

Supplementary data 13. Environmental factors responsible for glutathione deficiency.

Type 2 diabetes mellitus is a complex multifactorial disease and its etiology is attributable to numerous risk factors such as genetic, ethnicity, race, poor diet, physical inactivity, and smoking [13,14]. It is widely accepted that nutritional status is one of the major factors influencing the risk of type 2 diabetes [15], and dietary factors play an essential role in maintaining glutathione metabolism. Low consumption of food rich in sulfur-containing amino acids such as cysteine and methionine necessary for the biosynthesis of glutathione is an important factor responsible for endogenous deficiency of glutathione. To prevent this condition, predominantly plant protein-packed foods with glutathione precursors, co-factors, and also whole foods have been shown to boost glutathione stores such as brassica vegetables, fresh fruits, beans, legumes, eggs, seafood, dairy, green tea, and herbs [16], and insufficient intake of such food increases the risk of type 2 diabetes [17,18]. Psychological stress, low physical activity, or sedentary lifestyle are also important factors increasing the risk of type 2 diabetes. Numerous studies [19,20,21,22] have shown that acute and chronic life stresses are associated with a drop of endogenous glutathione. A systematic review and meta-analysis of numerous published studies provided strong evidence for an inverse association between physical activity and the risk of type 2 diabetes [23]. It is suggested that contracting skeletal muscle improves the sensitivity of tissues to insulin action, increases blood flow in the muscle, and enhances glucose uptake into the cells [24,25]. Interestingly, lifelong physical activity was shown to upregulate antioxidant systems, including tissue glutathione homeostasis: regular exercise enhances and chronic inactivity decreases glutathione content in skeletal muscle [26,27,28,29]. Bad habits such as drinking alcohol and tobacco smoking may affect intracellular glutathione content: both tobacco smoking [30,31,32] and alcohol use [33,34,35] were found to deplete GSH pools. Chemical agents of the environment may affect glutathione content in two ways: to deplete the endogenous GSH pool and/or inhibit the biosynthesis of glutathione. The Comparative Toxicogenomics Database (<http://ctdbase.org>, date of access: 13.10.2020) contains data on 284 chemicals that have been identified to inhibit glutathione biosynthetic processes (GO:0006750) in both humans and laboratory animals (i.e. *Mus musculus* and *Rattus norvegicus*). Five chemical agents such as bisphenol A, diethylhexyl phthalate, hydrogen peroxide, palmitic acid, and streptozocin have the potential to affect the levels of glutathione in the pancreas, and many of these chemicals are well-known risk factors for diabetes [36,37,38,39]. Exposure to agricultural chemicals and industrial pollutants increases the risk of type 2 diabetes [40,41,42,43]. In particular, pesticides such as endosulfan, chlorpyrifos, carbaryl, and organochlorine insecticides [44,45,46] have been associated with the risk of type 2 diabetes, and their causative effects are realized through the depletion of endogenous glutathione stores [47,48,49,50]. There are some examples for glutathione depleting drugs such as Acetaminophen (Tylenol or Paracetamol) [51,52], doxorubicin [51,53], Cyclophosphamide [54], and some other medications [55] that deplete glutathione. Many animal and human studies have reported that the levels of intracellular glutathione progressively declines with aging [56,57] and that the decreased levels of endogenous glutathione have been identified in a variety of chronic diseases such as cardiovascular, respiratory, liver diseases and cancer [58,59,60,61,62,63]. Thus, endogenous deficiency of glutathione can be considered as acquired condition attributable to many factors generally that impact intracellular glutathione content in two ways: to decrease/increase GSH biosynthesis and deplete the endogenous pool of glutathione. Summarizing literature data discussed above it is important to draw a conclusion that almost all environmental factors that affect intracellular glutathione levels are also shared with the development of type 2 diabetes.

Supplementary references

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