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Haitham Ahmed Al-Madhagi *

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Short Communication

Metabolic Memory of Type 1 Diabetes Revisited

Haitham Ahmed Al-Madhagi *

Biochemical Technology Program, Dhamar University, Yemen.

***Corresponding author:** Haitham Ahmed Al-Madhagi, Biochemical Technology Program, Dhamar University, Yemen.

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In 2021, there were 8.4 million cases of type 1 diabetes mellitus (T1DM) worldwide which projected to reach 17.4 million cases in 2040 [1]. Patients diagnosed with T1DM are on life-long insulin injections in order to regulate their blood glucose levels. The standard insulin therapy and subsequent monitoring HbA1c is no longer sufficient for T1DM patients management. Instead, postprandial hyperglycemia as well as glycemic variations should be minimized to reach near normoglycemic state. To do so, intensive insulin therapy should be introduced so as to restore homeostatic glycemic control [2]. Unfortunately, keeping HbA1c in the allowed range is alas not adequate to reduce the incidence of macro and microvascular complications of T1DM due the emerging "metabolic memory" [3].

The "metabolic memory" terminology was coined for the first time in 1987 documenting the relatively faster development of T1DM complications despite the control of blood glucose and HbA1c levels. This was followed by successive clinical trials demonstrating the reduced risk of suffering from complications in intensively-controlled patients as compared to regular therapy confirming the existence of such metabolic memory. Metabolic memory can be defined as the highly adaptable behavior of body to the external intervention in the first period after diabetes has established. There are 4 mechanisms that are most likely to be responsible for the formation of metabolic memory: oxidative stress, advanced glycated end products (AGE), epigenetic modifications, and chronic inflammation (Fig 1) [4]. Although oxidative stress and its consequence, AGEs, are contributing factors, interventions intended to block AGE formation failed to 'erase' metabolic memory consequences. Reactive species generation, the driving fuel of oxidative stress, is unavoidable within human body. In addition, hyperglycemia-induced reactive oxygen species generation also leads to activation of nuclear factor kappa B (NF-κB) which in turn triggers protein kinase C exaggerating the oxidative events. In result, NO and lipid peroxides are formed in smooth muscle cells, endothelial cells and adipocytes causing thereby low-grade inflammatory response [5]. In fact, oxidative stress and inflammation are firmly associated, i.e. oxidative stress signals the activation of different transcriptional factors that ultimately results in the differential expression of inflammation-inducing genes and, in contrast, inflammation feeds the oxidative stress vicious cycle [6].

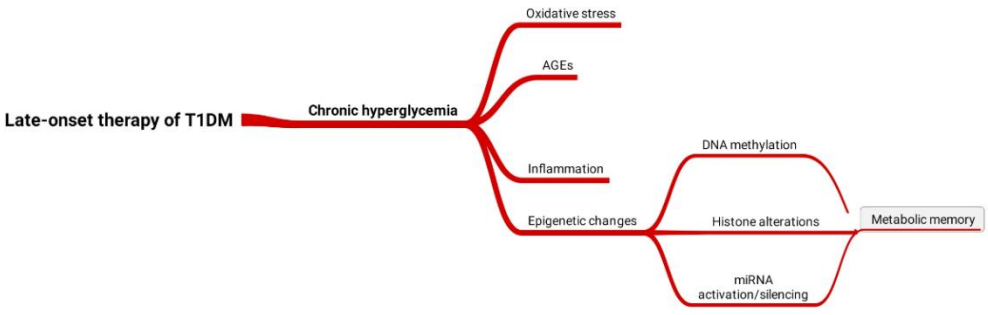

Figure 1: Mechanisms underlie the formation of metabolic memory.

Indeed, it has been proven that what lies behind the several, if not all, forms of long-term memory and adaptation to an effector is the epigenetic changes. These include 3 main players: DNA methylations, histone covalent modifications and miRNA biogenesis and action. Maternal nutritional status during pregnancy deeply influences fetal predisposition to T1DM. Additionally, fetal "critical period" which is the first 7 years after born, determines to a great extent the likelihood of disease development. Histone covalent modifications takes the largest part of implication to metabolic memory as represented by the many histone-modifying enzymes. Such changes take place in interplaying cells involving smooth muscle cells, endothelial cells, retinal and renal cells [3]. The good news here is that epigenetic alterations are reprogrammable, i.e. can be targeted by certain inhibitors so as to erase the formed memory. Hypermethylation of CpG islands in DNA of patients with end-stage

kidney failure and albuminuria was found. Similarly, upon putting aortic endothelial cells in hyperglycemic stress, H3K4me1 mark was persistently detected in the promoter of NF-κB even though the cells had been removed from hyperglycemic state [7]. Moreover, monocytes isolated from patients with a history of elevated HbA1c levels had more promotor regions enriched with H3K9Ac alterations. These promoters belong to genes related to numerous diabetes and diabetic complication-implicated pathways, including the TNFR2 signaling as well as the NF-κB pathway. Likewise, plenty of miRNAs were shown to contribute to the foundation of metabolic memory. miR-21, miR-192, miR-214, and miR-377 were observed in the kidneys of T1DM patients. miR-21 triggered fibronectin expression and renal cell hypertrophy through the activation of TORC1 activity. In addition, reduced PTEN levels were also correlated with increased expression of miR-214 as a consequence of hyperglycemia [7].

In conclusion, this highlights the pivotal role of the components of epigenetic alterations that underlie the development of metabolic memory in T1DM patients. Furthermore, targeting these components should be expanded to reach conclusive result regarding the late clinical intervention of T1DM which creates a hope to those patients.

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