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# Understanding Diabetes and its Complications for Biomedical Research

**Editorial**

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The understanding of the human disease(s) of diabetes and its complications and of its applicable animal models has considerable limitations as reflected by papers submitted to pharmacology-type journals and by discussion on various research forums. The major relevant areas are the aetiology and the consequences of diabetes the latter being mostly cardiovascular disease and in that area there is also considerable disparity between the human disease of atherosclerosis and relevant animal models [1-3]. Models are best used as representative of various but specific aspects of the diabetes cardiovascular disease continuum rather than providing a holistic approach and answers.

Diabetes is a range of genetically and environmentally derived conditions diagnosed somewhat pragmatically on the basis on plasma glucose levels or relative hyperglycaemia. The current classifications of diabetes cover a variety of conditions but the two major forms in terms of prevalence are Type 1 and Type 2. It is perhaps somewhat surprising to know that the distinction between what we now know as Type 1 and Type 2 diabetes only became clearly apparent as recently as 1951 when Bornstein and Lawrence published a paper based on studies in a newly developed hypophysectomized, adrenalectomized, alloxan-diabetic rat model showing that plasma from patients with Type 1 diabetes contained no insulin whereas that of patients with what we now know as Type 2 diabetes had variable but substantial amounts of insulin[4]. This lead to names such as Insulin- and Non-Insulin Dependent Diabetes Mellitus (IDDM and NIDDM) and the awkward naming corollary that a patient with late stage NIDDM had Insulin-requiring Non-insulin Dependent Diabetes Mellitus [5,6]. After several naming iterations, diabetes was most recently redefined and classified by all the major international diabetes organisations in 1999 – see publications on behalf of the American Diabetes Association, the European Association for the Study of Diabetes, the Australian diabetes Society, the International Diabetes Federation [7-9] – the major forms were classified by Type and number – as to Type it can be type or Type but as to number the 1999 classifications are specifically 1 and 2 and not I and II (the use of "I" and "II" and expressions such as Non-insulin Dependent Diabetes Mellitus thus refer to classifications before 1999). To expand briefly on the aetiology, Type 1 diabetes is an immunological disease resulting from a chronic immunological attack on the insulin-secreting beta cells of the pancreas and in its clinical manifestation usually a very rapid decrease in the ability to produce insulin – this results in a rapid onset dramatic hyperglycaemia – glucose levels may reach 40 – 50 mM precipitating polyuria and potentially life-threatening dehydration requiring hospitalisation and stabilisation. Type 2 diabetes in the majority of cases (approximately 80 per cent) arises from increased obesity driving increasing insulin resistance due to undefined mechanisms thought to be lipophilic metabolites inhibiting insulin signalling[10]. The insulin resistance can persist for a considerable time ("pre-diabetes") [9], during which plasma glucose is not elevated but early stages of complications are developing [11]. The early stages of insulin resistance and Type 2 diabetes are associated with increasing insulin secretion and somewhat normal blood glucose levels with perhaps excursions under stresses such as post-prandial. So the early phase of Type 2 diabetes is characterised by hyperglycaemia and hyperinsulinemia (refer below to comments on Streptozotocin (STZ) and Type 2 diabetes). After a prolonged period of insulin resistance, glucolipotoxicity towards pancreatic beta cells induces pancreatic insufficiency (relative insulin deficiency) and a decompensation phase resulting in hyperglycaemia i.e. the occurrence of hyperglycaemia ("diabetes") requires a reduced capacity to secrete insulin [1,12,13]. There is a substantial subset of people with Type 2 diabetes who are lean and in this situation the disease occurs due to glucolipotoxicity (in contrast to the immune toxicity of Type 1 diabetes) of beta cells and a failure to secrete sufficient insulin leading to hyperglycaemia [14]. Although this beta cell toxicity state might be compared to the use of STZ in animal models this is not the major and common form of Type 2 diabetes which is dependent upon insulin resistance and later insulin insufficiency.

Others have reviewed the properties of various models of "diabetes" but the properties of the individual models should be compared against the natural history, aetiology and pathology described above [15-17] – individual models are best considered for the component of the pathological condition of diabetes that they best represent and not an overall model of diabetes – indeed the definitions apply to human disease and animal models should be referred to as animal models and not as animals having the human disease. Similarly, the outcomes of studies to reduce hyperglycaemia or to prevent the consequences of the hyperglycaemia should be stated explicitly for the specific activity with careful extrapolation to the human disease(s).

What of the consequences of diabetes? The diagnostic criterion is hyperglycaemia but the pathological consequences almost certainly arise from a multitude of factors in addition to hyperglycaemia [18-23]. Some of these factors may be related to the diabetes such as low HDL Cholesterol levels but others such as hypertension may be mechanistically unrelated co-morbidities [22,24]. There are two considerations – the impact of hyperglycaemia on cardiovascular pathology and the impact of treatment in reducing the disease process [12,23,25]. The two major parameters are the extent of hyperglycaemia and also the duration of the hyperglycaemia – hyperglycaemia has an acute effect of vessels such as on the endothelium (endothelial dysfunction) but later persistent effect on the vascular smooth muscle. Both small vessel microvascular disease and larger vessel macrovascular disease are positively correlated with increasing hyperglycaemia [12,25]. The relationship is steeper for microvascular disease than macrovascular disease – this indicates that microvascular disease arises from hyperglycaemia but that other factors are involved in the pathology of macrovascular disease. Accordingly, reducing hyperglycaemia has profound effects on reducing microvascular disease [12,25]. Treatment of hyperglycaemia and reducing macrovascular disease is a very controversial area – few medical interventions can be shown to reduce cardiovascular events based on targeting hyperglycaemia and even for positive studies the effects are generally so small as to not impact on overall survival; in comparison, the effects are not nearly as strong or consistent as, for example, the efficacy of statins in lowering plasma cholesterol and reducing cardiovascular events [12,25,26]. Furthermore, diabetes (hyperglycaemia) appears to have effects on the cardiovascular system such that the longer the duration of the hyperglycaemia the more difficult it becomes to reverse the effects and obtain improved cardiovascular outcomes. The low efficacy of some anti-hyperglycaemic drug treatment in patients with well-established Type 2 diabetes lead to suggestions that earlier intervention was required.

The same parameters which relate to the use of animal models on studies of diabetes also relate to the study of the macrovascular complications of diabetes – there is overwhelming evidence that the time of onset is shortened and the rate of progression of atherosclerosis is considerably enhanced in people with Type 2 diabetes[11,18]. However, it has been extremely difficult to produce animal models which reproduce this pathological response with a high degree of fidelity [27,28]. This perhaps relates to an understanding of the aetiology of atherosclerosis in humans versus animal models [3,29-32]. In an analysis of the factors precipitating atherosclerosis in humans and relevant rodent models it was concluded: "Finally, the mechanism of disease initiation and progression are quite different between mice and humans, with the former being a macrophage-rich disease and the latter occurring in a smooth-muscle-cell-rich environment with an extracellular matrix rich in proteoglycans, collagen, and entrapped lipids with sheets of calcification" [3]. In animal models of hyperglycaemia, the inflammatory phase is enhanced and accelerated [33,34] but this type of inflammatory response is a late and variable response in humans [3]. Thus, not only has this inflammation has been very difficult to prevent in animal models the nature of its contribution to human atherosclerosis is problematical.

At the next level there are many studies based on applying high glucose concentrations to cardiovascular cells such as endothelial and vascular smooth muscle cells [35-37] and the biochemical mechanisms causing the vascular complications of diabetes have been reviewed [38,39]. Studies have been conducted with glucose concentrations of 40 mM or higher [40-43]. The highest blood glucose concentrations observed in even poorly medically treated patients with diabetes are around 20 mM (other than people with Type 1 diabetes at the time of diagnosis). Despite the basic requirement of science that effects are dose or concentration dependent very few studies provide glucose dose response relationships; further it is necessary to account for the possible osmotic effect of raising glucose concentration and the effect of adding additions glucose (d-glucose or dextrose) to cells should, be compared to the effect of adding metabolically inert l-glucose, or sodium chloride or mannitol or other suitable agents. Even the manner in which these solutions are prepared can determine the results of some experiments – in our laboratory we have observed different responses [36] from preparing elevated glucose solutions by mixing low and high solutions compared to adding sterile concentrated glucose solutions to low glucose media – the reasons for this phenomena remain unknown.

Life spans in developed countries have been increasing over the last several decades due to reduced childhood deaths, improved nutrition, reduced cigarette smoking and improved treatment of hypertension and hyperlipidemia. However, the recent societal trends of reduced physical activity, increased sedentary time, and excessive energy intake are driving increased rates of obesity and diabetes leading to increased cardiovascular and a multitude of other diseases. If this trend continues, as it appears at present, then a coming generation may experience a shorter life expectancy than the preceding generation as well as experiencing the devastating morbidity associated with chronic metabolic illness. So in this setting the need for research in this area is profound – what is required is a consolidation of existing research methodologies and a quantum shift forward in animal models of diabetes and its complications.

In summary, research covering the addition of $5^{+}$ mM (up to say 25 mM) glucose to cell cultures called diabetes research or STZ treated rodents called Type 1 diabetes research or STZ treated rodents on high fat diet and referred to as a Type 2 diabetes model is experimentally valid in its own right but it is suggested that the extrapolations to the mentioned clinical entities are too great and do not reflect the clinical complexity of diabetes as outlined in brief above. Additionally the types of diabetes are specifically clinical diagnosis of disease in humans. So, some caution is warranted in presenting research in this area when most studies represent a component, for example hyperglycaemia, rather than a complete clinical entity.

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