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Editorial

Diabetes: What the Past tells us about the Future

Kevin G Culligan*

Department of Medical Sciences, Royal College of Surgeons in Ireland ,Bahrain

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Description

Diabetology, the science of diabetes, aims to discover the underlying causes contributing to the onset of both type 1 and type 2 Diabetes mellitus. Regrettably, healthcare providers gain very little insight into the medicine they provide through knowledge of its history. The first reference to Diabetes, for example dates back to third dynasty Egyptian times. In the Ebers Papyrus, a consolidation of ancient practices of medicine, the writings of Hesy-Ra detail a remedy for excessive urination, or polyuria. Later in the time of Hippocrates and his contemporaries Galen and Aretaeus, the term diabetes was coined. Taken from the Greek word 'diabainein', meaning 'siphon', the ailment was described as 'diarrhea of the urine', being equated to the 'melting down of the flesh and limbs into urine'. They observed that with reduced food intake, the level of sugar in the urine reduced, and hence promoted a healthier lifestyle amongst Diabetes sufferers.

Although a thousand years previously Hindus had used the term Honey urine, diagnosis of Diabetes in medieval times (if the physician could afford them) was by the use of 'water tasters', who tasted the urine of suspected diabetes patients for its sweetness. Given the term 'pissing evil', the sweet taste resulted in the addition of 'mellitus', or honey to the term Diabetes. It wasn't until the late 18th century that a distinction between Diabetes mellitus (DM) and Diabetes insipidus was introduced. From thence, the discovery of insulin-producing pancreatic beta cells, the isolation of insulin and utilization of recombinant insulin in the treatment of DM were not long to follow.

Detection and diagnosis of diabetes was first achieved based on high levels of glucose breaching the renal threshold. Water tasters of the past were able to detect the increased glucose in the urine. Detection can be as simple as by the use of ants (attracted to its sweetness) to the utilization of dipsticks. The invention of the first glucose meter in the 1970s led to the development of more hi-Tec methods of diagnoses, with finger prick tests routinely used by diabetic subjects from home to self-monitor glucose levels.

In the recent past, Type 2 DM was classified as a disease of older age. Usually, diagnoses were not made until an individual was in their fifth decade. However, in certain countries nowadays diagnoses of Type 2 DM are being made in individuals in their second decade. What can this be attributed to? Statistics from the World Health Organization show that the average Body Mass Index is increasing at an alarming rate. Individuals are less active than in the past, and convenience has contributed to a more sedentary lifestyle. Of concern also is the rate of increase of adiposity of an individual per decade of life, with some countries exhibiting up to 2.5 times the average increase in adiposity per decade. Therefore, paralleling an increase in the average obesity is the speed at which adipose tissue is accumulated.

Why should this be of concern to us? Given the substantial increase seen in obesity, we can expect to see a parallel increase in the cases of Type 2 DM. Over 90% of individuals who are obese will develop in parallel Type 2 DM. Such is the tightness of association between obesity and Type 2 DM, it has led to the creation of the term 'Diabesity' to encompass the molecular links between obesity and diabetes.

Key to this association is the accumulation of visceral fat. Once thought of as purely a storage depot for triglycerides, adipose tissue has now been re-classified as an endocrine gland; a bioactive organ with secretory properties. Part of the adipocyte secretome contains a subfamily of cytokines termed adipokines. However, the functional attributes of these adipokines remain largely uncertain, spawning a whole new area in Diabetes research.

What adds to the functional complexity of these cytokines is the lack of corroboration between animal and human data in models of obesity and Diabetes. In mice, several of the adipokines such as leptin and adiponectin are found to be localized in white adipose

***Corresponding Author:** Kevin GC, Department of Medical Sciences, Royal College of Surgeons in Ireland – Bahrain, Tel: 0879008172; E-mail: kgculligan@gmail.com

tissue where the quantity released related to the volume of the adipocyte. However, in humans different tissue specificity occurs. Resistin in humans, for example is found to be predominantly secreted from activated macrophages of the sub-clinical chronic low grade inflammation that accompanies visceral adipocyte accumulation. Indeed the functional attributes of these adipokines also differs cross-species. In mice, resistin conveys resistance to insulin, decreasing sensitivity to the actions of insulin on certain tissues, giving rise to its nomenclature. However, owing to the different cellular localization in humans, the function of human resistin still remains unclear. Indeed, it is believed that resistin plays a role in humans as an inflammatory mediator, rather than insulin mimetic. What remains to be determined however is whether the increase in resistin is a direct contributor to the inflammatory-related condition, or elevated as a result of the condition. Several areas outside of obesity are being explored to elaborate on the function of resistin in humans, including some forms of cancer, cardiovascular disease and inflammatory processes.

Determination of cause or effect of molecular aspects of DM would result in not only a greater understanding of the molecular mechanisms behind T1 and T2 DM, but also in a more targeted approach to diabetic therapy. The Hippocratic approach to treatment of DM in ancient Greek times involved alteration of lifestyle conditions to alleviate the effect of DM; a part-approach still used. Common to all the current therapeutic approaches in the treatment of T2DM is that none of the treatments targets the root cause of the insulin defect. The majority work by targeting the effect of poorly functioning insulin release. In general, oral hypoglycemic agents work to reduce glucose levels in the blood. The most common oral hypoglycemic agent, metformin, reduces hepatic glucose production while increasing skeletal muscle uptake of glucose. Sulfonylureas such as tolbutamine cause an increased release of insulin from pancreatic beta cells by enhancing depolarization. Thiazolidinidiones (TZDs) reduce plasma glucose by alteration of insulin-sensitive genes through inhibition of PPARγ. Therefore, they are in essence treating the effects of defective insulin actions or altering defective pathways, rather than addressing the root cause of the defect.

A greater understanding of the molecular mechanisms behind the causes of DM can identify novel strategies that deviate from current DM treatments. Understanding the molecular changes in turn allows greater selectivity in the approach to targeted therapies, which may yield further specific treatment options; treating the cause of DM rather than its downstream effects. This targeted therapeutic approach therefore highlights an exciting new avenue of research into the substrates of diabetes, and ushers in a next-generation approach to developing treatments for this widespread condition.