

## OXIDATIVE STRESS AND „METABOLIC MEMORY” -A VICIOUS CIRCLE IN DIABETES MELLITUS TYPE 1

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### Abstract

*Diabetes is a serious public health problem associated with multiple metabolic alterations and principal of these is hyperglycemia. The reduced life expectancy and increased morbidity are a result of diabetic complications due to chronic glucotoxicity. Oxidative stress is considered to have a key role not only in generation of long-term complications, but also in supporting the so called phenomenon „metabolic memory”. This phenomenon was first observed in preclinical studies and was later confirmed in clinical trials and it describes beneficial effects of immediate treatment of hyperglycemia. Hyperglycemic memory can also appear even when good glycemic control is achieved. Early normalization of glycemia can halt hyperglycemia-induced pathological processes associated with increased oxidative stress. Furthermore, the emergence of this „metabolic memory” suggests the need for very early and aggressive treatment in diabetic patients.*

**Keywords:** oxidative stress, reactive oxygen species, metabolic memory, diabetes mellitus.

## STRESUL OXIDATIV ȘI „MEMORIA METABOLICĂ” – UN CERC VICIOS ÎN DIABETUL ZAHARAT DE TIP I

### Rezumat

*Diabetul zaharat tip I reprezintă o problemă serioasă de sănătate publică care asociază multiple alterări metabolice, dintre care cea mai importantă este hiperglicemia. Scăderea speranței de supraviețuire și creșterea morbidității se datorează complicațiilor apărute secundar glucotoxicității. Stresul oxidativ este considerat având un rol cheie nu numai în generarea complicațiilor pe termen lung, cât și în menținerea așa-numitului fenomen „memorie metabolică”. Acest fenomen a fost observat prima dată în studiile preclinice, iar apoi a fost confirmat în trialurile clinice și descrie efectele benefice imediate ale tratamentului hiperglicemiei. Memoria hiperglicemică poate însă să apară și atunci când există un control glicemic bun. Normalizarea timpurie a glicemiei poate diminua patologia indusă de hiperglicemie și stres oxidativ. Astfel, memoria metabolică sugerează nevoia imperioasă de tratament agresiv și timpuriu al hiperglicemiei la pacienții cu diabet zaharat tip I.*

**Cuvinte cheie:** stres oxidativ, specii reactive ale oxigenului, memorie metabolică, diabet zaharat.

### INTRODUCTION

Free radicals are reactive chemical species that can cause oxidation injury in human beings by attacking the macromolecules like lipids, carbohydrates, proteins and nucleic acids. In normal conditions, there is a critical

balance in the generation of oxygen free radicals and antioxidant defence used by organisms to protect against free radical toxicity [1,2].

Oxidative stress (OS) is defined as a significant imbalance between the production of reactive oxygen species (ROS) and antioxidants. Because of the important alterations in signalling pathways, OS is known to be a component of tissue damage [3,4].

Diabetes is associated with several metabolic

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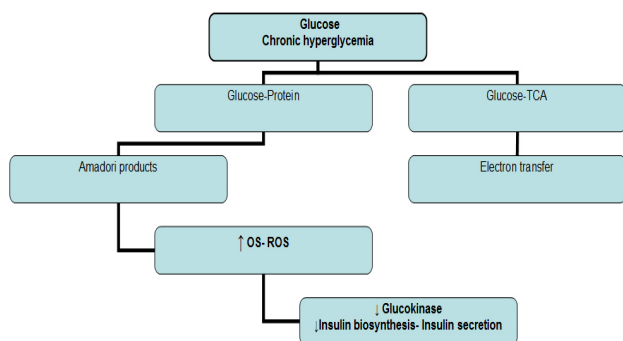
alterations, but the most important is chronic hyperglycemia. Even in healthy individuals, glucose alteration is known to increase formation of cellular oxidative stress [5]. Despite significant advances in hyperglycemia treatment, blood glucose monitoring and markers of glycemic control, debilitating complications remain in most diabetic patients.

„Metabolic memory” describes the association between delayed development of diabetic complications and prolonged exposure to glucotoxicity [6]. So the concept of „metabolic memory”, that is of diabetic vascular stress, persists after glucose normalization, suggests the need for early aggressive treatment and metabolic control [7].

### OXIDATIVE STRESS AND GLUCOSE TOXICITY

Glucose homeostasis is maintained by the interaction of three processes – insulin secretion, tissue glucose uptake and hepatic glucose production. Thereby, normal glucose is being sustained by the balance between intake, tissue utilization and endogenous production [8,9]. Acute hyperglycemia is known to cause injury to many organs. On the other hand, chronic hyperglycemia leads to complications observed only several years after the beginning of diabetes.

Under conditions of health, cellular processes associated with oxidation and inflammation, function as compensatory and homeostatic mechanisms that maintain a physiologic balance [10]. The oxidative - inflammation relation is modulated by mediators of the immune and metabolic systems and maintained through a positive feedback loop [11].



**Figure 1.** Increase glucose state causing oxidative stress and high levels of reactive oxygen species, and therefore reduction of insulin secretion due to glucose toxicity.

OS is associated with the molecular mechanism of decreased insulin biosynthesis and secretion, which is the main etiology of glucose toxicity. It is known that pancreas may be more susceptible to OS than other tissue or organ [12,13]. Metabolic reactions continuously produce ROS, but several antioxidant enzymes help to maintain a low level of ROS. There are strong indications that OS may be a key event in diabetic complications [14]. High levels

of ROS seem to be linked to chronic hyperglycemia in diabetes. Various pathways are involved in the increase of OS and thereby in a hyperglycemic state and low insulin secretion (Figure1).

### „METABOLIC MEMORY” - THE NEW CHALLENGE OF DIABETES

There is a growing evidence that early, intensive treatment of new-onset diabetes mellitus aimed at tight glucose control reduces the risk of vascular complications. A delay in treatment of hyperglycemia in diabetic patient may cause adverse biological reactions in vascular endothelial cells and these processes cannot be stopped at later stage even if normal glucose level is achieved [15]. This particular phenomenon is defined as metabolic memory [16].

The existence of this phenomenon was suggested in 1980s when it was first observed in preclinical studies. Since then, the hypothesis of metabolic memory has been supported by various clinical trials. The Diabetes Complications and Control Trial (DCCT) and its follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) trial showed the real evidence of this phenomenon in clinical practice and pointed the effect of intensive as compared with conventional therapy on the risk of long-term complications in diabetic patients [17,18].

Many clinicians seek the answer to the question of why the effect of good glycemic control at an early stage of diabetes is maintained over many years after its discontinuation. It is believed that chronic hyperglycemia creates environment in which diabetic patients develop chronic complications.

One of the key factors responsible for the long-term complications in diabetes is the cascade oxidative stress-metabolic memory. The cycle of events in the vascular cells might suggest that oxidative stress, associated with delayed therapeutical intervention is essential in the phenomenon of metabolic memory [6].

Along with oxidative stress, chronic hyperglycemia, the mitochondria is an important player in propagating the metabolic memory. The formation of advanced glycation end-products (AGEs) in the mitochondria, plays a crucial role in diabetic complications. A recent study described a direct relationship between AGEs, mitochondrial decline function and the excess formation of mitochondrial reactive species [19]. It is possible that AGEs formation is an irreversible phenomenon and could be responsible for metabolic memory. Finally, studies show that AGEs and its receptors may be involved in metabolic memory, based on the evidence that engagement of AGEs and receptors elicits oxidative stress [20].

### THERAPEUTIC IMPLICATIONS

Hyperglycemia leaves a very early imprint on the development of vascular implications, and has an important

therapeutical implication: it seems mandatory to begin an aggressive treatment from the onset of diabetes type 1. Tight control of glycemia is the key strategy and especially concerning the postprandial hyperglycemia which is accompanied by high levels of reactive species [21], not only in plasma but also intracellularly [22].

Another possible strategy is the prevention of over production of free radicals. The use of antioxidants may theoretically reduce the production of ROS, but this prevents only partially the effect of metabolic memory [23]. However, it is well established that available antioxidants do not have any specific effects in diabetes, at least the doses used in the available trials [24].

Only one strategy could envision the future treatment: precisions control of hyperglycemia together with compounds targeting mitochondrial reactive species. This therapeutical approach has the potencial to reduce metabolic memory effect of hyperglycemia on diabetic complications.

In summary, oxidative stress seems to be a pivotal pathway not only in diabetic complications, but also in metabolic memory, therefore the possibility of „switching off” the metabolic memory could be an important strategy for the prevention of diabetic complications.

Additionally, if we can determine critical steps that are involved in hyperglycemic memory it might be possible to interrupt the pathways that determine this vicious circle in the natural history of diabetes mellitus type 1.

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