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Review

Metabolic memory phenomenon in diabetes mellitus: Achieving and perspectives

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ABSTRACT

Diabetes mellitus (DM) exhibits raised prevalence worldwide. There is a large body of evidence regarding the incidence of DM closely associates with cardiovascular (CV) complications. In this context, hyperglycaemia, oxidant stress, and inflammation are key factors that contribute in CV events and disease in type1 and type 2 DM, even when metabolic control was optimal and/or intensive glycemic control was implemented. It has been suggested that the effect of poor metabolic control or even transient episodes of hyperglycemia in DM associates in particularly with worsening ability of endogenous vasoreparative systems that are mediated epigenetic changes in several cells (progenitor cells, stem cells, mononuclears, immune cells), and thereby lead to so called "vascular glycemic memory" or "metabolic memory". Both terms are emphasized the fact that prior glucose control has sustained effects that persist even after return to more usual glycemic control. The mechanisms underlying the cellular "metabolic memory" induced by high glucose remain unclear. The review is discussed pathophysiology and clinical relevance of "metabolic" memory phenomenon in DM. The role of oxidative stress, inflammation, and epigenetics in DM and its vascular complications are highlighted. The effects of several therapeutic approaches are discussed.

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1. Introduction

Despite increase prevalence of diabetes mellitus (DM) worldwide [1–3] and well-developed diagnostic approaches and contemporary medical care [4–6], relatively little is known about disease progression at early stage [7]. Under diagnosis of DM is a critical

Abbreviations: DM, diabetes mellitus; CV, cardiovascular; IL, interleukin; IGF-1, insulin-like growth factor-1; miRNA, micro RNA; NF-κB, nuclear factor κB; PPARγ, peroxisome proliferator-activated receptor γ; PAI-1, plasminogen activator inhibitor-1; ROS, reactive oxygen species; SGLT2, sodium-glucose linked transporters; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

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problem affected prevention of acute and chronic cardiovascular (CV) complications and target-organ damage including diabetes-related nephropathy and retinopathy [8–10]. However, recent clinical and observational studies have revealed that DM complications were highly prevalent among subjects with both diagnosed and undiagnosed DM, even when metabolic control was optimal and/or intensive glycemic control was implemented [11–13]. Taking into consideration that CV complications of DM may significantly impact the CV and all cause mortality, well being, and quality of life, the risk stratification of the DM individuals at early stage of the disease appears to be essential for further medical approaches. On the one hand, the period of poor metabolic control within evolution of the disease leads to negative consequences, such as an increase in the development of endothelial dysfunction, atherosclerosis, cardiomyopathies, heart failure, kidney disease, and progression of CV complications. On the other hand, CV complications may seriously limit the efficacy of glucose-lowering therapy because of full glucose control has usually not achieved. Overall, it has been resumed that DM patients with the high levels of CV co-morbidity may receive diminished CV benefit from intensive blood glucose control [14,15]. Moreover, CV co-morbidity should be considered when tailoring glucose-lowering therapy in patients with type 1 and type 2 DM [16]. Unfortunately, after period of poor glycemic control in DM individuals it was not possible to completely prevent a manifestation of CV complications or achieve a reverse of disease progression [17]. Indeed, type 1 DM have been exhibited a close link between hyperglycemia existed prior to glucose-lowering therapy and both micro- and macro-vascular DM complications [11]. Large randomized studies have established that optimize glycemic control in type 1 DM may reduce DM-related target-organs' damage, whereas the risk of disease progression has not minimized completely. The results of the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have been shown intensive glycemic control added to multi factorial intervention might reduce the CV incidence and improve clinical outcomes. Contrary, results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, and Veterans Affairs Diabetes Trial (VADT) have shown that intensive glycemic control to near normoglycemia might have potentially detrimental effect on CV outcomes in type 2 DM individuals [18–23]. It has been suggested that the effect of poor metabolic control or even transient episodes of hyperglycemia in DM associates in particularly with worsening ability of endogenous vasoreparative systems that are mediated epigenetic changes in several cells (progenitor cells, stem cells, mononuclears, immune cells), and thereby lead to so called "vascular glycemic memory" or "metabolic memory". This phenomenon is induced via inflammatory, metabolic, and oxidative stimuli, direct cell-to-cell cooperation, microvesicles' secretion, and plays a pivotal role in DM-related CV complications irrespective tight metabolic control. The aim of the mini review is summary knowledge about pathophysiology and clinical relevance of "metabolic memory" phenomenon in DM.

2. Definition of glycemic memory

Glycemic memory phenomenon defined as the persistence of DM complications even after glycemic control has been pharmacologically achieved [24]. Glycemic memory is considered a part of generally term "metabolic memory" that is mostly wide and usually use as definition of systemic metabolic dysregulation in DM [25]. Both terms "metabolic memory" and "glycemic memory" are emphasized the fact that prior glucose control has sustained effects that persist even after return to more usual glycemic control. Consequently, glycemic memory phenomenon is clinical term, which describes tissue dysfunctions associated with DM unless glucose control, whereas metabolic memory is pathophysiologic term expanded to all molecular mechanisms and biochemical pathways underlying development of DM complications. Although both terms "metabolic memory" and "glycemic memory" are widely used as synonyms, obviously "metabolic memory" appears to be more than just tight glucose control necessary to prevent DM complications [26,27]. Indeed, clinically, the emergence of this "metabolic memory" suggests the need for a very early aggressive treatment aiming to "normalize" the metabolic control and the addition of agents which reduce cellular reactive species and glycation in addition to normalizing glucose levels in DM in order to minimize long-term complications [25–27].

3. Pathophysiology of "glycemic memory phenomenon"

The exact molecular mechanisms of "glycemic memory phenomenon" remain unexplained [28]. There is paradigm that has been postulated being of causality link between hyperglycemia and this "memory phenomenon" [29]. This paradigm has suggested that hyperglycemia exert long-lasting detrimental effects on the CV system through several mechanisms, i.e. over production of free reactive species and accumulation of advanced glycation end products (AGE), which lead to glycation of mitochondrial proteins, lipids and nucleic acids. AGEs not only inhibit DNA synthesis in target cells, but also elicit vascular hyper permeability, pathological angiogenesis, and thrombogenic reactions by inducing vascular endothelial growth factor (VEGF) and plasminogen activator inhibitor-1 (PAI-1) through the interaction with the receptor for AGEs (RAGE). Thus, biochemical products of the advanced enzymatic and non-enzymatic glycation pathways are considered an integral clue implicated in metabolic memory, tissue damage and DM-related CV complications. However, the production of reactive species unrelated to the presence of hyperglycemia may associate with the previous production of AGEs, which maintains RAGE over-expression, level of glycation of mitochondrial proteins and the amount of mitochondrial DNA produced [29]. Indeed, AGEs have correlated with retinopathy progression, independently of HbA1c level [30]. Interestingly, that risk progression of retinopathy and neuropathy but not nephropathy has associated well with AGEs [30]. Moreover, hyperglycemia induces directly polyol pathway activity, which evidently contributes in accumulation of superoxide and nitric oxide (NO) levels leaded to forming peroxynitrite. Peroxynitrite may induce lipid and protein oxidation, nitration of proteins and via impaired viability and increased cell death may contribute to the micro-angiopathy development [31]. Hyperglycemia-induced superoxide production, primarily from mitochondria, is able to increase protein kinase C activity and through activation of a redox-sensitive nuclear transcriptional factor and NF-kappa B to induce NO and lipid peroxides production in several types of cells (i.e. endothelial cells, cardiomycites, smoth muscle cells, adipocites, and pericytes) leaded to persisted low-grading inflammation. Furthermore, systemic oxidative stress activates poly (ADP-ribose) polymerase and leads to 4-hydoxynonenal adduct accumulation that correlated with large and small nerve fiber dysfunction [32].

Thus, AGE and reactive oxygen species (ROS) generation via molecular glucose-induced epigenetic changes might up regulate various genes, including the p65 subunit of NF-κB, monocyte chemoattractant protein-1 (MCP-1) and vascular cell adhesion molecule-1 (VCAM-1) in target cells that lead to low-grading inflammation, direct tissue injury, pro-thrombotic state. Therefore, accumulation of AGE and free radicals might induce an altered gene expression even when hyperglycemia is resolved.

Fig. 1 is reported a principal scheme explained interrelation between hyperglycemia, genetic predisposition, environmental