Nutrition, Metabolism & Cardiovascular Diseases (2009) **19**, 365–377

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Nutrition, Metabolism & Cardiovascular Diseases

REVIEW

Glucose toxicity: The leading actor in the pathogenesis and clinical history of type 2 diabetes — mechanisms and potentials for treatment

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Received 3 February 2009; received in revised form 18 February 2009; accepted 11 March 2009

KEYWORDS
Glucose toxicity;
Glucotoxicity;
Lipotoxicity;
Insulin resistance;
Beta cell;
Diabetes pathogenesis;
Diabetes treatment;
Hexosamine;
Oxidative stress

Abstract *Aim:* Although it is now well established that the deleterious effects of chronic hyperglycaemia (i.e., glucose toxicity) play an important role in the progressive impairment of insulin secretion and sensitivity, the two major actors of the pathogenesis of type 2 diabetes mellitus, the precise biochemical and molecular mechanisms responsible for the defects induced by glucose toxicity still remain to be defined.
Data synthesis: here we will briefly report on convincing evidence that glucose toxicity acts through oxidative stress, modifications in the exosamine pathway, protein kinase C and others. After inducing or contributing to the genesis of type 2 diabetes, these same mechanisms are considered responsible for the appearance and worsening of diabetic specific microvascular complications, while its role in increasing the risk of cardiovascular diseases is less clear. Recent intervention studies (ADVANCE, ACCORD, VADT), conducted to evaluate the effects of strict glycaemic control, apparently failed to demonstrate an effect of glucose toxicity on cardiovascular diseases, at least in secondary prevention or when diabetes is present for a prolonged time. The re-examination, 20 years later, of the population studied in the UKPDS study, however, clearly demonstrated that the earliest is the strict glycaemic control reached, the lowest is the incidence of cardiovascular diseases observed, including myocardial infarction.
Conclusion: The acquaintance of the role of glucose toxicity should strongly influence the usual therapeutic choices and glycaemic targets where the reduced or absent risk of hypoglycaemia, durability of action, and data on prolonged safety should be the preferred characteristics of the drug of choice in the treatment of type 2 diabetes mellitus.

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doi:10.1016/j.numecd.2009.03.018