily to (postprandial) hyperglycemia. Acute hyperglycemia induces further impairment of endothelial dysfunction and via this mechanism some additional rise in blood pressure. At the same time, hyperglycemia induces changes in many metabolic pathways leading to acute generation of free oxygen radicals, activation of protein kinase C and diacylglycerol which enhance vascular wall changes and inflammatory steps and the generation of advanced glycation end products which increase vascular permeability, cell proliferation, coagulability and production of extracellular matrix proteins[7,8]. Thus, there are many direct and indirect mechanisms by which (repetitive postprandial) hyperglycemia may promote atherogenesis and predispose diabetic and non-diabetic individuals to cardiovascular disease.

The complex relationship between impaired glucose metabolism and cardiovascular damage suggests, however, multiple therapeutic approaches in order to reduce or prevent hyperglycemia and, accordingly, hyperglycemia-induced cardiovascular disease: insulin resistance is counteracted by weight reduction. Hyperglycemia may be (partially) reduced/prevented by appropriate diet. Most importantly, endothelial function is enhanced by exercise and physical training[9]. Obviously, hyperglycemic plasma glucose values are normalized by pharmacological antidiabetic agents; in this context, acarbose which specifically lowers postprandial hyperglycemia might be particularly suitable in the stage of impaired glucose tolerance[10]. The sequelae of insulin resistance which are classified as classical cardiovascular risk factors can be successfully treated such as hyperlipidemia with statins, low high-density lipoprotein levels by physical exercise and nicotin acid[11] and hypertension with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers which have been shown to be very effective in reducing the occurrence of diabetes in hypertensive patients[12]. Finally, inflammatory/thrombotic processes may be counteracted by the respective agents, most commonly by the use of aspirin.

Indeed, there is increasing evidence from large trials that the very development of diabetes mellitus may be prevented/delayed by most of these approaches. In the group of lifestyle changes, which imply weight reduction of 10%, diet and 30 min exercise daily, three studies have demonstrated impressive success with a relative risk reduction for the development of diabetes in the range of 50%[13-15]. In the group of pharmacological antidiabetic agents, this risk reduction has been shown to be around 30% for metformin[15] and acarbose[10]. Acarbose has also reduced the risk for the development of hypertension by 34% and, additionally, for cardiac events by 49% confirming in this way the intertwined relationship between intermittent hyperglycemia and cardiovascular disease. Particularly interesting is a 50% risk reduction for the development of diabetes mellitus in the TRIPOD study[16] where a glitazone was used to reduce insulin resistance in Hispanic female individuals. Finally, even treatment of classical cardiovascular risk factors by angiotensin-converting enzyme inhibitors[17], angiotensin-receptor blockers[12] or statins[18] has been shown to be effective with a 30% risk reduction for developing diabetes mellitus, thus confirming the intricate crosslinking/identity between cardiovascular pathology and hyperglycemia.

In summary, impaired glucose metabolism must be considered a vascular disease which is manifest/diagnosed by elevated (postprandial) plasma glucose. It certainly is a unique chance for the hitherto undiagnosed patients combined with a considerable challenge for modern cardiologists, diabetologists and general practitioners. There is a *continuum* of risk with elevated blood glucose like with elevated blood pressure. Therefore, in the treatment of cardiovascular risk, it is effective to address not only inflammatory/thrombotic, hypertensive and hyperlipidemic elements but in particular postprandial hyperglycemia far beyond the present definitions for therapy of diabetes mellitus. In this context, lifestyle modifications should be the first choice[19,20].

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